QUINAZOLINE DERIVATIVES FOR TREATMENT OF CANCER

The present invention relates to quinazoline derivatives for use in the treatment of disease in particular proliferative diseases such as cancer and in the preparation of medicaments for the treatment of proliferative diseases, and to processes for their preparation, as well as pharmaceutical compositions containing them as active ingredient.

Cancer (and other hyperproliferative diseases) are characterised by uncontrolled cellular proliferation. The loss of the normal regulation of cell proliferation often appears to occur as the result of genetic damage to cellular pathways that control progress through the cell cycle.

In eukaryotes, an ordered cascade of protein phosphorylation is thought to control the cell cycle. Several families of protein kinases that play critical roles in this cascade have now been identified. The activity of many of these kinases is increased in human tumours when compared to normal tissue. This can occur by either increased levels of expression of the protein (as a result of gene amplification for example), or by changes in expression of co activators or inhibitory proteins.

The first identified, and most widely studied of these cell cycle regulators have been the cyclin dependent kinases (or CDKs). Activity of specific CDKs at specific times is essential for both initiation and coordinated progress through the cell cycle. For example, the CDK4 protein appears to control entry into the cell cycle (the G0-G1-S transition) by phosphorylating the retinoblastoma gene product pRb. This stimulates the release of the transcription factor E2F from pRb, which then acts to increase the transcription of genes necessary for entry into S phase. The catalytic activity of CDK4 is stimulated by binding to a partner protein, Cyclin D. One of the first demonstrations of a direct link between cancer and the cell cycle was made with the observation that the Cyclin D1 gene was amplified and cyclin D protein levels increased (and hence the activity of CDK4 increased) in many human tumours (Reviewed in Sherr, 1996, Science 274: 1672-1677; Pines, 1995, Seminars in Cancer Biology 6: 63-72). Other studies (Loda et al., 1997, Nature Medicine 3(2): 231-234; Gemma et al., 1996, International Journal of Cancer 68(5): 605-11; Elledge et al. 1996, Trends in Cell Biology 6; 388-392) have shown that negative regulators of CDK function are frequently down regulated or deleted in human tumours again leading to inappropriate activation of these kinases.

More recently, protein kinases that are structurally distinct from the CDK family have been identified which play critical roles in regulating the cell cycle and which also appear to be important in oncogenesis. These include the newly identified human homologues of the *Drosophila* aurora and *S.cerevisiae* Ipl1 proteins. The three human homologues of these genes Aurora-A, Aurora-B and Aurora-C (also known as aurora2, aurora1 and aurora3 respectively) encode cell cycle regulated serine-threonine protein kinases (summarised in Adams *et al.*, 2001, Trends in Cell Biology. 11(2): 49-54). They show a peak of expression and kinase activity through G2 and mitosis. Several observations implicate the involvement of human aurora proteins in cancer. This evidence is strong for Aurora-A. The Aurora-A gene maps to chromosome 20q13, a region that is frequently amplified in human tumours including both breast and colon tumours. Aurora-A may be the major target gene of this amplicon, since Aurora-A DNA is amplified and mRNA overexpressed in greater than 50% of primary human colorectal cancers. In these tumours Aurora-A protein levels appear greatly elevated compared to adjacent normal tissue. In addition, transfection of rodent fibroblasts with human Aurora-A leads to transformation, conferring the ability to grow in soft agar and form tumours in nude mice (Bischoff et al., 1998, The EMBO Journal. 17(11): 3052-3065). Other work (Zhou et al., 1998, Nature Genetics. 20(2): 189-93) has shown that artificial overexpression of Aurora-A leads to an increase in centrosome number and an increase in aneuploidy, a known event in the development of cancer. Further work has shown an increase in expression of Aurora-B (Adams *et al.*, 2001, Chromsoma. 110(2):65-74) and Aurora-C (Kimura *et al.*, 1999, Journal of Biological Chemistry, 274(11): 7334-40) in tumour cells when compared to normal cells.

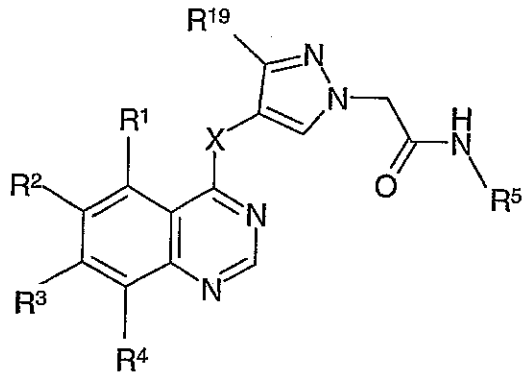
Importantly, it has also been demonstrated that abrogation of Aurora-A expression and function by antisense oligonucleotide treatment of human tumour cell lines (WO97/22702 and WO99/37788) leads to cell cycle arrest and exerts an antiproliferative effect in these tumour cell lines. Additionally, small molecule inhibitors of Aurora-A and Aurora-B have been demonstrated to have an antiproliferative effect in human tumour cells (Keen *et al.* 2001, Poster #2455, American Association of Cancer research annual meeting), as has selective abrogation of Aurora-B expression alone by siRNA treatment (Ditchfield et al., 2003, Journal of Cell Biology, 161(2): 267-280). This indicates that inhibition of the function of Aurora-A and/or Aurora-B will have an antiproliferative effect that may be useful in the treatment of human tumours and other hyperproliferative diseases. Inhibition of Aurora kinases as a therapeutic approach to these diseases may have significant advantages over targeting signalling pathways upstream of the cell cycle (e.g. those activated by growth factor receptor

tyrosine kinases such as epidermal growth factor receptor (EGFR) or other receptors). Since the cell cycle is ultimately downstream of all of these diverse signalling events, cell cycle directed therapies such as inhibition of Aurora kinases would be predicted to be active across all proliferating tumour cells, whilst approaches directed at specific signalling molecules (e.g. EGFR) would be predicted to be active only in the subset of tumour cells which express those receptors. It is also believed that significant "cross talk" exists between these signalling pathways meaning that inhibition of one component may be compensated for by another.

A number of quinazoline derivatives have been proposed hitherto for use in the inhibition of Aurora kinases. For example, WO01/21594, WO01/21595 and WO01/215968 describe the use of certain phenyl-quinazoline compounds as Aurora-A kinase inhibitors, which may be useful in the treatment of proliferative diseases and WO01/21597 discloses other quinazoline derivatives as inhibitors of Aurora-A kinase. Additionally, WO02/00649 discloses quinazoline derivative bearing a 5-membered heteroaromatic ring where the ring is, in particular, substituted thiazole or substituted thiophene. However despite the compounds of WO02/00649 there still exists a need for further compounds having Aurora kinase inhibitory properties. In addition inhibitors are required which have physical and pharmacological properties suitable for use in the treatment of disease.

The applicants have been successful in finding a novel series of compounds which inhibit the effects of the Aurora kinases and in particular Aurora-A kinase and/or Aurora-B kinase which are thus of use in the treatment of proliferative diseases such as cancer. The cancer may occur as either solid or haematological tumours, and in particular includes colorectal, breast, lung, prostate, bladder, renal or pancreatic cancer or leukaemia or lymphoma. In addition certain aspects of the invention provide compounds that have favourable solubility properties that make them useful in the formulation of medicaments for the treatment of disease.

According to one aspect of the invention there is provided a compound of formula (I)



formula (I)

or a salt, ester or prodrug thereof;

where:

X is O or NR^6;

$\mathbf{R^6}$ is hydrogen or C_{1-4}alkyl;

$\mathbf{R^1}$ is hydrogen, halo, or $-X^1R^{11}$;

$\mathbf{X^1}$ is a direct bond, $-CH_2=CH_2-$, -O-, -NH-, $-N(C_{1-6}alkyl)-$, -C(O)-, -C(O)O-, -OC(O)-, -NHC(O)-, $-N(C_{1-6}alkyl)C(O)-$, -C(O)NH- or $-C(O)N(C_{1-6}alkyl)-$;

$\mathbf{R^{11}}$ is hydrogen, or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, heterocyclyl, heterocyclylC_{1-4}alkyl, heterocyclylC_{2-4}alkenyl and heterocyclylC_{2-4}alkynyl which group is optionally substituted by 1 or 2 substituents independently selected from halo, hydroxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, $-NR^9R^{10}$, $-C(O)R^9$, $-C(O)NR^9R^{10}$ and $-C(O)OR^9$;

$\mathbf{R^2}$ is hydrogen, halo, nitro, cyano or $-X^2R^{12}$;

$\mathbf{X^2}$ is a direct bond, -O-, -NH-, $-N(C_{1-6}alkyl)-$, -OC(O)- or -C(O)O-;

$\mathbf{R^{12}}$ is hydrogen, or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, aryl, arylC_{1-4}alkyl, arylC_{2-4}alkenyl, arylC_{2-4}alkynyl, heterocyclyl, heterocyclylC_{1-4}alkyl, heterocyclylC_{2-4}alkenyl and heterocyclylC_{2-4}alkynyl, which group is optionally substituted by 1, 2 or 3 substituents selected from halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, $-NR^{15}R^{16}$, $-NHC(O)NR^{15}R^{16}$, $-C(O)R^{15}$ and $-C(O)OR^{15}$;

$\mathbf{R^3}$ is hydrogen, halo or $-X^3R^{13}$;

$\mathbf{X^3}$ is a direct bond, $-CH_2=CH_2-$, -O-, -NH-, $-N(C_{1-6}alkyl)-$, -C(O)-, -C(O)O-, -OC(O)-, -NHC(O)-, $-N(C_{1-6}alkyl)C(O)-$, -C(O)NH- or $-C(O)N(C_{1-6}alkyl)-$;

$\mathbf{R^{13}}$ is hydrogen or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, aryl, arylC_{1-4}alkyl, arylC_{2-4}alkenyl, arylC_{2-4}alkynyl, heterocyclyl,

heterocyclylC_{1-4}alkyl, heterocyclylC_{2-4}alkenyl and heterocyclylC_{2-4}alkynyl which group is optionally substituted by 1 or 2 substituents independently selected from $-NR^7R^8$, $-C(O)NR^7R^8$, halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, hydroxyC_{1-4}alkylcarbonyl, C_{1-4}alkylcarbonyl, aminoC_{1-4}alkylcarbonyl, C_{1-4}alkylaminoC_{1-4}alkylcarbonyl and bis(C_{1-4}alkyl)aminoC_{1-4}alkylcarbonyl;

$\mathbf{R^7}$ and $\mathbf{R^8}$ are independently selected from hydrogen, heterocyclyl, heterocyclylC_{1-4}alkyl, C_{1-4}alkylheterocyclylC_{1-4}alkyl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-4}alkoxyC_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-4}alkyl, hydroxyC_{3-6}cycloalkyl, hydroxyC_{1-4}alkylC_{3-6}cycloalkyl, hydroxyC_{1-4}alkylC_{3-6}cycloalkylC_{1-4}alkyl, hydroxyC_{3-6}cycloalkylC_{1-4}alkyl, C_{1-4}alkoxyC_{3-6}cycloalkyl, C_{1-4}alkoxyC_{3-6}cycloalkylC_{1-4}alkyl, haloC_{1-6}alkyl, haloC_{3-6}cycloalkyl, haloC_{3-6}cycloalkylC_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, cyanoC_{1-4}alkyl, aminoC_{1-6}alkyl, C_{1-4}alkylaminoC_{1-6}alkyl, bis(C_{1-4}alkyl)aminoC_{1-6}alkyl, hydroxyC_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkylcarbonyl, C_{1-4}alkylcarbonyl, aminoC_{1-4}alkylcarbonyl, C_{1-4}alkylaminoC_{1-4}alkylcarbonyl and bis(C_{1-4}alkyl)aminoC_{1-4}alkylcarbonyl;

or $\mathbf{R^7}$ and $\mathbf{R^8}$ together with the nitrogen to which they are attached form a heterocyclic ring which ring is monocyclic or bicyclic and comprises 4 to 7 ring atoms of which one is nitrogen and of which another is optionally selected from N, NH, O, S, SO and SO_2, and which ring is optionally substituted on carbon or nitrogen by 1 or 2 substituents independently selected from C_{1-4}alkyl, hydroxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkoxy, hydroxyC_{1-4}alkylcarbonyl, C_{1-4}alkylcarbonyl, aminoC_{1-4}alkylcarbonyl, C_{1-4}alkylaminoC_{1-4}alkylcarbonyl and bis(C_{1-4}alkyl)aminoC_{1-4}alkylcarbonyl, and where a ring $-CH_2-$ is optionally replaced with $-C(O)-$;

$\mathbf{R^4}$ is selected from hydrogen, halo or $-X^4R^{14}$;

$\mathbf{X^4}$ is a direct bond, -O-, -NH- or $-N(C_{1-6}alkyl)-$;

$\mathbf{R^{14}}$ is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl;

$\mathbf{R^5}$ is aryl or heteroaryl optionally substituted by 1, 2 or 3 substituents independently selected from halo, hydroxy, cyano, nitro, amino, C_{1-4}alkylamino, bis(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, $-C(O)NHR^{17}$, $-NHC(O)R^{18}$ $-SR^{17}$, $-S(O)R^{17}$ and $-S(O)OR^{17}$;

$\mathbf{R^9}$, $\mathbf{R^{10}}$, $\mathbf{R^{15}}$ and $\mathbf{R^{16}}$ are independently selected from hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl,

C_{3-6}cycloalkylC_{1-4}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-4}alkylaminoC_{1-6}alkyl and bis(C_{1-4}alkyl)aminoC_{1-6}alkyl;

or $\mathbf{R^9}$ and $\mathbf{R^{10}}$ together with the nitrogen to which they are attached form a heterocyclic ring which ring is monocyclic or bicyclic and comprises 4 to 7 ring atoms of which one is nitrogen and of which another is optionally selected from N, NH, O, S, SO and SO_2, and which ring is optionally substituted on carbon or nitrogen by 1 or 2 substituents independently selected from C_{1-4}alkyl, hydroxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkoxy, hydroxyC_{1-4}alkylcarbonyl, C_{1-4}alkylcarbonyl, aminoC_{1-4}alkylcarbonyl, C_{1-4}alkylaminoC_{1-4}alkylcarbonyl and bis(C_{1-4}alkyl)aminoC_{1-4}alkylcarbonyl, and where a ring $-CH_2-$ is optionally replaced with $-C(O)-$;

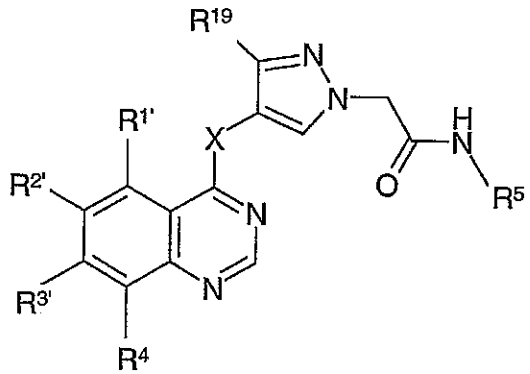
$\mathbf{R^{17}}$ and $\mathbf{R^{18}}$ are independently selected from hydrogen, C_{1-4}alkyl, C_{3-6}cycloalkyl, C_{2-4}alkenyl and C_{2-4}alkynyl;

$\mathbf{R^{19}}$ is hydrogen, hydroxyC_{1-4}alkyl, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-C(O)NR^{20}R^{21}$, $-NHC(O)R^{20}$ or $-NHC(O)OR^{20}$;

$\mathbf{R^{20}}$ are $\mathbf{R^{21}}$ are independently selected from hydrogen, C_{1-4}alkyl and aryl.

As a further aspect a compound of formula (I) or a pharmaceutically acceptable salt thereof is provided.

In a further aspect the invention provides a compound of formula (IA)



formula (IA)

or salt or ester thereof

where X, X^1, X^2, X^3, R^4, R^5 and R^{19} are as defined in relation to formula (I) and

$\mathbf{R^{1'}}$ is hydrogen, halo, or $-X^1R^{11'}$;

$\mathbf{R^{11'}}$ is hydrogen, phosphonooxy or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, heterocyclyl, heterocyclylC_{1-4}alkyl, heterocyclylC_{2-4}alkenyl

and heterocyclylC_{2-4}alkynyl which group is optionally substituted by a substituent selected from halo, hydroxy, phosphonooxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkyl, $-NR^{9'}R^{10'}$, $-C(O)R^{9'}$, $-C(O)NR^{9'}R^{10'}$ and $-C(O)OR^{9'}$;

$\mathbf{R^{2'}}$ is hydrogen, halo, nitro, cyano or $-X^2R^{12'}$;

$\mathbf{R^{12'}}$ is hydrogen, phosphonooxy or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, aryl, arylC_{1-4}alkyl, arylC_{2-4}alkenyl, arylC_{2-4}alkynyl, heterocyclyl, heterocyclylC_{1-4}alkyl, heterocyclylC_{2-4}alkenyl and heterocyclylC_{2-4}alkynyl, which group is optionally substituted by 1, 2 or 3 substituents selected from halo, hydroxy, phosphonooxy, C_{1-4}alkyl, C_{1-4}alkoxy, $-NR^{15}R^{16}$, $-NHC(O)NR^{15}R^{16}$, $-C(O)R^{15}$ and $-C(O)OR^{15}$;

$\mathbf{R^{3'}}$ is hydrogen, halo or $-X^3R^{13'}$;

$\mathbf{R^{13'}}$ is hydrogen, phosphonooxy or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, aryl, arylC_{1-4}alkyl, arylC_{2-4}alkenyl, arylC_{2-4}alkynyl, heterocyclyl, heterocyclylC_{1-4}alkyl, heterocyclylC_{2-4}alkenyl and heterocyclylC_{2-4}alkynyl which group is optionally substituted by 1 or 2 substituents independently selected from $-NR^{7'}R^{8'}$, $-C(O)NR^{7'}R^{8'}$, halo, hydroxy, phosphonooxy, C_{1-4}alkyl, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, phosponooxyC_{1-4}alkyl, hydroxyC_{1-4}alkylcarbonyl, phosphonooxyC_{1-4}alkylcarbonyl, C_{1-4}alkylcarbonyl, aminoC_{1-4}alkylcarbonyl, C_{1-4}alkylaminoC_{1-4}alkylcarbonyl and bis(C_{1-4}alkyl)aminoC_{1-4}alkylcarbonyl;

$\mathbf{R^{7'}}$ and $\mathbf{R^{8'}}$ are independently selected from hydrogen, heterocyclyl, heterocyclylC_{1-4}alkyl, C_{1-4}alkylheterocyclylC_{1-4}alkyl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, phosphonooxyC_{1-6}alkyl, C_{1-4}alkoxyC_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-4}alkyl, hydroxyC_{3-6}cycloalkyl, phosphonooxyC_{3-6}cycloalkyl, hydroxyC_{1-4}alkylC_{3-6}cycloalkyl, phosphonooxyC_{1-4}alkylC_{3-6}cycloalkyl, hydroxyC_{3-6}cycloalkylC_{1-4}alkyl, phosphonooxyC_{3-6}cycloalkylC_{1-4}alkyl, hydroxyC_{1-4}alkylC_{3-6}cycloalkylC_{1-4}alkyl, phosphonooxyC_{1-4}alkylC_{3-6}cycloalkylC_{1-4}alkyl, C_{1-4}alkoxyC_{3-6}cycloalkyl, C_{1-4}alkoxyC_{3-6}cycloalkylC_{1-4}alkyl, haloC_{1-6}alkyl, haloC_{3-6}cycloalkyl, haloC_{3-6}cycloalkylC_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, cyanoC_{1-4}alkyl, aminoC_{1-6}alkyl, C_{1-4}alkylaminoC_{1-6}alkyl, bis(C_{1-4}alkyl)aminoC_{1-6}alkyl, hydroxyC_{1-4}alkoxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkylcarbonyl, phosphonooxyC_{1-4}alkylcarbonyl, C_{1-4}alkylcarbonyl, aminoC_{1-4}alkylcarbonyl, C_{1-4}alkylaminoC_{1-4}alkylcarbonyl and bis(C_{1-4}alkyl)aminoC_{1-4}alkylcarbonyl;

or $R^{7'}$ and $R^{8'}$ together with the nitrogen to which they are attached form a heterocyclic ring which ring is monocyclic or bicyclic and comprises 4 to 7 ring atoms of which one is nitrogen and of which another is optionally selected from N, NH, O, S, SO and SO_2, and which ring is optionally substituted on carbon or nitrogen by 1 or 2 substituents independently selected from C_{1-4}alkyl, hydroxy, phosphonooxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkoxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkoxy, hydroxyC_{1-4}alkylcarbonyl, phosphonooxyC_{1-4}alkylcarbonyl, C_{1-4}alkylcarbonyl, aminoC_{1-4}alkylcarbonyl, C_{1-4}alkylaminoC_{1-4}alkylcarbonyl and bis(C_{1-4}alkyl)aminoC_{1-4}alkylcarbonyl, and where a ring $-CH_2-$ is optionally replaced with $-C(O)-$;

$R^{9'}$, $R^{10'}$, $R^{15'}$ and $R^{16'}$ are independently selected from hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-3}alkyl, hydroxyC_{1-6}alkyl, phosphonooxyC_{1-6}alkyl, haloC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl and bis(C_{1-6}alkyl)aminoC_{1-6}alkyl;

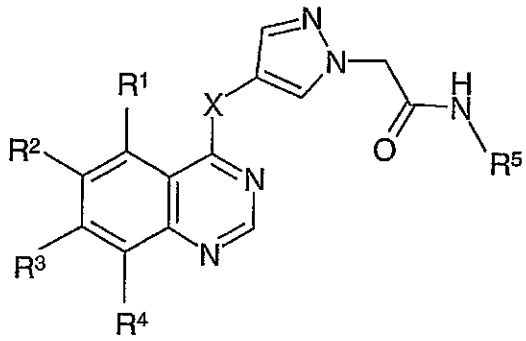
or $R^{9'}$ and $R^{10'}$ together with the nitrogen to which they are attached form a heterocyclic ring which ring is monocyclic or bicyclic and comprises 4 to 7 ring atoms of which one is nitrogen and of which another is optionally selected from N, NH, O, S, SO and SO_2, and which ring is optionally substituted on carbon or nitrogen by 1 or 2 substituents independently selected from C_{1-4}alkyl, hydroxy, phosphonooxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkoxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkoxy, hydroxyC_{1-4}alkylcarbonyl, phosphonooxyC_{1-4}alkylcarbonyl, C_{1-4}alkylcarbonyl, aminoC_{1-4}alkylcarbonyl, C_{1-4}alkylaminoC_{1-4}alkylcarbonyl and bis(C_{1-4}alkyl)aminoC_{1-4}alkylcarbonyl, and where a ring $-CH_2-$ is optionally replaced with $-C(O)-$;

provided that a compound of formula (IA) contains at least one phosphonooxy group.

In a preferred embodiment a compound of formula (IA) contains only one phosphonooxy group.

In further aspects of the invention there is also provided a compound of formula (I) or a salt ester or prodrug thereof or a compound of formula (IA) or a salt, ester or prodrug thereof as described below.

A compound of formula (I) comprises



formula (I)

or a salt, ester or prodrug thereof;

where:

X is O or NR^6;

$\mathbf{R^6}$ is hydrogen or C_{1-4}alkyl;

$\mathbf{R^1}$ is hydrogen, halo, or $-X^1R^{11}$;

$\mathbf{X^1}$ is a direct bond, -O-, -NH- or $-N(C_{1-6}alkyl)-$;

$\mathbf{R^{11}}$ is hydrogen, heterocyclyl or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkenyl where the group is optionally substituted by heterocyclyl, halo, hydroxy, C_{1-4}alkoxy or $-NR^9R^{10}$;

$\mathbf{R^2}$ is hydrogen, halo, nitro, cyano or $-X^2R^{12}$;

$\mathbf{X^2}$ is a direct bond, -O-, -NH- or $-N(C_{1-6}alkyl)-$;

$\mathbf{R^{12}}$ is hydrogen, heterocyclyl or a group selected from aryl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkenyl where the group is optionally substituted by aryl, heterocyclyl, halo, hydroxy or $-NR^{15}R^{16}$;

$\mathbf{R^3}$ is hydrogen, halo or $-X^3R^{13}$;

$\mathbf{X^3}$ is a direct bond, $-CH_2=CH_2-$, -O-, -NH- or $-N(C_{1-6}alkyl)-$;

$\mathbf{R^{13}}$ is hydrogen, heterocyclyl or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkenyl where the group is optionally substituted by $-NR^7R^8$, heterocyclyl, halo, hydroxy or C_{1-4}alkoxy;

$\mathbf{R^7}$ and $\mathbf{R^8}$ are independently selected from hydrogen, heterocyclyl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-3}alkoxyC_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-3}alkyl, hydroxyC_{3-6}cycloalkyl, hydroxyC_{1-4}alkylC_{3-6}cycloalkyl, hydroxyC_{3-6}cycloalkylC_{1-3}alkyl, C_{1-3}alkoxyC_{3-6}cycloalkyl, C_{1-3}alkoxyC_{3-6}cycloalkylC_{1-3}alkyl, haloC_{1-6}alkyl, haloC_{3-6}cycloalkyl, haloC_{3-6}cycloalkylC_{1-3}alkyl,

C_{2-6}alkenyl, C_{2-6}alkynyl, cyanoC_{1-4}alkyl, aminoC_{1-6}alkyl, C_{1-3}alkylaminoC_{1-6}alkyl and di(C_{1-3}alkyl)aminoC_{1-6}alkyl;

or $\mathbf{R^7}$ and $\mathbf{R^8}$ together with the nitrogen to which they are attached form a heterocyclic ring which ring comprises 4 to 7 ring atoms of which one is nitrogen and of which another is optionally selected from N, NH, O, S, SO and SO_2, and which ring is optionally substituted on carbon or nitrogen by 1 or 2 groups independently selected from C_{1-4}alkyl, hydroxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, hydroxyC_{1-4}alkoxyC_{1-4}alkyl and C_{1-4}alkoxyC_{1-4}alkoxy, and where a ring $-CH_2-$ is optionally replaced with –C(O)-;

$\mathbf{R^4}$ is selected from hydrogen, halo or $-X^4R^{14}$;

$\mathbf{X^4}$ is a direct bond, -O-, -NH- or $-N(C_{1-6}alkyl)-$;

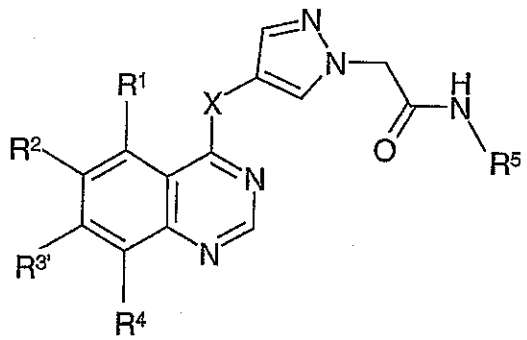
$\mathbf{R^{14}}$ is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl;

$\mathbf{R^5}$ is aryl or heteroaryl optionally substituted by 1, 2 or 3 substituents independently selected from halo, hydroxy, cyano, nitro, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, $C(O)NHR^{17}$, $NHC(O)R^{18}$ and $S(O)_pR^{19}$ where p is 0, 1 or 2;

$\mathbf{R^9}$, $\mathbf{R^{10}}$, $\mathbf{R^{15}}$ and $\mathbf{R^{16}}$ are independently selected from hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-3}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl and di(C_{1-6}alkyl)aminoC_{1-6}alkyl;

$\mathbf{R^{17}}$, $\mathbf{R^{18}}$ and $\mathbf{R^{19}}$ are independently selected from hydrogen, C_{1-4}alkyl, C_{3-6}cycloalkyl, C_{2-4}alkenyl and C_{2-4}alkynyl.

A compound of formula (IA) comprises:



formula (IA)

where X, R^1, R^2, R^4 and R^5 are as defined in relation to formula (I) and

$R^{3'}$ is hydrogen, halo or $-X^{3'}R^{13'}$;

$\mathbf{X^{3'}}$ is a direct bond, $-CH_2=CH_2-$, -O-, -NH- or $-N(C_{1-6}alkyl)-$;

$\mathbf{R^{13'}}$ is a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkenyl where the group is substituted by $-NR^{7'}R^{8'}$;

$R^{7'}$ and $R^{8'}$ are independently selected from hydrogen, heterocyclyl, C_{1-6}alkyl, phosphonooxyC_{1-6}alkyl, C_{1-3}alkoxyC_{1-6}alkyl, phosphonooxyC_{1-4}alkoxyC_{1-4}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-3}alkyl, phosphonooxyC_{3-6}cycloalkyl, phosphonooxyC_{1-4}alkylC_{3-6}cycloalkyl, phosphonooxyC_{3-6}cycloalkylC_{1-3}alkyl, C_{1-3}alkoxyC_{3-6}cycloalkyl, C_{1-3}alkoxyC_{3-6}cycloalkylC_{1-3}alkyl, haloC_{1-6}alkyl, haloC_{3-6}cycloalkyl, haloC_{3-6}cycloalkylC_{1-3}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, cyanoC_{1-4}alkyl, aminoC_{1-6}alkyl, C_{1-3}alkylaminoC_{1-6}alkyl and di(C_{1-3}alkyl)aminoC_{1-6}alkyl; provided that at least one of $R^{7'}$ and $R^{8'}$ contains a phosphonooxy substituent;

or $R^{7'}$ and $R^{8'}$ together with the nitrogen to which they are attached form a heterocyclic ring which ring comprises 4 to 7 ring atoms of which one is nitrogen and of which another is optionally selected from N, NH, O, S, SO and SO_2, and which ring is substituted on carbon or nitrogen by 1 or 2 groups independently selected from phosphonooxy, phoshonooxyC_{1-4}alkyl and phosphonooxyC_{1-4}alkoxyC_{1-4}alkyl, and where a ring -CH_2- is optionally replaced with a –C(O)-.

In this specification the term alkyl when used either alone or as a suffix or prefix includes straight-chain and branched-chain saturated structures comprising carbon and hydrogen atoms. References to individual alkyl groups such as propyl are specific for the straight-chain version only and references to individual branched-chain alkyl groups such as *tert*-butyl are specific for the branched chain version only. An analogous convention applies to other generic terms such as alkenyl and alkynyl.

Cycloalkyl is a monocyclic alkyl group, and cycloalkenyl and cycloalkynyl are monocyclic alkenyl and alkynyl groups respectively.

The prefix C_{m-n} in C_{m-n}alkyl and other terms (where m and n are integers) indicates the range of carbon atoms that are present in the group, for example C_{1-3}alkyl includes C_1alkyl (methyl), C_2alkyl (ethyl) and C_3alkyl (propyl or isopropyl).

The terms C_{m-n}alkoxy comprise –O-C_{m-n}alkyl groups.

The term halo includes fluoro, chloro, bromo and iodo.

Aryl groups are aromatic carbocyclic rings which may be monocyclic or bicyclic.

Unless otherwise stated heteroaryl groups are monocyclic or bicyclic aromatic rings containing 5 to 10 ring atoms of which 1, 2, 3 or 4 ring atoms are chosen from nitrogen, sulphur or oxygen where a ring nitrogen or sulphur may be oxidised.

Heterocyclyl is a saturated, unsaturated or partially saturated, monocyclic or bicyclic ring containing 4 to 7 ring atoms of which 1, 2 or 3 ring atoms are selected from nitrogen,

sulphur or oxygen, which ring may be carbon or nitrogen linked, wherein a ring -CH_2- group is optionally replaced by a -C(O) group; wherein a ring nitrogen or sulphur atom is optionally oxidised to form the N-oxide or S-oxide(s); wherein a ring –NH- is optionally substituted by acetyl, formyl, methyl or mesyl; and which ring is optionally substituted by 1 or 2 groups selected from C_{1-4}alkyl, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, hydroxy and haloC_{1-4}alkyl. In one aspect of the invention when used within the definition of R^1, R^2 or R^3 heterocyclyl is a saturated monocyclic ring containing 4 to 7 ring atoms of which 1 ring atom is nitrogen and another ring atom is optionally nitrogen or oxygen which ring is optionally substituted by C_{1-4}alkyl, hydroxyC_{1-4}alkyl and hydroxy.

Phosphonooxy is in one aspect a group of formula $-OP(O)(OH)_2$. However the term phosphonooxy also includes salts such as those formed with alkali metal ions such as sodium or potassium ions or alkaline earth metal ions, for example calcium or magnesium ions.

This specification also makes use of several composite terms to describe groups comprising more than one functionality. Such terms are to be interpreted as is understood in the art. For example C_{m-n}cycloalkylC_{m-n}alkyl comprises C_{m-n}alkyl substituted by C_{m-n}cycloalkyl, and heterocyclylC_{m-n}alkyl comprises C_{m-n}alkyl substituted by heterocyclyl.

HaloC_{m-n}alkyl is a C_{m-n}alkyl group that is substituted by 1, 2 or 3 halo substituents. Similarly, haloC_{m-n}cycloalkyl and haloC_{m-n}cycloalkylC_{m-n}alkyl groups may contain 1, 2 or 3 halo substituents.

HydroxyC_{m-n}alkyl is a C_{m-n}alkyl group that is substituted by 1, 2 or 3 hydroxy substituents. Similarly, hydroxyC_{m-n}cycloalkyl and hydroxyC_{m-n}cycloalkylC_{m-n}alkyl groups may contain 1, 2 or 3 hydroxy substituents.

C_{m-n}alkoxyC_{m-n}alkyl is a C_{m-n}alkyl group that is substituted by 1, 2 or 3 C_{m-n}alkoxy substituents. Similarly, C_{m-n}alkoxyC_{m-n}cycloalkyl and C_{m-n}alkoxyC_{m-n}cycloalkylC_{m-n}alkyl groups may contain 1, 2 or 3 C_{m-n}alkoxy substituents.

Where optional substituents are chosen from 1 or 2 or from 1, 2, or 3 groups or substituents it is to be understood that this definition includes all substituents being chosen from one of the specified groups i.e. all substituents being the same or the substituents being chosen from two or more of the specified groups i.e. the substituents not being the same.

Unless specifically stated the bonding atom of a group may be any atom of that group so for example propyl includes prop-1-yl and prop-2-yl.

Compounds of the present invention have been named with the aid of computer software (ACD/Name version 6.6 or ACD Name Batch version 6.0).

Suitable values for any R group or any part or substituent for such groups include examples selected from:

for C_{1-4}alkyl: methyl, ethyl, propyl, isopropyl, butyl, isobutyl and tert-butyl;

for C_{1-6}alkyl: C_{1-4}alkyl, pentyl, neopentyl, 1,3-dimethylbutyl and hexyl;

for C_{2-4}alkenyl: vinyl, allyl and but-2-enyl;

for C_{2-6}alkenyl: C_{2-4}alkenyl, 3-methylbut-2-enyl and 3-methylpent-2-enyl;

for C_{2-4}alkynyl: ethynyl, propargyl and prop-1-ynyl;

for C_{2-6}alkynyl: C_{2-4}alkynyl, pent-4-ynyl and 2-methylpent-4-ynyl;

for C_{3-6}cycloalkyl: cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl;

for C_{3-6}cycloalkenyl: cyclobutenyl, cyclopentenyl, cyclohexenyl and cyclohex-1,4-dienyl;

for C_{3-6}cycloalkylC_{1-4}alkyl: cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclopropylethyl and cyclobutylethyl;

for C_{1-4}alkoxy: methoxy, ethoxy, propoxy, isopropoxy, butoxy and *tert*-butoxy;

for C_{1-4}alkoxyC_{1-4}alkyl: methoxymethyl, 2-methoxyethyl, 3-methoxypropyl and 2-ethoxyethyl;

for C_{1-4}alkoxyC_{1-6}alkyl: C_{1-4}alkoxyC_{1-4}alkyl, 4-methoxybutyl and 2-ethoxybutyl;

for C_{1-4}alkoxyC_{3-6}cycloalkyl: methoxycyclobutyl, methoxycyclopentyl and ethoxycyclopentyl;

for C_{1-4}alkoxyC_{3-6}cycloalkylC_{1-4}alkyl: methoxycyclobutylmethyl and methoxycyclopentylmethyl;

for C_{1-4}alkoxyC_{1-4}alkoxy: methoxymethoxy, 2-methoxyethoxy and 2-ethoxyethoxy;

for hydroxyC_{1-4}alkyl: hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropoxy, 2-hydroxypropyl, 2-hydroxy-1-methylethyl, 2,3-dihydroxypropyl, 2-hydroxy-1,1-dimethylethyl;

for hydroxyC_{1-6}alkyl: hydroxyC_{1-4}alkyl, 3-hydroxypentyl, 3-hydroxy-2,2-dimethylpropyl, 3-hydroxy-1,1-dimethylpropyl, 1-hydroxymethyl-2-methylpropyl and 6-hydroxyhexyl;

for hydroxyC_{3-6}cycloalkyl: 2-hydroxycyclopropyl, 2-hydroxycyclobutyl, 2-hydroxycyclopentyl and 4-hydroxycyclohexyl;

for hydroxyC_{3-6}cycloalkylC_{1-4}alkyl: 2-hydroxycyclopropylmethyl and 2-hydroxycyclobutylmethyl;

for hydroxyC_{1-4}alkylC_{3-6}cycloalkyl: 1-(hydroxymethyl)cyclopentyl and 2-(hydroxymethyl)cyclohexyl;

for hydroxyC_{1-4}alkylC_{3-6}cycloalkylC_{1-4}alkyl: 1-(hydroxymethyl)cyclopropylmethyl;

for hydroxyC_{1-4}alkoxyC_{1-4}alkyl: 2-(2-hydroxyethoxy)ethyl;

for C_{1-4}alkylcarbonyl: acetyl, ethylcarbonyl and isopropylcarbonyl;

for C_{1-4}alkoxycarbonyl; methoxycarbonyl, ethoxycarbonyl and tert-butoxycarbonyl;

for C_{1-4}alkoxyC_{1-4}alkylcarbonyl: methoxymethylcarbonyl and tert-butylmethylcarbonyl;

for hydroxyC_{1-4}alkylcarbonyl: glycoloyl (hydroxymethylcarbonyl);

for haloC_{1-6}alkyl: chloromethyl, 2-chloroethyl, 3-chloropropyl, trifluoromethyl and 3,3,3-trifluoropropyl;

for haloC_{3-6}cycloalkyl: 2-chlorocyclopropyl and 2-chlorocyclobutyl;

for haloC_{3-6}cycloalkylC_{1-4}alkyl: 2-chlorocyclopropylmethyl and 2-chlorocyclobutylmethyl;

for cyanoC_{1-4}alkyl: cyanomethyl and 2-cyanoethyl;

for aminoC_{1-4}alkyl: aminomethyl, 2-aminoethyl, 2-aminopropyl and 4-aminobutyl;

for aminoC_{1-6}alkyl: aminoC_{1-4}alkyl and 6-aminohexyl;

for C_{1-4}alkylaminoC_{1-4}alkyl: 2-(methylamino)ethyl and 3-(ethylaminopropyl);

for C_{1-4}alkylaminoC_{1-6}alkyl: C_{1-4}alkylaminoC_{1-4}alkyl and 2-(methylamino)hexyl;

for bis(C_{1-4}alkyl)aminoC_{1-4}alkyl: 2-(dimethylamino)ethyl, 2-[methyl(ethyl)amino]ethyl and 2-(diethylamino)ethyl;

for bis(C_{1-4}alkyl)aminoC_{1-6}alkyl: bis(C_{1-4}alkyl)aminoC_{1-4}alkyl and 2-[methyl(ethyl)amino]pentyl;

for C_{1-4}alkylamino: methylamino, ethylamino, propylamino and isopropylamino;

for bis(C_{1-4}alkyl)amino: dimethylamine, methyl(ethyl)amino and diethylamino;

for aminoC_{1-4}alkylcarbonyl: glycyl (aminomethylcarbonyl);

for C_{1-4}alkylaminoC_{1-4}alkylcarbonyl: N-methylglycyl;

for bis(C_{1-4}alkyl)aminoC_{1-4}alkylcarbonyl: N,N-dimethylglycyl;

for C_{1-4}alkanoylamino: acetylamino

for aryl: phenyl and naphthyl;

for arylC_{1-4}alkyl: benzyl, 2-phenylethyl;

for arylC_{2-4}alkenyl: 3-phenylallyl;

for arylC_{2-4}alkynyl: 3-phenylprop-2-ynyl;

for heteroaryl: furyl, thienyl, pyrrolyl, pyrazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinazolinyl and quinolinyl

for heterocyclyl: azetidinyl, pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, azepanyl, diazepanyl, pyridyl, imidazolyl, tetrahydrofuranyl, tetrahydropyranyl, furanyl, pyranyl, tetrahydrothienyl, thienyl, isoxazolyl, tetrahydro-2H-pyranyl, morpholinyl, 2-oxopyrrolidinyl, 3-oxopiperazinyl and 4-oxopiperdinyl;

for heterocyclylC_{1-4}alkyl: pyrrolidinylmethyl, 2-pyrrolidinylethyl, 2-morpholinylethyl, 3-morpholinylpropyl, tetrahydrofuranylmethyl, 2-(2-oxopyrrolidinyl)ethyl and 3-(3-oxopiperazinyl)propyl;

for heterocyclylC_{2-4}alkenyl: 3-pyrrolidinylallyl;

for heterocyclylC_{2-4}alkynyl: 3-pyrrolidinylprop-2-ynyl;

for C_{1-4}alkylheterocyclylC_{1-4}alkyl: 5-methylisoxazol-3-ylmethyl;

for phosphonooxyC_{1-4}alkyl: phosphonooxymethyl, 2-phosphonooxyethyl and 3-phosphonooxypropyl, 2-phosphonooxypropyl, 2-phosphonooxy-1-methylethyl, 2-hydroxy-3-hydroxypropyl, 2-phosphonooxy-3-hydroxypropyl and 2-phosphonooxy-1,1-dimethylethyl;

for phosphonooxyC_{1-6}alkyl: phosphonooxyC_{1-4}alkyl and 3-phosphonooxy-1,1-dimethylpropyl, 3-phosphonooxy, 3-phosphonooxy-2,2-dimethylpropyl, 1-phosphonooxymethyl-2-methylpropyl and 6-phosphonooxyhexyl;

for phosphonooxyC_{3-6}cycloalkyl: 2-phosphonooxycyclopropyl, 2-phosphonooxycyclobutyl, 2-phosphonooxycyclopentyl and 4-phosphonooxycyclohexyl;

for phosphonooxyC_{3-6}cycloalkylC_{1-4}alkyl: 2-phosphonooxycyclopropylmethyl and 2-phosphonooxycyclobutylmethyl;

for phosphonooxyC_{1-4}alkylC_{3-6}cycloalkyl: 1-(phosphonooxymethyl)cyclopentyl and 2-(hydroxymethyl)cyclohexyl;

for phosphonooxyC_{1-4}alkoxyC_{1-4}alkyl: 2-(2-phosphonooxyethoxy)ethyl;

for phosphonooxyC_{1-4}alkylcarbonyl: phosphonooxymethylcarbonyl;

Within the present invention, it is to be understood that, insofar as certain of compounds of formula (I) or formula (IA) herein defined may exist in optically active or

racemic forms by virtue of one or more asymmetric carbon or sulphur atoms, the invention includes in its definition any such optically active or racemic form which possesses aurora kinase inhibitory activity and in particular Aurora-A and/or Aurora-B kinase inhibitory activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to herein.

Within the present invention it is to be understood that a compound of formula (I) or formula (IA) or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which has Aurora kinase inhibitory activity and in particular Aurora-A and/or Aurora-B kinase inhibitory activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings.

It is also to be understood that certain compounds of formula (I) or formula (IA) and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which have Aurora kinase inhibitory activity and in particular Aurora-A and/or Aurora-B kinase inhibitory activity.

The present invention relates to the compounds of formula (I) or formula (IA) as herein defined as well as to the salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula (I) or formula (IA) and their pharmaceutically acceptable salts. Pharmaceutically acceptable salts of the invention may, for example, include acid addition salts of compounds of formula (I) or formula (IA) as herein defined which are sufficiently basic to form such salts. Such acid addition salts include but are not limited to furmarate, methanesulphonate, hydrochloride, hydrobromide, citrate and maleate salts and salts formed with phosphoric and sulphuric acid. In addition where compounds of formula (I) or formula (IA) are sufficiently acidic, salts are base salts and examples include but are not limited to, an alkali metal salt for example sodium or potassium, an alkaline earth metal salt for example calcium or magnesium, or organic amine salt for example triethylamine, ethanolamine, diethanolamine, triethanolamine, morpholine, *N*-methylpiperidine, *N*-ethylpiperidine, dibenzylamine or amino acids such as lysine.

The compounds of formula (I) or formula (IA) may also be provided as esters and in particular *in vivo* hydrolysable esters. An *in vivo* hydrolysable ester of a compound of formula (I) or formula (II) containing carboxy or hydroxy group is, for example a pharmaceutically acceptable ester which is cleaved in the human or animal body to produce the parent acid or alcohol. Such esters can be identified by administering, for example, intravenously to a test animal, the compound under test and subsequently examining the test animal's body fluid.

Suitable pharmaceutically acceptable esters for carboxy include C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

Suitable pharmaceutically-acceptable esters for hydroxy include inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α-acyloxyalkyl ethers and related compounds which as a result of the *in-vivo* hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in-vivo* hydrolysable ester forming groups for hydroxy include C_{1-10}alkanoyl, for example formyl, acetyl; benzoyl; phenylacetyl; substituted benzoyl and phenylacetyl, C_{1-10}alkoxycarbonyl (to give alkyl carbonate esters), for example ethoxycarbonyl; di-C_{1-4}alkylcarbamoyl and *N*-(di-C_{1-4}alkylaminoethyl)-*N*-C_{1-4}alkylcarbamoyl (to give carbamates); di-C_{1-4}alkylaminoacetyl and carboxyacetyl. Examples of ring substituents on phenylacetyl and benzoyl include aminomethyl, C_{1-4}alkylaminomethyl and di-(C_{1-4}alkyl)aminomethyl, and morpholino or piperazino linked from a ring nitrogen atom via a methylene linking group to the 3- or 4- position of the benzoyl ring. Other interesting *in vivo* hydrolysable esters include, for example, $R^A C(O)OC_{1-6}$alkyl-CO-, wherein R^A is for example, benzyloxy-C_{1-4}alkyl, or phenyl). Suitable substituents on a phenyl group in such esters include, for example, 4-C_{1-4}piperazino-C_{1-4}alkyl, piperazino-C_{1-4}alkyl and morpholino-C_{1-4}alkyl.

The compounds of the formula (I) may be also be administered in the form of a prodrug which is broken down in the human or animal body to give a compound of the formula (I). Examples of prodrugs include in vivo hydrolysable esters of a compound of the

formula (I). Various forms of prodrugs are known in the art. For examples of such prodrug derivatives, see:

a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985);

b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);

c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

d) H. Bundgaard, et al., Journal of Pharmaceutical Sciences, 77, 285 (1988); and

e) N. Kakeya, et al., Chem Pharm Bull, 32, 692 (1984).

Preferred values of X, R^1, R^2, R^3, R^4, R^5 and R^{19} for a compound of formula (I) are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined herein.

In one aspect of the invention X is NR^6. In another aspect X is NH.

In one aspect of the invention R^6 is hydrogen or methyl. In another aspect R^6 is hydrogen.

In one aspect of the invention R^1 is hydrogen, halo or $-OR^{11}$. In a further aspect R^1 is hydrogen or $-OR^{11}$. In another aspect R^1 is hydrogen, fluoro, hydroxy, methoxy, isopropoxy, pyrrolidin-2-ylmethoxy, 1-(2-hydroxyethyl)pyrrolidin-2-ylmethoxy, 1-glycoloylpyrrolidin-2-ylmethoxy, 1-(N,N-dimethylglycyl)pyrrolidin-2-ylmethoxy, 2-(5-hydroxymethyl-2-oxo-pyrrolidin-1-yl)ethoxy, 3-(5-hydroxymethyl-2-oxo-pyrrolidin-1-yl)propoxy, 2-(6-hydroxymethyl-2-oxo-piperazin-1-yl)ethoxy, 3-(6-hydroxymethyl-2-oxo-piperazin-1-yl)propoxy, 2-(5-hydroxymethyl-3-oxo-piperazin-1-yl)ethoxy or 3-(5-hydroxymethyl-3-oxo-piperazin-1-yl)propoxy. In yet a further aspect R^1 is hydrogen, fluoro, hydroxy, methoxy, isopropoxy, pyrrolidin-2-ylmethoxy, 1-(2-hydroxyethyl)pyrrolidin-2-ylmethoxy, 1-glycoloylpyrrolidin-2-ylmethoxy or 1-(N,N-dimethylglycyl)pyrrolidin-2-ylmethoxy. In another aspect R^1 is hydrogen.

In one aspect of the invention X^1 is a direct bond, -O-, -NH- or $-N(C_{1-4}alkyl)-$. In a further aspect X^1 is a direct bond or -O-. In another aspect X^1 is a direct bond. In yet another aspect X^1 is –O-.

In one aspect of the invention R^{11} is hydrogen or a group selected from C_{1-6}alkyl, heterocyclyl, heterocyclylC_{1-4}alkyl, heterocyclylC_{2-4}alkenyl and heterocyclylC_{2-4}alkynyl which

group is optionally substituted by a substituent selected from hydroxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, amino, C_{1-4}alkylamino, bis(C_{1-4}alkyl)amino, hydroxycarbonyl, C_{1-4}alkoxycarbonyl, hydroxyC_{1-4}alkylcarbonyl, C_{1-4}alkoxyC_{1-4}alkylcarbonyl, aminoC_{1-4}alkylcarbonyl, C_{1-4}alkylaminoC_{1-4}alkylcarbonyl and bis(C_{1-4}alkyl)aminoC_{1-4}alkylcarbonyl. In a further aspect R^{11} is hydrogen or a group selected from C_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-4}alkyl, which group is optionally substituted by a substituent selected from hydroxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, hydroxyC_{1-4}alkylcarbonyl, aminoC_{1-4}alkylcarbonyl, C_{1-4}alkylaminoC_{1-4}alkylcarbonyl and bis(C_{1-4}alkyl)aminoC_{1-4}alkylcarbonyl. In another aspect R^{11} is hydrogen, methyl, ethyl, propyl, isopropyl or a group selected from pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolidinylpropyl, 2-oxopyrrolidin-1-ylmethyl, 2-oxopyrrolidin-1-ylethyl, 2-oxopyrrolidin-1-ylpropyl, 3-oxopyrrolidin-1-ylmethyl, 3-oxopyrrolidin-1-ylethyl, 3-oxopyrrolidin-1-ylpropyl, piperidinylmethyl, piperidinylethyl, piperidinylpropyl, 2-oxopiperidinylmethyl, 2-oxopiperidinylethyl, 2-oxopiperidinylpropyl, 3-oxopiperidinylmethyl, 3-oxopiperidinylethyl, 3-oxopiperidinylpropyl, 4-oxopiperidinylmethyl, 4-oxopiperidinylethyl, 4-oxopiperidinylpropyl, piperazinylmethyl, piperazinylethyl, piperazinylpropyl, 2-oxopiperazinylmethyl, 2-oxopiperazinylethyl, 2-oxopiperazinylpropyl, 3-oxopiperazinylmethyl, 3-oxopiperazinylethyl and 3-oxopiperazinylpropyl, which group is optionally substituted by hydroxy, hydroxymethyl, 2-hydroxyethyl, tert-butoxycarbonyl, glycoloyl, glycyl, N-methylglycyl or N,N-dimethylglycyl. In a further aspect R^{11} is hydrogen, methyl, ethyl, propyl, isopropyl, pyrrolidinylmethyl which pyrrolidinylmethyl is optionally substituted by 2-hydroxyethyl, glycoloyl or N,N-dimethylglycyl or R^{11} is 2-(2-oxopyrrolidin-1-yl)ethyl, 3-(2-oxopyrrolidin-1-yl)propyl, 2-(2-oxopiperazin-1-yl)ethyl, 3-(2-oxopiperazin-1-yl)propyl, 2-(3-oxopiperazin-1-yl)ethyl or 3-(3-oxopiperazin-1-yl)propyl optionally substituted by hydroxymethyl or 2-hydroxyethyl. In yet a further aspect R^{11} is hydrogen, methyl, ethyl, propyl, isopropyl or pyrrolidinylmethyl which pyrrolidinylmethyl is optionally substituted by 2-hydroxyethyl, glycoloyl or N,N-dimethylglycyl. In yet another aspect R^{11} is hydrogen, C_{1-4}alkyl or C_{1-4}alkoxy. In a further aspect R^{11} is hydrogen.

In one aspect of the invention R^2 is hydrogen, halo, $-OR^{12}$ or $-OC(O)R^{12}$. In a further aspect R^2 is hydrogen, fluoro, hydroxy, methoxy, 2-methoxyethoxy, benzoyloxy, 2-morpholin-4-ylethoxy, 3-morpholin-4-ylpropoxy or 1-methylpyrrolidin-2-yloxy. In another aspect R^2 is hydrogen or methoxy. In a further aspect R^2 is hydrogen. In yet a further aspect R^2 is methoxy.

In one aspect of the invention X^2 is a direct bond, -O- or –OC(O)-. In another aspect of the invention X^2 is a direct bond or -O-.

In one aspect of the invention R^{12} is hydrogen or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, aryl, arylC_{1-4}alkyl, heterocyclyl and heterocyclylC_{1-4}alkyl, which group is optionally substituted by 1, 2 or 3 substituents selected from halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, $-NR^{15}R^{16}$, $-NHC(O)NR^{15}R^{16}$, $-C(O)R^{15}$ and $-C(O)OR^{15}$. In a further aspect R^{12} is hydrogen or a group selected from C_{1-4}alkyl, aryl, heterocyclyl and heterocyclylC_{1-4}alkyl which group is optionally substituted by a substituent selected from C_{1-4}alkyl and C_{1-4}alkoxy. In yet another aspect R^{12} is hydrogen or group selected from methyl, 2-morpholinylethyl, 3-morpholinylpropyl, 2-methoxyethyl and pyrrolidinyl which group is optionally substituted by methyl. In another aspect R^{12} is hydrogen or C_{1-4}alkyl. In another aspect of the invention R^{12} is hydrogen. In a further aspect of the invention R^{12} is methyl.

In one aspect of the invention R^3 is hydrogen or $-X^3R^{13}$. In another aspect R^3 is hydrogen, hydroxy, methoxy, 3-chloropropoxy, 2-chloroethoxy, 2,2-dimethoxyethoxy, 3-[2-(hydroxymethyl)pyrrolidin-1-yl]propoxy, 3-[(2-hydroxyethyl)(isobutyl)amino]propoxy, 3-[(2-hydroxyethyl)(propyl)amino]propoxy, 3-piperidin-1-ylpropoxy, 3-pyrrolidin-1-ylpropoxy, 3-(diethylamino)propoxy, 3-piperazin-1-ylpropoxy, 3-[(2-hydroxyethyl)(methyl)amino]propoxy, 3-(cyclopropylamino)propoxy, 3-{[2-(dimethylamino)ethyl](methyl)amino}propoxy, 3-(4-methylpiperazin-1-yl)propoxy, 3-(4-hydroxypiperidin-1-yl)propoxy, 3-[bis(2-hydroxyethyl)amino]propoxy, 3-[ethyl(methyl)amino]propoxy, 3-[ethyl(2-hydroxyethyl)amino]propoxy, 3-{[2-(dimethylamino)ethyl](ethyl)amino}propoxy, 3-[2-(2-hydroxyethyl)piperidin-1-yl]propoxy, 3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy, 3-[(cyclopropylmethyl)amino]propoxy, 3-[4-(2-hydroxyethyl)piperidin-1-yl]propoxy, 3-[methyl(prop-2-yn-1-yl)amino]propoxy, 3-[allyl(methyl)amino]propoxy, 3-[isobutyl(methyl)amino]propoxy, 3-(3-hydroxypiperidin-1-yl)propoxy, 3-[4-(hydroxymethyl)piperidin-1-yl]propoxy, 3-[methyl(propyl)amino]propoxy, 3-[cyclopropylmethyl(propyl)amino]propoxy, 3-{[2-(diethylamino)ethyl](methyl)amino}propoxy, 3-{[2-(diethylamino)ethyl](ethyl)amino}propoxy, 3-(4-methyl-1,4-diazepan-1-yl)propoxy, 3-[(2-hydroxyethyl)(isopropyl)amino]propoxy, 3-[cyclopropyl(2-hydroxyethyl)amino]propoxy, 3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy, 3-[cyclobutyl(2-hydroxyethyl)amino]propoxy, 3-[cyclopropylmethyl(2-hydroxyethyl)amino]propoxy, 3-[cyclobutylmethyl(2-hydroxyethyl)amino]propoxy, 3-[(2-hydroxy)prop-2-yn-1-

lyamino]propoxy, 3-[allyl(2-hydroxyethyl)amino]propoxy, 3-[(2,2-dimethylpropyl(2-hydroxyethyl)amino]propoxy, 3-[(2-hydroxyethyl)(3,3,3-trifluoropropyl)amino]propoxy, 3-azetidin-1-ylpropoxy, 3-(dimethylamino)propoxy, 2-[(2-hydroxymethyl)pyrrolidin-1-yl]ethoxy, 2-{4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl}ethoxy, 2-[2-(2-hydroxyethyl)piperidin-1-yl]ethoxy, 2-[2-(hydroxymethyl)piperidin-1-yl]ethoxy, 2-[(2-hydroxy-1,1-dimethylethyl)amino]ethoxy, 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethoxy, 2-[(4-hydroxycyclohexyl)amino]ethoxy, 2-[3-(hydroxymethyl)piperidin-1-yl]ethoxy, 2-{[1-(hydroxymethyl)cyclopentyl]amino}ethoxy, 2-[4-(3-hydroxypropyl)piperazin-1-yl]ethoxy, 2-[cyclohexyl(2-hydroxyethyl)amino]ethoxy, 2-[(2-hydroxyethyl)(propyl)amino]ethoxy, 2-[(3-hydroxy-2,2-dimethylpropyl)amino]ethoxy, 2-tetrahydro-2*H*-pyran-4-ylamino)ethoxy, 2-[cyclobutyl(2-hydroxyethyl)amino]ethoxy, 2-[(2-hydroxyethyl)(tetrahydro-2*H*-pyran-4-yl)amino]ethoxy, 3-[cyclopentyl(2-hydroxyethyl)amino]propoxy, 3-[(3-hydroxy-1,1-dimethylpropyl)amino]propoxy, 3-[(2-cyanoethyl)(2-hydroxyethyl)amino]propoxy, 3-morpholin-4-ylpropoxy, 3-[(3-hydroxy-2,2-dimethylpropyl)amino]propoxy, 3-[(3-hydroxypropyl)amino]propoxy, 3-[(3-hydroxypropyl)(propyl)amino]propoxy, 3-[(3-hydroxypropyl)(ethyl)amino]propoxy, 3-[4-(2-hydroxyethyl)-3-oxopiperazin-1-yl]propoxy, 3-(propylamino)propoxy, 3-[glycoloyl(propyl)amino]propoxy, 3-(4-glycoloylpiperazin-1-yl)propoxy, 3-{[2-(hydroxymethyl)cyclohexyl]amino}propoxy, 3-[{1α,5α,6α)-6-(hydroxymethyl)-3-azabicyclo[3.1.0]hex-3-yl]propoxy, 3-{[2-hydroxypropyl]amino}propoxy, 3-{[2-hydroxy-1-methylethyl]amino}propoxy, 3-[(2-hydroxy-1,1-dimethylethyl)amino]propoxy, 3-[(2,3-dihydroxypropyl)amino]propoxy, 3-{[2-(2-hydroxyethoxy)ethyl]amino}propoxy, 3-(4-acetylpiperazin-1-yl)propoxy, 3-[(tetrahydrofuran-2-ylmethyl)amino]propoxy, 3-(allylamino)propoxy, 3-{[1-(hydroxymethyl)-2-methylpropyl]amino}propoxy, 3-{[(5-methylisoxazol-3-yl)methyl]amino}propoxy, 3-(tetrahydro-2*H*-pyran-4-ylamino)propoxy, 3-[3-(hydroxymethyl)pyrrolidin-1-yl]propoxy, 3-aminopropoxy, 3-[-4-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy, 2-(cyclopropylamino)ethoxy, 2-(cyclobutylamino)ethoxy, 2-(cyclopentylamino)ethoxy, 2-[{2-hydroxyethyl)(tetrahydro-2*H*-pyran-4-yl)amino]ethoxy, 2-[cyclopentyl(2-hydroxyethyl)amino]ethoxy, 2-[cyclopropyl(2-hydroxyethyl)amino]ethoxy, 2-[cyclopentyl(3-hydroxypropyl)amino]ethoxy, 2-[cyclopentyl(glycoloyl)amino]ethoxy, 2-[3-(hydroxymethyl)-4-methylpiperazin-1-yl]ethoxy, 2-[2-(hydroxymethyl)-4-methylpiperazin-1-yl]ethoxy, 2-[4-(hydroxymethyl)piperidin-1-yl]ethoxy, 2-[4-(2-hydroxyethyl)piperidin-1-yl]ethoxy, 2-[(2-

hydroxyethyl)amino]ethoxy, 2-{[2-(hydroxymethyl)cyclohexyl]amino}ethoxy, 3-[(2-hydroxyethyl)amino]propoxy, 3-[(2-hydroxyethyl)(tetrahydrofuran-3-yl)amino]propoxy, pyrrolidin-2-ylmethoxy, [1-(2-hydroxyethyl)pyrrolidin-2-yl]methoxy, [1-glycoloyopyrrolidin-2-yl]methoxy, pyrrolidin-3-ylmethoxy, [1-(2-hydroxyethyl)pyrrolidin-3-yl]methoxy, (1-glycoloylpyrrolidin-3-yl)methoxy, 3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy, (2-hydroxyethyl)amino]propoxy, 2-(5-hydroxymethyl-2-oxo-pyrrolidin-1-yl)ethoxy, 3-(5-hydroxymethyl-2-oxo-pyrrolidin-1-yl)propoxy, 2-(6-hydroxymethyl-2-oxo-piperazin-1-yl)ethoxy, 3-(6-hydroxymethyl-2-oxo-piperazin-1-yl)propoxy, 2-(5-hydroxymethyl-3-oxo-piperazin-1-yl)ethoxy, 3-(5-hydroxymethyl-3-oxo-piperazin-1-yl)propoxy, 3-(3-hydroxymethyl-4-methylpiperazin-1yl)propoxy, 3-(2-hydroxymethylmorpholin-4-yl)propoxy, 3-(glycoloylamino)propoxy or 3-(4-hydroxymethylpiperazin-1-yl)propoxy. In a further aspect R^3 is selected from 3-chloropropoxy, 3-[2-(hydroxymethyl)pyrrolidin-1-yl]propoxy, 3-[(2-hydroxyethyl)(isobutyl)amino]propoxy, 3-[(2-hydroxyethyl)(propyl)amino]propoxy, 3-piperidin-1-ylpropoxy, 3-pyrrolidin-1-ylpropoxy, 3-(diethylamino)propoxy, 3-piperazin-1-ylpropoxy, 3-[(2-hydroxyethyl)(methyl)amino]propoxy, 3-(cyclopropylamino)propoxy, 3-{[2-(dimethylamino)ethyl](methyl)amino}propoxy, 3-(4-methylpiperazin-1-yl)propoxy, 3-(4-hydroxypiperidin-1-yl)propoxy, 3-[bis(2-hydroxyethyl)amino]propoxy, 3-[ethyl(methyl)amino]propoxy, 3-[ethyl(2-hydroxyethyl)amino]propoxy, 3-{[2-(dimethylamino)ethyl](ethyl)amino}propoxy, 3-[2-(2-hydroxyethyl)piperidin-1-yl]propoxy, 3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy, 3-[(cyclopropylmethyl)amino]propoxy, 3-[4-(2-hydroxyethyl)piperidin-1-yl]propoxy, 3-[methyl(propargyl)amino]propoxy, 3-[allyl(methyl)amino]propoxy, 3-[isobutyl(methyl)amino]propoxy, 3-(3-hydroxypiperidin-1-yl)propoxy, 3-[4-(hydroxymethyl)piperidin-1-yl]propoxy, 3-[methyl(propyl)amino]propoxy, 3-[cyclopropylmethyl(propyl)amino]propoxy, 3-{[2-(diethylamino)ethyl](methyl)amino}propoxy, 3-{[2-(diethylamino)ethyl](ethyl)amino}propoxy, 3-(4-methyl-1,4-diazepan-1-yl)propoxy, 3-[(2-hydroxyethyl)(isopropyl)amino]propoxy, 3-[cyclopropyl(2-hydroxyethyl)amino]propoxy, 3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy, 3-[cyclobutyl(2-hydroxyethyl)amino]propoxy, 3-[cyclopropylmethyl(2-hydroxyethyl)amino]propoxy, 3-[cyclobutylmethyl(2-hydroxyethyl)amino]propoxy, 3-[(2-hydroxy)propargylamino]propoxy, 3-[allyl(2-hydroxyethyl)amino]propoxy, 3-[(2-hydroxyethyl)neopentylamino]propoxy, 3-[(2-hydroxyethyl)(3,3,3-trifluoropropyl)amino]propoxy, 3-azetidin-1-ylpropoxy, 3-[cyclopentyl(2-hydroxyethyl)amino]propoxy, 3-[(3-hydroxy-1,1-dimethylpropyl)amino]propoxy, 3-[(2-

cyanoethyl)(2-hydroxyethyl)amino]propoxy and 3-(dimethylamino)propoxy. In another aspect R^3 is selected from 3-[2-(hydroxymethyl)pyrrolidin-1-yl]propoxy, 3-[(2-hydroxyethyl)(isobutyl)amino]propoxy, 3-[(2-hydroxyethyl)(propyl)amino]propoxy, 3-[ethyl(2-hydroxyethyl)amino]propoxy, 3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy, 3-[4-(2-hydroxyethyl)piperidin-1-yl]propoxy, 3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy, 3-[cyclobutyl(2-hydroxyethyl)amino]propoxy, 3-[cyclopropylmethyl(2-hydroxyethyl)amino]propoxy and 3-[(3-hydroxy-1,1-dimethylpropyl)amino]propoxy.

In one aspect of the invention X^3 is a direct bond, -CH_2=CH_2-, -O-, -NH- or –N(C_{1-6}alkyl)-. In a further aspect X^3 is -CH_2=CH_2-, -O- or -NH-. In another aspect X^3 is a direct bond or -O-. In yet another aspect X^3 is -O-.

In one aspect of the invention R^{13} is hydrogen or a group selected from C_{1-6}alkyl, aryl, arylC_{1-4}alkyl, heterocyclyl and heterocyclylC_{1-4}alkyl, which group is optionally substituted by 1 or 2 substituents independently selected from –NR^7R^8, –C(O)NR^7R^8, halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, hydroxyC_{1-4}alkylcarbonyl and C_{1-4}alkylcarbonyl. In another aspect R^{13} is hydrogen, methyl, ethyl, propyl, heterocyclyl, heterocyclylmethyl, heterocyclylethyl or heterocyclylpropyl which methyl, ethyl or propyl are optionally substituted by –NR^7R^8, –C(O)NR^7R^8 or 1 or 2 halo, hydroxy or C_{1-4}alkoxy substituents and which heterocyclylmethyl, heterocyclylethyl or heterocyclylpropyl are optionally substituted on heterocyclyl by hydroxy, C_{1-4}alkyl, hydroxyC_{1-4}alkyl or hydroxyC_{1-4}alkylcarbonyl. In a further aspect R^{13} is hydrogen, methyl, ethyl, propyl or piperidinyl which methyl, ethyl or propyl are substituted by chloro, 1 or 2 hydroxy, 1 or 2 methoxy, –NR^7R^8 or a heterocyclyl selected from pyrrolidinyl and piperidinyl which heterocyclyl is optionally substituted by hydroxy, methyl, hydroxymethyl, 2-hydroxyethyl or glycoloyl. In a further aspect R^{13} is ethyl or propyl, both of which are substituted by –NR^7R^8, heterocyclyl or halo. In yet a further aspect R^{13} is propyl substituted by chloro, –NR^7R^8 or a heterocyclyl selected from pyrrolidinyl, piperidinyl, piperazinyl, diazepanyl and azetidinyl which heterocyclyl is optionally substituted by hydroxy, methyl, hydroxymethyl or 2-hydroxyethyl. In another aspect R^{13} is ethyl or propyl substituted by chloro or –NR^7R^8. In yet another aspect R^{13} is ethyl or propyl substituted by –NR^7R^8. In a further aspect R^{13} is propyl substituted by –NR^7R^8.

In one aspect of the invention R^7 and R^8 are independently selected from hydrogen, heterocyclyl, heterocyclylC_{1-4}alkyl, C_{1-4}alkylheterocyclylC_{1-4}alkyl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-4}alkyl, hydroxyC_{3-6}cycloalkyl, hydroxyC_{1-4}alkylC_{3-6}cycloalkyl, haloC_{1-6}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, cyanoC_{1-4}alkyl,

aminoC$_{1-4}$alkyl, C$_{1-4}$alkylaminoC$_{1-4}$alkyl, bis(C$_{1-4}$alkyl)aminoC$_{1-4}$alkyl, hydroxyC$_{1-4}$alkoxyC$_{1-4}$alkyl and hydroxyC$_{1-4}$alkylcarbonyl; or R^7 and R^8 together with the nitrogen to which they are attached form a heterocyclic ring selected from azetidine, pyrrolidine, piperidine, morpholine, piperazine, diazepane, 1,4-diazepane and azabicyclo[3.1.0]hexane which ring is optionally substituted on carbon or nitrogen by 1 or 2 substituents independently selected from C$_{1-4}$alkyl, hydroxy, hydroxyC$_{1-4}$alkyl, C$_{1-4}$alkoxyC$_{1-4}$alkyl, hydroxyC$_{1-4}$alkoxyC$_{1-4}$alkyl, C$_{1-4}$alkylcarbonyl and hydroxyC$_{1-4}$alkylcarbonyl, and where a ring –CH_2- is optionally replaced with –C(O)-. In another aspect R^7 and R^8 are independently selected from hydrogen, heterocyclyl, C$_{1-6}$alkyl, hydroxyC$_{1-6}$alkyl, hydroxyC$_{1-4}$alkylC$_{3-6}$cycloalkyl, C$_{1-4}$alkoxyC$_{1-4}$alkyl, C$_{3-6}$cycloalkyl, C$_{3-6}$cycloalkylC$_{1-4}$alkyl, haloC$_{1-6}$alkyl, C$_{2-6}$alkenyl, C$_{2-6}$alkynyl, cyanoC$_{1-4}$alkyl, and bis(C$_{1-4}$alkyl)aminoC$_{1-6}$alkyl; or R^7 and R^8 together with the nitrogen to which they are attached form a heterocyclic ring which ring comprises 4 to 7 ring atoms of which one is nitrogen and of which another is optionally NH and which ring is optionally substituted on carbon or nitrogen by a group selected from C$_{1-4}$alkyl, hydroxy, hydroxyC$_{1-4}$alkyl and hydroxyC$_{1-4}$alkoxyC$_{1-4}$alkyl, and where a ring –CH_2- is optionally replaced with –C(O)-. In a further aspect R^7 and R^8 are independently selected from hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl, hydroxymethyl, 2-hydroxyethyl, 2-hydroxy-1-methylethyl, 2-hydroxy-1,1-dimethylethyl, 3-hydroxypropyl, 3-hydroxy-2,2-dimethylpropyl, 3-hydroxy-1,1-dimethylpropyl, 2-hydroxypropyl, 2,3-dihydroxypropyl, 1-hydroxymethyl-2-methylpropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-hydroxycyclohexyl, 1-hydroxymethylcyclopentyl, 2-hydroxymethylcyclohexyl, cyclopropylmethyl, cyclobutylmethyl, tetrahydro-2H-pyran-4-yl, tetrahydrofuran-3-yl, tetrahydrofuran-2-ylmethyl, 5-methylisoxazol-3-yl, 2-cyanoethyl, allyl, prop-2-ynyl, 2-methoxyethyl, 3,3,3-trifluoropropyl, 2-(2-hydroxyethoxy)ethyl, 2-(dimethylamino)ethyl, 2-(diethylamino)ethyl, 3-aminopropyl, 3-(propylamino)propyl and glycoloyl; or R^7 and R^8 together with the nitrogen to which they are attached form a heterocyclic ring selected from azetidine, pyrrolidine, piperidine, morpholine, piperazine, diazepane or 1,4-diazepane which ring is optionally substituted by 1 or 2 substituents independently selected from methyl, hydroxy, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-(2-hydroxyethoxy)ethyl, glycoloyl, acetyl, methoxymethyl and oxo. In a further aspect R^7 and R^8 are independently selected from hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl, hydroxymethyl, 2-hydroxyethyl, 2-hydroxy-1-methylethyl, 2-hydroxy-1,1-dimethylethyl, 3-hydroxypropyl, 3-hydroxy-2,2-dimethylpropyl, 3-hydroxy-1,1-

dimethylpropyl, 2-hydroxypropyl, 2,3-dihydroxypropyl, 1-hydroxymethyl-2-methylpropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-hydroxycyclohexyl, 1-hydroxymethylcyclopentyl, 2-hydroxymethylcyclohexyl, cyclopropylmethyl, cyclobutylmethyl, tetrahydro-2H-pyran-4-yl, tetrahydrofuran-3-yl, tetrahydrofuran-2-ylmethyl, 5-methylisoxazol-3-yl, 2-cyanoethyl, allyl, prop-2-ynyl, 2-methoxyethyl, methoxymethyl, 3,3,3-trifluoropropyl, 2-(2-hydroxyethoxy)ethyl, 2-(dimethylamino)ethyl, 2-(diethylamino)ethyl, 3-aminopropyl, 3-(propylamino)propyl and glycoloyl. In yet another aspect R^7 and R^8 together with the nitrogen to which they are attached form azetidine, pyrrolidine, piperidine, morpholine, piperazine, diazepane, 1,4-diazepane, azabicyclo[3.1.0]hexane 4-methylpiperazine, 4-methyl–1,4-diazepane, 4-hydroxypiperidine, 3-hydroxypiperidine, 2-hydroxymethylpyrrolidine, 3-hydroxymethylpyrrolidine, 2-hydroxymethylpiperidine, 3-hydroxymethylpiperidine, 4-hydroxymethylpiperidine, 2-(2-hydroxyethyl)piperidine, 4-(2-hydroxyethyl)piperidine, 4-(2-hydroxyethyl)piperazine, 4-(3-hydroxypropyl)piperazine, 4-[2-(2-hydroxyethoxy)ethyl]piperazine, 4-glycoloylpiperazine, 4-acylpiperazine, 3-hydroxymethyl-4-methylpiperazine, 2-hydroxymethylmorphine 3-hydroxymethyl-4-methylpiperazine, 3-methoxymethyl-4-methylpiperazine, 4-(2-hydroxyethyl)-3-oxopiperazine or (1α,5α,6α)-6-(hydroxymethyl)-3-azobicyclo[3.1.0]hexane, 4-hydroxy-2-hydroxymethylpyrrolidine, 5-hydroxymethyl-2-oxopyrrolidine, 6-hydroxymethyl-2-oxopiperazine or 5-hydroxymethyl-3-oxopiperazine. In a further aspect R^7 and R^8 are independently selected from hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl, hydroxymethyl, 2-hydroxyethyl, 3-hydroxy-1,1-dimethylpropyl, methoxymethyl, 2-methoxyethyl, 2-ethoxyethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, allyl, propargyl, 2-(dimethylamino)ethyl and 2-(diethylamino)ethyl; or R^7 and R^8 together with the nitrogen to which they are attached form a heterocyclic ring selected from pyrrolidinyl, piperidinyl, piperazinyl, diazepanyl and azetidinyl where the ring is optionally substituted by hydroxy, methyl, hydroxymethyl or 2-hydroxyethyl. In yet another aspect R^7 and R^8 are independently selected from hydrogen, ethyl, propyl, isobutyl, 3-hydroxy-1,1-dimethyl, 2-methoxyethyl, cyclobutyl and cyclopropylmethyl; or R^7 and R^8 together with the nitrogen to which they are attached form a heterocyclic ring selected from pyrrolidinyl, piperidinyl and piperazinyl, where the ring is optionally substituted by hydroxymethyl or 2-hydroxyethyl.

In one aspect of the invention R^4 is hydrogen.

In one aspect of the invention R^5 is aryl optionally substituted by 1 or 2 halo. In another aspect R^5 is phenyl optionally substituted by 1 or 2 fluoro or chloro. In a further aspect R^5 is phenyl optionally substituted by 1 or 2 fluoro. In yet another aspect R^5 is 2,3-difluorophenyl, 3-fluorophenyl, 2-fluorophenyl or 2,6-difluorophenyl. In yet another aspect R^5 is 2,3-difluorophenyl or 3-fluorophenyl.

In one aspect of the invention R^9 is hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkyl or bis(C_{1-4}alkyl)aminoC_{1-4}alkyl. In a further aspect R^9 is hydroxyC_{1-4}alkyl or bis(C_{1-4}alkyl)aminoC_{1-4}alkyl.

In one aspect of the invention R^{19} is hydrogen, hydroxycarbonyl, C_{1-4}alkoxycarbonyl, aminocarbonyl or C_{1-4}alkanoylamino. In another aspect R^{19} is hydrogen, hydroxycarbonyl, ethoxycarbonyl, aminocarbonyl and acetylamino. In yet another aspect R^{19} is hydrogen.

In one aspect of the invention R^{10}, R^{15}, R^{16}, R^{17}, R^{18}, R^{20} and R^{21} are each independently hydrogen, methyl or ethyl.

Preferred values of $R^{1'}$, $R^{2'}$ and $R^{3'}$ for a compound of formula (IA) are as follows and preferred values of X, X^1, X^2, X^3, R^4, R^5 and R^{19} for a compound of formula (IA) are as defined for a compound of formula (I). Such values may be used where appropriate with any of the definitions, claims or embodiments defined herein.

In one aspect of the invention $R^{1'}$ is hydrogen, halo or $-OR^{11'}$. In a further aspect $R^{1'}$ is hydrogen or $-OR^{11'}$. In another aspect $R^{1'}$ is hydrogen, fluoro, hydroxy, phosphonooxy, methoxy, isopropoxy, pyrrolidin-2-ylmethoxy, 1-(2-hydroxyethyl)pyrrolidin-2-ylmethoxy, -(2-phosphonooxyethyl)pyrrolidin-2-ylmethoxy, 1-glycoloylpyrrolidin-2-ylmethoxy, 1-phosponooxymethylcarbonylpyrrolidin-2-ylmethoxy, 1-(N,N-dimethylglycyl)pyrrolidin-2-ylmethoxy, 2-(5-hydroxymethyl-2-oxo-pyrrolidin-1-yl)ethoxy, 2-(5-phosphonooxymethyl-2-oxo-pyrrolidin-1-yl)ethoxy, 3-(5-hydroxymethyl-2-oxo-pyrrolidin-1-yl)propoxy, 3-(5-phosphonooxymethyl-2-oxo-pyrrolidin-1-yl)propoxy, 2-(6-hydroxymethyl-2-oxo-piperazin-1-yl)ethoxy, 2-(6-phosphonooxymethyl-2-oxo-piperazin-1-yl)ethoxy, 3-(6-hydroxymethyl-2-oxo-piperazin-1-yl)propoxy, 3-(6-phosphonooxymethyl-2-oxo-piperazin-1-yl)propoxy, 2-(5-hydroxymethyl-3-oxo-piperazin-1-yl)ethoxy, 2-(5-phosphonooxymethyl-3-oxo-piperazin-1-yl)ethoxy, 3-(5-hydroxymethyl-3-oxo-piperazin-1-yl)propoxy or 3-(5-phosphonooxymethyl-3-oxo-piperazin-1-yl)propoxy. In yet a further aspect $R^{1'}$ is hydrogen, fluoro, methoxy, isopropoxy, pyrrolidin-2-ylmethoxy, 1-(2-hydroxyethyl)pyrrolidin-2-ylmethoxy, 1-(2-phosphonooxyethyl)pyrrolidin-2-ylmethoxy, 1-glycoloylpyrrolidin-2-ylmethoxy, 1-

phosponooxymethylcarbonylpyrrolidin-2-ylmethoxy or 1-(N,N-dimethylglycyl)pyrrolidin-2-ylmethoxy. In another aspect $R^{1'}$ is hydrogen.

In one aspect of the invention $R^{11'}$ is hydrogen, phosponooxy or a group selected from C_{1-6}alkyl, heterocyclyl, heterocyclylC_{1-4}alkyl, heterocyclylC_{2-4}alkenyl and heterocyclylC_{2-4}alkynyl which group is optionally substituted by a substituent selected from hydroxy, phosphonooxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkyl, amino, C_{1-4}alkylamino, bis(C_{1-4}alkyl)amino, hydroxycarbonyl, C_{1-4}alkoxycarbonyl, hydroxyC_{1-4}alkylcarbonyl, phosphonooxyC_{1-4}alkylcarbonyl, C_{1-4}alkoxyC_{1-4}alkylcarbonyl, aminoC_{1-4}alkylcarbonyl, C_{1-4}alkylaminoC_{1-4}alkylcarbonyl and bis(C_{1-4}alkyl)aminoC_{1-4}alkylcarbonyl. In a further aspect $R^{11'}$ is hydrogen, phosphonooxy or a group selected from C_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-4}alkyl, which group is optionally substituted by a substituent selected from hydroxy, phosphonooxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkyl, hydroxyC_{1-4}alkylcarbonyl, phosphonooxyC_{1-4}alkylcarbonyl, aminoC_{1-4}alkylcarbonyl, C_{1-4}alkylaminoC_{1-4}alkylcarbonyl and bis(C_{1-4}alkyl)aminoC_{1-4}alkylcarbonyl. In another aspect $R^{11'}$ is hydrogen, methyl, ethyl, propyl, isopropyl or a group selected from pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolidinylpropyl, 2-oxopyrrolidin-1-ylmethyl, 2-oxopyrrolidin-1-ylethyl, 2-oxopyrrolidin-1-ylpropyl, 3-oxopyrrolidin-1-ylmethyl, 3-oxopyrrolidin-1-ylethyl, 3-oxopyrrolidin-1-ylpropyl, piperidinylmethyl, piperidinylethyl, piperidinylpropyl, 2-oxopiperidinylmethyl, 2-oxopiperidinylethyl, 2-oxopiperidinylpropyl, 3-oxopiperidinylmethyl, 3-oxopiperidinylethyl, 3-oxopiperidinylpropyl, 4-oxopiperidinylmethyl, 4-oxopiperidinylethyl, 4-oxopiperidinylpropyl, piperazinylmethyl, piperazinylethyl, piperazinylpropyl, 2-oxopiperazinylmethyl, 2-oxopiperazinylethyl, 2-oxopiperazinylpropyl, 3-oxopiperazinylmethyl, 3-oxopiperazinylethyl and 3-oxopiperazinylpropyl, which group is optionally substituted by hydroxy, phosphonooxy, hydroxymethyl, phosphonooxymethyl, 2-hydroxyethyl, 2-phosphonooxyethyl, tert-butoxycarbonyl, glycoloyl, phosphonooxymethylcarbonyl, glycyl, N-methylglycyl or N,N-dimethylglycyl. In a further aspect R^{11} is hydrogen, methyl, ethyl, propyl, isopropyl, pyrrolidinylmethyl which pyrrolidinylmethyl is optionally substituted by 2-hydroxyethyl, 2-phosphonooxyethyl, glycoloyl, phosphonooxymethylcarbonyl or N,N-dimethylglycyl or R^{11} is 2-(2-oxopyrrolidin-1-yl)ethyl, 3-(2-oxopyrrolidin-1-yl)propyl, 2-(2-oxopiperazin-1-yl)ethyl, 3-(2-oxopiperazin-1-yl)propyl, 2-(3-oxopiperazin-1-yl)ethyl or 3-(3-oxopiperazin-1-yl)propyl optionally substituted by hydroxymethyl, phosphonooxymethyl, 2-hydroxyethyl or 2-phosphonooxyethyl. In another aspect $R^{11'}$ is hydrogen, methyl, ethyl, propyl, isopropyl or a group selected from

pyrrolidinylmethyl, pyrrolidinylethyl, piperidinylmethyl and piperidinylethyl which group is optionally substituted by hydroxy, phosphonooxy, hydroxymethyl, phosphonooxymethyl, 2-hydroxyethyl, 2-phosphonooxyethyl, tert-butoxycarbonyl, glycoloyl, phosphonooxymethylcarbonyl, glycyl, N-methylglycyl or N,N-dimethylglycyl. In a further aspect $R^{11'}$ is hydrogen, methyl, ethyl, propyl, isopropyl or pyrrolidinylmethyl which pyrrolidinylmethyl is optionally substituted by 2-hydroxyethyl, 2-phosphonooxyethyl, glycoloyl, phosphonooxymethylcarbonyl or N,N-dimethylglycyl. In yet another aspect $R^{11'}$ is hydrogen, C_{1-4}alkyl or C_{1-4}alkoxy. In a further aspect $R^{11'}$ is hydrogen.

In one aspect of the invention $R^{2'}$ is hydrogen, halo, $-OR^{12'}$ or $-OC(O)R^{12'}$. In a further aspect $R^{2'}$ is hydrogen, fluoro, hydroxy, phosphonooxy, methoxy, 2-methoxyethoxy, benzoyloxy, 2-morpholin-4-ylethoxy, 3-morpholin-4-ylpropoxy or 1-methylpyrrolidin-2-yloxy. In yet a further aspect $R^{2'}$ is hydrogen, methoxy, phosphonooxy or fluoro. In another aspect $R^{2'}$ is hydrogen or methoxy. In a further aspect $R^{2'}$ is hydrogen. In yet a further aspect $R^{2'}$ is methoxy.

In one aspect of the invention $R^{12'}$ is hydrogen, phosphonooxy or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, aryl, arylC_{1-4}alkyl, heterocyclyl and heterocyclylC_{1-4}alkyl, which group is optionally substituted by 1, 2 or 3 substituents selected from halo, hydroxy, phosphonooxy, C_{1-4}alkyl, C_{1-4}alkoxy, $-NR^{15'}R^{16'}$, $-NHC(O)NR^{15'}R^{16'}$, $-C(O)R^{15'}$ and $-C(O)OR^{15'}$. In a further aspect $R^{12'}$ is hydrogen, phosphonooxy or a group selected from C_{1-4}alkyl, aryl, heterocyclyl and heterocyclylC_{1-4}alkyl which group is optionally substituted by a substituent selected from C_{1-4}alkyl and C_{1-4}alkoxy. In yet another aspect $R^{12'}$ is hydrogen or group selected from methyl, 2-morpholinylethyl, 3-morpholinylpropoxy, 2-methoxyethyl and pyrrolidinyl which group is optionally substituted by methyl. In another aspect $R^{12'}$ is hydrogen or C_{1-4}alkyl. In another aspect of the invention $R^{12'}$ is hydrogen. In a further aspect of the invention $R^{12'}$ is methyl.

In one aspect of the invention $R^{3'}$ is hydrogen, phosponooxy or $-X^3R^{13'}$.

In another aspect $R^{3'}$ is hydrogen, hydroxy, phosphonooxy, methoxy, 3-chloropropoxy, 2-chloroethoxy, 2,2-dimethoxyethoxy, 3-[2-(hydroxymethyl)pyrrolidin-1-yl]propoxy, 3-[2-(phosphonooxymethyl)pyrrolidin-1-yl]propoxy, 3-[(2-hydroxyethyl)(isobutyl)amino]propoxy, 3-[2-phosphonooxyethyl)(isobutyl)amino]propoxy, 3-[(2-hydroxyethyl)(propyl)amino]propoxy, 3-[(2-phosphonooxyethyl)(propyl)amino]propoxy, 3-piperidin-1-ylpropoxy, 3-pyrrolidin-1-ylpropoxy, 3-(diethylamino)propoxy, 3-piperazin-1-ylpropoxy, 3-[(2-hydroxyethyl)(methyl)amino]propoxy, 3-[(2-

phosphonooxyethyl)(methyl)amino]propoxy, 3-(cyclopropylamino)propoxy, 3-{[2-(dimethylamino)ethyl](methyl)amino}propoxy, 3-(4-methylpiperazin-1-yl)propoxy, 3-(4-hydroxypiperidin-1-yl)propoxy, 3-(4-phosphonooxypiperidin-1-yl)propoxy, 3-[bis(2-hydroxyethyl)amino]propoxy, 3-[(2-hydroxyethyl)(2-phosphonooxyethyl)amino]propoxy, 3-[ethyl(methyl)amino]propoxy, 3-[ethyl(2-hydroxyethyl)amino]propoxy, 3-[ethyl(2-phosphonooxyethyl)amino]propoxy, 3-{[2-(dimethylamino)ethyl](ethyl)amino}propoxy, 3-[2-(2-hydroxyethyl)piperidin-1-yl]propoxy, 3-[2-(2-phosphonooxyethyl)piperidin-1-yl]propoxy, 3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy, 3-[4-(2-phosponooxyethyl)piperazin-1-yl]propoxy, 3-[(cyclopropylmethyl)amino]propoxy, 3-[4-(2-hydroxyethyl)piperidin-1-yl]propoxy, 3-[4-(2-phosphonooxyethyl)piperidin-1-yl]propoxy, 3-[methyl(prop-2-yn-1-yl)amino]propoxy, 3-[allyl(methyl)amino]propoxy, 3-[isobutyl(methyl)amino]propoxy, 3-(3-hydroxypiperidin-1-yl)propoxy, 3-(3-phosphonooxypiperidin-1-yl)propoxy, 3-[4-(hydroxymethyl)piperidin-1-yl]propoxy, 3-[4-(phosphonooxymethyl)piperidin-1-yl]propoxy, 3-[methyl(propyl)amino]propoxy, 3-[cyclopropylmethyl(propyl)amino]propoxy, 3-{[2-(diethylamino)ethyl](methyl)amino}propoxy, 3-{[2-(diethylamino)ethyl](ethyl)amino}propoxy, 3-(4-methyl-1,4-diazepan-1-yl)propoxy, 3-[(2-hydroxyethyl)(isopropyl)amino]propoxy, 3-[(2-phosphonooxyethyl)(isopropyl)amino]propoxy, 3-[cyclopropyl(2-hydroxyethyl)amino]propoxy, 3-[cyclopropyl(2-phosphonooxyethyl)amino]propoxy, 3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy, 3-[(2-phosphonooxyethyl)(2-methoxyethyl)amino]propoxy, 3-[cyclobutyl(2-hydroxyethyl)amino]propoxy, 3-[cyclobutyl(2-phosphonooxyethyl)amino]propoxy, 3-[cyclopropylmethyl(2-hydroxyethyl)amino]propoxy, 3-[cyclopropylmethyl(2-phosphonooxyethyl)amino]propoxy, 3-[cyclobutylmethyl(2-hydroxyethyl)amino]propoxy, 3-[cyclobutylmethyl(2-phosphonooxyethyl)amino]propoxy, 3-[(2-hydroxyethyl)prop-2-yn-1-lyamino]propoxy, 3-[(2-phosphonooxyethyl)prop-2-yn-1-lyamino]propoxy, 3-[allyl(2-hydroxyethyl)amino]propoxy, 3-[allyl(2-phosphonooxyethyl)amino]propoxy, 3-[(2,2-dimethylpropyl(2-hydroxyethyl)amino]propoxy, 3-[(2,2-dimethylpropyl(2-phosphonooxyethyl)amino]propoxy, 3-[(2-hydroxyethyl)(3,3,3-trifluoropropyl)amino]propoxy, 3-[(2-phosphonooxyethyl)(3,3,3-trifluoropropyl)amino]propoxy, 3-azetidin-1-ylpropoxy, 3-(dimethylamino)propoxy, 2-[(2-hydroxymethyl)pyrrolidin-1-yl]ethoxy, 2-[(2-phosphonooxymethyl)pyrrolidin-1-yl]ethoxy, 2-{4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl}ethoxy, 2-{4-[2-(2-phosphonooxyethoxy)ethyl]piperazin-1-yl}ethoxy, 2-[2-(2-hydroxyethyl)piperidin-1-

yl]ethoxy, 2-[2-(2-phosphonooxyethyl)piperidin-1-yl]ethoxy, 2-[2-(hydroxymethyl)piperidin-1-yl]ethoxy, 2-[2-(phosphonooxymethyl)piperidin-1-yl]ethoxy, 2-[(2-hydroxy-1,1-dimethylethyl)amino]ethoxy, 2-[(2-phosphonooxy-1,1-dimethylethyl)amino]ethoxy, 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethoxy, 2-[4-(2-phosphonooxyethyl)piperazin-1-yl]ethoxy, 2-[(4-hydroxycyclohexyl)amino]ethoxy, 2-[(4-phosphonooxycyclohexyl)amino]ethoxy, 2-[3-(hydroxymethyl)piperidin-1-yl]ethoxy, 2-[3-(phosphonooxymethyl)piperidin-1-yl]ethoxy, 2-{[1-(hydroxymethyl)cyclopentyl]amino}ethoxy, 2-{[1-{phosphonooxymethyl)cyclopentyl]amino}ethoxy, 2-[4-(3-hydroxypropyl)piperazin-1-yl]ethoxy, 2-[4-(3-phosphonooxypropyl)piperazin-1-yl]ethoxy, 2-[cyclohexyl(2-hydroxyethyl)amino]ethoxy, 2-[cyclohexyl(2-phosphonooxyethyl)amino]ethoxy, 2-[(2-hydroxyethyl)(propyl)amino]ethoxy, 2-[(2-phosphonooxyethyl)(propyl)amino]ethoxy, 2-[(3-hydroxy-2,2-dimethylpropyl)amino]ethoxy, 2-[(3-phosphonooxy-2,2-dimethylpropyl)amino]ethoxy, 2-(tetrahydro-2*H*-pyran-4-ylamino)ethoxy, 2-[cyclobutyl(2-hydroxyethyl)amino]ethoxy, 2-[cyclobutyl(2-phosphonooxyethyl)amino]ethoxy, 2-[(2-hydroxyethyl)(tetrahydro-2*H*-pyran-4-yl)amino]ethoxy, 2-[(2-phosphonooxyethyl)(tetrahydro-2*H*-pyran-4-yl)amino]ethoxy, 3-[cyclopentyl(2-hydroxyethyl)amino]propoxy, 3-[cyclopentyl(2-phosphonooxyethyl)amino]propoxy, 3-[(3-hydroxy-1,1-dimethylpropyl)amino]propoxy, 3-[(3-phosphonooxy-1,1-dimethylpropyl)amino]propoxy, 3-[(2-cyanoethyl)(2-hydroxyethyl)amino]propoxy, 3-[(2-cyanoethyl)(2-phosphonooxyethyl)amino]propoxy, 3-morpholin-4-ylpropoxy, 3-[(3-hydroxy-2,2-dimethylpropyl)amino]propoxy, 3-[(3-phosphonooxy-2,2-dimethylpropyl)amino]propoxy, 3-[(3-hydroxypropyl)amino]propoxy, 3-[(3-phosphonooxypropyl)amino]propoxy, 3-[(3-hydroxypropyl)(propyl)amino]propoxy, 3-[(3-phosphonooxypropyl)(propyl)amino]propoxy, 3-[(3-hydroxypropyl)(ethyl)amino]propoxy, 3-[(3-phosphomooxypropyl)(ethyl)amino]propoxy, 3-[4-(2-hydroxyethyl)-3-oxopiperazin-1-yl]propoxy, 3-[4-(2-phosphonooxyethyl)-3-oxopiperazin-1-yl]propoxy, 3-(propylamino)propoxy, 3-[glycoloyl(propyl)amino]propoxy, 3-[phosphonooxymethylcarbonyl(propyl)amino]propoxy, 3-(4-glycoloylpiperazin-1-yl)propoxy, 3-(4-phosphonooxymethylcarbonylpiperazin-1-yl)propoxy, 3-{[2-(hydroxymethyl)cyclohexyl]amino}propoxy, 3-{[2-(phosphonooxymethyl)cyclohexyl]amino}propoxy, 3-[{1α,5α,6α)-6-(hydroxymethyl)-3-azabicyclo[3.1.0]hex-3-yl]propoxy, 3-[{1α,5α,6α)-6-(phosphonooxymethyl)-3-

azabicyclo[3.1.0]hex-3-yl]propoxy, 3-{[2-hydroxypropyl]amino}propoxy, 3-{[2-phosphonooxypropyl]amino}propoxy, 3-{[2-hydroxy-1-methylethyl]amino}propoxy, 3-{[2-phosphonooxy-1-methylethyl]amino}propoxy, 3-[(2-hydroxy-1,1-dimethylethyl)amino]propoxy, 3-[(2-phosphonooxy-1,1-dimethylethyl)amino]propoxy, 3-[(2,3-dihydroxypropyl)amino]propoxy, 3-[(2-phosphonoxy-3-hydroxypropyl)amino]propoxy, 3-[(2-hydroxy-3-phosphonooxypropyl)amino]propoxy, 3-{[2-(2-hydroxyethoxy)ethyl]amino}propoxy, 3-{[2-(2-phosphonooxyethoxy)ethyl]amino}propoxy, 3-(4-acetylpiperazin-1-yl)propoxy, 3-[(tetrahydrofuran-2-ylmethyl)amino]propoxy, 3-(allylamino)propoxy, 3-{[1-(hydroxymethyl)-2-methylpropyl]amino}propoxy, 3-{[1-(phosphonooxymethyl)-2-methylpropyl]amino}propoxy, 3-{[(5-methylisoxazol-3-yl)methyl]amino}propoxy, 3-(tetrahydro-2*H*-pyran-4-ylamino)propoxy, 3-[3-(hydroxymethyl)pyrrolidin-1-yl]propoxy, 3-[3-(phosphonooxymethyl)pyrrolidin-1-yl]propoxy, 3-aminopropoxy, 3-[-4-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy, 3-[-4-phosphonooxy-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy, 3-[-4-hydroxy-2-(phosphonooxymethyl)pyrrolidin-1-yl]propoxy, 2-(cyclopropylamino)ethoxy, 2-(cyclobutylamino)ethoxy, 2-(cyclopentylamino)ethoxy, 2-[{2-hydroxyethyl)(tetrahydro-2*H*-pyran-4-yl)amino]ethoxy, 2-[{2-phosphonooxyethyl)(tetrahydro-2*H*-pyran-4-yl)amino]ethoxy, 2-[cyclopentyl(2-hydroxyethyl)amino]ethoxy, 2-[cyclopentyl(2-phosphonooxyethyl)amino]ethoxy, 2-[cyclopropyl(2-hydroxyethyl)amino]ethoxy, 2-[cyclopropyl(2-phosphonooxyethyl)amino]ethoxy, 2-[cyclopentyl(3-hydroxypropyl)amino]ethoxy, 2-[cyclopentyl(3-phosphonooxypropyl)amino]ethoxy, 2-[cyclopentyl(glycoloyl)amino]ethoxy, 2-[cyclopentyl(phosphonooxymethylcarbonyl)amino]ethoxy, 2-[3-(hydroxymethyl)-4-methylpiperazin-1-yl]ethoxy, 2-[3-(phosphonooxymethyl)-4-methylpiperazin-1-yl]ethoxy, 2-[2-(hydroxymethyl)-4-methylpiperazin-1-yl]ethoxy, 2-[2-(phosphonooxymethyl)-4-methylpiperazin-1-yl]ethoxy, 2-[4-(hydroxymethyl)piperidin-1-yl]ethoxy, 2-[4-(phosphonooxymethyl)piperidin-1-yl]ethoxy, 2-[4-(2-hydroxyethyl)piperidin-1-yl]ethoxy, 2-[4-(2-phosphonooxyethyl)piperidin-1-yl]ethoxy, 2-[(2-hydroxyethyl)amino]ethoxy, 2-[(2-phosphonooxyethyl)amino]ethoxy, 2-{[2-(hydroxymethyl)cyclohexyl]amino}ethoxy, 2-{[2-(phosphonooxymethyl)cyclohexyl]amino}ethoxy, 3-[(2-hydroxyethyl)amino]propoxy, 3-[(2-phosphonooxyethyl)amino]propoxy, 3-[(2-hydroxyethyl)(tetrahydrofuran-3-yl)amino]propoxy, 3-[(2-phosphonooxyethyl)(tetrahydrofuran-3-yl)amino]propoxy, pyrrolidin-2-ylmethoxy, [1-(2-hydroxyethyl)pyrrolidin-2-yl]methoxy, [1-(2-

phosphonooxyethyl)pyrrolidin-2-yl]methoxy, [1-glycoloylpyrrolidin-2-yl]methoxy, [1-phosphonooxymethylcarbonylpyrrolidin-2-yl]methoxy, pyrrolidin-3-ylmethoxy, [1-(2-hydroxyethyl)pyrrolidin-3-yl]methoxy, [1-(2-phosphonooxyethyl)pyrrolidin-3-yl]methoxy, (1-glycoloylpyrrolidin-3-yl)methoxy, (1-phoshonooxymethylcarbonylpyrrolidin-3-yl)methoxy, 3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy, 3-[(2-phosphonooxyethyl)(2-methoxyethyl)amino]propoxy, (2-hydroxyethyl)amino]propoxy, (2-phosphonooxyethyl)amino]propoxy, 2-(5-hydroxymethyl-2-oxo-pyrrolidin-1-yl)ethoxy, 2-(5-phosphonooxymethyl-2-oxo-pyrrolidin-1-yl)ethoxy, 3-(5-hydroxymethyl-2-oxo-pyrrolidin-1-yl)propoxy, 3-(5-phosphonooxymethyl-2-oxo-pyrrolidin-1-yl)propoxy, 2-(6-hydroxymethyl-2-oxo-piperazin-1-yl)ethoxy, 2-(6-phosphonooxymethyl-2-oxo-piperazin-1-yl)ethoxy, 3-(6-hydroxymethyl-2-oxo-piperazin-1-yl)propoxy, 3-(6-phosphonooxymethyl-2-oxo-piperazin-1-yl)propoxy, 2-(5-hydroxymethyl-3-oxo-piperazin-1-yl)ethoxy, 2-(5-phosphonooxymethyl-3-oxo-piperazin-1-yl)ethoxy, 3-(5-hydroxymethyl-3-oxo-piperazin-1-yl)propoxy, 3-(5-phosphonooxymethyl-3-oxo-piperazin-1-yl)propoxy, 3-(3-hydroxymethyl-4-methylpiperazin-1yl)propoxy, 3-(3-phosphonooxymethyl-4-methylpiperazin-1yl)propoxy, 3-(2-hydroxymethylmorpholin-4-yl)propoxy, 3-(2-phosphonooxymorpholin-4-yl)propoxy, 3-(glycoloylamino)propoxy, 3-(phosphonooxymethylcarbonylamino)propoxy, 3-(4-hydroxymethylpiperazin-1-yl)propoxy or 3-(4-phosphonooxymethylpiperazin-1-yl)propoxy.

In one aspect of the invention $R^{13'}$ is hydrogen or a group selected from C_{1-6}alkyl, aryl, arylC_{1-4}alkyl, heterocyclyl and heterocyclylC_{1-4}alkyl, which group is optionally substituted by 1 or 2 substituents independently selected from $-NR^{7'}R^{8'}$, $-C(O)NR^{7'}R^{8'}$, halo, hydroxy, phosphonooxy, C_{1-4}alkyl, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkyl, hydroxyC_{1-4}alkylcarbonyl, phosphonooxyC_{1-4}alkylcarbonyl and C_{1-4}alkylcarbonyl. In another aspect $R^{13'}$ is hydrogen, methyl, ethyl or propyl, which methyl, ethyl or propyl are optionally substituted by $-NR^{7'}R^{8'}$, $-C(O)NR^{7'}R^{8'}$, heterocyclyl or 1 or 2 halo, hydroxy, phosphonooxy or C_{1-4}alkoxy substituents and which heterocyclyl is optionally substituted by hydroxy, phosphonooxy, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkyl, hydroxyC_{1-4}alkylcarbonyl or phosphonooxyC_{1-4}alkylcarbonyl. In a further aspect $R^{13'}$ is methyl, ethyl or propyl substituted by chloro, 1 or 2 hydroxy, 1 phosphonooxy, 1 or 2 methoxy, $-NR^{7'}R^{8'}$ or a heterocyclyl selected from pyrrolidinyl and piperidinyl which heterocyclyl is optionally substituted by hydroxy, phosphonooxy, methyl, hydroxymethyl, phosphonooxymethyl, 2-hydroxyethyl, 2-phosphonooxyethyl, glycoloyl or phosphonooxymethylcarbonyl. In a further aspect of the invention $R^{13'}$ is ethyl or propyl, both of which are substituted by $-NR^{7'}R^{8'}$,

heterocyclyl or halo. In yet a further aspect of the invention $R^{13'}$ is propyl substituted by chloro, $-NR^{7'}R^{8'}$ or a heterocyclyl selected from pyrrolidinyl, piperidinyl, piperazinyl, diazepanyl and azetidinyl where the heterocyclyl is optionally substituted by hydroxy, phosphonooxy, methyl, hydroxymethyl, phosphonooxymethyl, 2-hydroxyethyl or 2-phosphonooxyethyl. In another aspect $R^{13'}$ is ethyl or propyl substituted by chloro or $-NR^{7'}R^{8'}$. In yet another aspect $R^{13'}$ is ethyl or propyl substituted by $-NR^{7'}R^{8'}$. In a further aspect $R^{13'}$ is propyl substituted by $-NR^{7'}R^{8'}$.

In one aspect of the invention $R^{7'}$ and $R^{8'}$ are independently selected from hydrogen, heterocyclyl, heterocyclylC_{1-4}alkyl, C_{1-4}alkylheterocyclylC_{1-4}alkyl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, phosphonooxyC_{1-6}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-4}alkyl, hydroxyC_{3-6}cycloalkyl, phosphonooxyC_{3-6}cycloalkyl, hydroxyC_{1-4}alkylC_{3-6}cycloalkyl, phosphonooxyC_{1-4}alkylC_{3-6}cycloalkyl, haloC_{1-6}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, cyanoC_{1-4}alkyl, aminoC_{1-4}alkyl, bis(C_{1-4}alkyl)aminoC_{1-4}alkyl, hydroxyC_{1-4}alkoxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkylcarbonyl and phosphonooxyC_{1-4}alkylcarbonyl; or $R^{7'}$ and $R^{8'}$ together with the nitrogen to which they are attached form a heterocyclic ring selected from azetidine, pyrrolidine, piperidine, morpholine, piperazine, diazepane, 1,4-diazepane and azabicyclo[3.1.0]hexane which ring is optionally substituted on carbon or nitrogen by 1 or 2 substituents independently selected from C_{1-4}alkyl, hydroxy, phosphonooxy, hydroxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkoxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl, hydroxyC_{1-4}alkylcarbonyl and phosphonooxyC_{1-4}alkylcarbonyl, and where a ring $-CH_2-$ is optionally replaced with –C(O)-. In another aspect $R^{7'}$ and $R^{8'}$ are independently selected from hydrogen, heterocyclyl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, phosphonooxyC_{1-6}alkyl, hydroxyC_{1-4}alkylC_{3-6}cycloalkyl, phosphonooxyC_{1-4}alkylC_{3-6}cycloalkyl, C_{1-4}alkoxyC_{1-4}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-4}alkyl, haloC_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, cyanoC_{1-4}alkyl, aminoC_{1-6}alkyl, C_{1-4}alkylaminoC_{1-6}alkyl and bis(C_{1-4}alkyl)aminoC_{1-6}alkyl; or $R^{7'}$ and $R^{8'}$ together with the nitrogen to which they are attached form a heterocyclic ring which ring comprises 4 to 7 ring atoms of which one is nitrogen and of which another is optionally NH and which ring is optionally substituted on carbon or nitrogen by a group selected from C_{1-4}alkyl, hydroxy, phosphonooxy, hydroxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkyl, hydroxyC_{1-4}alkoxyC_{1-4}alkyl, and phosphonooxyC_{1-4}alkoxyC_{1-4}alkyl, and where a ring $-CH_2-$ is optionally replaced with –C(O). In a further aspect $R^{7'}$ and $R^{8'}$ are independently selected from hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl, hydroxymethyl,

phosphonooxymethyl, 2-hydroxyethyl, 2-phosphonooxyethyl, 2-hydroxy-1,1-dimethylethyl, 2-phosphonooxy-1,1-dimethylethyl, 3-hydroxypropyl, 3-phosphonooxypropyl, 3-hydroxy-2,2-dimethylpropyl, 3-phosphonooxy-2,2-dimethylpropyl, 3-hydroxy-1,1-dimethylpropyl, 3-phosphonooxy-1,1-dimethylpropyl, 2-hydroxypropyl, 2-phosphonooxypropyl, 2,3-dihydroxypropyl, 2-hydroxy-3-phosphonooxypropyl, 2-phosphonooxy-3-hydroxypropyl, 1-hydroxymethyl-2-methylpropyl, 1-phosphonooxymethyl-2-methylpropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-hydroxycyclohexyl, 4-phosphonooxycyclohexyl, 1-hydroxymethylcyclopentyl, 1-phosphonooxymethylcyclopentyl, 2-hydroxymethylcyclohexyl, 2-phosphonooxymethylcyclohexyl, cyclopropylmethyl, cyclobutylmethyl, tetrahydro-2H-pyran-4-yl, tetrahydrofuran-3-yl, tetrahydrofuran-2-ylmethyl, 5-methylisoxazol-3-yl, 2-cyanoethyl, allyl, prop-2-ynyl, 2-methoxyethyl, methoxymethyl, 3,3,3-trifluoropropyl, 2-(2-hydroxyethoxy)ethyl, 2-(2-phosphonooxyethoxy)ethyl, 2-(dimethylamino)ethyl, 2-(diethylamino)ethyl, 3-aminopropyl, 3-(propylamino)propyl, glycoloyl and phosphonooxymethylcarbonyl; or $R^{7'}$ and $R^{8'}$ together with the nitrogen to which they are attached form a heterocyclic ring selected from azetidine, pyrrolidine, piperidine, morpholine, piperazine, diazepane or 1,4-diazepane which ring is optionally substituted by 1 or 2 substituents independently selected from methyl, hydroxy, phosphonooxy, hydroxymethyl, phosphonooxymethyl, 2-hydroxyethyl, 2-phosphonooxyethyl, 3-hydroxypropyl, 3-phosphonooxypropyl, 2-(2-hydroxyethoxy)ethyl, 2-(2-phosphonooxyethyl)ethyl, glycoloyl, phosphonooxymethylcarbonyl, acetyl, methoxymethyl and oxo. In a further aspect $R^{7'}$ and $R^{8'}$ are independently selected from hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl, hydroxymethyl, phosphonooxymethyl, 2-hydroxyethyl, 2-phosphonooxyethyl, 2-hydroxy-1,1-dimethylethyl, 2-phosphonooxy-1,1-dimethylethyl, 3-hydroxypropyl, 3-phosphonooxypropyl, 3-hydroxy-2,2-dimethylpropyl, 3-phosphonooxy-2,2-dimethylpropyl, 3-hydroxy-1,1-dimethylpropyl, 3-phosphonooxy-1,1-dimethylpropyl, 2-hydroxypropyl, 2-phosphonooxypropyl, 2,3-dihydroxypropyl, 2-hydroxy-3-phosphonooxypropyl, 2-phosphonooxy-3-hydroxypropyl, 1-hydroxymethyl-2-methylpropyl, 1-phosphonooxymethyl-2-methylpropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-hydroxycyclohexyl, 4-phosphonooxycyclohexyl, 1-hydroxymethylcyclopentyl, 1-phosphonooxymethylcyclopentyl, 2-hydroxymethylcyclohexyl, 2-phosphonooxymethylcyclohexyl, cyclopropylmethyl, cyclobutylmethyl, tetrahydro-2H-pyran-4-yl, tetrahydrofuran-3-yl, tetrahydrofuran-2-ylmethyl, 5-methylisoxazol-3-yl, 2-cyanoethyl, allyl, prop-2-ynyl, 2-methoxyethyl, methoxymethyl, 3,3,3-trifluoropropyl, 2-(2-

hydroxyethoxy)ethyl, 2-(2-phosphonooxyethoxy)ethyl, 2-(dimethylamino)ethyl, 2-(diethylamino)ethyl, 3-aminopropyl, 3-(propylamino)propyl, glycoloyl and phosphonooxymethylcarbonyl. In yet another aspect $R^{7'}$ and $R^{8'}$ together with the nitrogen to which they are attached form 4-methylpiperazine, 4-methyl–1,4-diazepane, 4-hydroxypiperidine, 4-phosphonooxypiperidine, 3-hydroxypiperidine, 3-phosphonooxypiperidine, 2-hydroxymethylpyrrolidine, 2-phosphonooxymethylpyrrolidine, 3-hydroxymethylpyrrolidine, 3-phosphonooxymethylpyrrolidine, 2-hydroxymethylpiperidine, 2-phosphonooxymethylpiperidine, 3-hydroxymethylpiperidine, 3-phosphonooxymethylpiperidine, 4-hydroxymethylpiperidine, 4-phosphonooxymethylpiperidine, 2-(2-hydroxyethyl)piperidine, 2-(2-phosphonooxyethyl)piperidine, 4-(2-hydroxyethyl)piperidine, 4-(2-phosphonooxyethyl)piperidine, 4-(2-hydroxyethyl)piperazine, 4-(2-phosphonooxyethyl)piperazine, 4-(3-hydroxypropyl)piperazine, 4-(3-phosphonooxypropyl)piperazine, 4-[2-(2-hydroxyethoxy)ethyl]piperazine, 4-[2-(2-phosphonooxyethoxy)ethyl]piperazine, 4-glycoloylpiperazine, 4-phosphonooxymethylcarbonylpiperazine, 4-acylpiperazine, 3-hydroxymethyl-4-methylpiperazine, 3-phosphonooxymethyl-4-methylpiperazine, 2-hydroxymethylmorphine, 2-phosphonooxy methylmorphine, 3-hydroxymethyl-4-methylpiperazine, 3-methoxymethyl-4-methylpiperazine, 4-(2-hydroxyethyl)-3-oxopiperazine, 4-(2-phosphonooxyethyl)-3-oxopiperazine, (1α,5α,6α)-6-(hydroxymethyl)-3-azobicyclo[3.1.0]hexane, (1α,5α,6α)-6-(phosphonooxymethyl)-3-azobicyclo[3.1.0]hexane, 4-hydroxy-2-hydroxymethylpyrrolidine, 4-phosphonooxy-2-hydroxymethylpyrrolidine, 4-hydroxy-2-phosphonooxymethylpyrrolidine, 5-hydroxymethyl-2-oxopyrrolidine, 6-hydroxymethyl-2-oxopiperazine or 5-hydroxymethyl-3-oxopiperazine. In yet another aspect $R^{7'}$ and $R^{8'}$ are independently selected from hydrogen, methyl, ethyl, propyl, cyclopropyl, cyclobutyl, cyclopentyl, 2-phosphonooxyethyl, 2-phosphonooxypropyl, 3-phosphonooxy-1,1-dimethylpropyl, 2-methoxyethyl, phosphonooxymethylcarbonyl and tetrahydro-2*H*-furan-4-yl; or $R^{7'}$ and $R^{8'}$ together with the nitrogen to which they are attached form 2-phosphonooxymethylpyrrolidine, 4-(2-phosphonooxyethyl)piperazine or 4-(phosphonooxymethylcarbonyl)piperazine.

In one aspect of the invention $R^{9'}$ is hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkyl, aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkyl or bis(C_{1-4}alkyl)aminoC_{1-4}alkyl. In a further aspect $R^{9'}$ is hydroxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkyl or bis(C_{1-4}alkyl)aminoC_{1-4}alkyl.

In one aspect of the invention $R^{10'}$, $R^{15'}$ and R^{16} are each independently hydrogen, methyl or ethyl.

A preferred class of compounds is of formula (I) wherein:

X is NR^6;

R^6 is hydrogen or methyl;

R^1 is hydrogen, halo, or $-X^1R^{11}$;

X^1 is a direct bond, -O-, -NH- or $-N(C_{1-4}alkyl)-$;

R^{11} is hydrogen or a group selected from C_{1-6}alkyl, heterocyclyl, heterocyclylC_{1-4}alkyl, heterocyclylC_{2-4}alkenyl and heterocyclylC_{2-4}alkynyl which group is optionally substituted by a substituent selected from hydroxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, amino, C_{1-4}alkylamino, bis(C_{1-4}alkyl)amino, hydroxycarbonyl, C_{1-4}alkoxycarbonyl, hydroxyC_{1-4}alkylcarbonyl, C_{1-4}alkoxyC_{1-4}alkylcarbonyl, aminoC_{1-4}alkylcarbonyl, C_{1-4}alkylaminoC_{1-4}alkylcarbonyl and bis(C_{1-4}alkyl)aminoC_{1-4}alkylcarbonyl;

R^2 is hydrogen, halo, nitro, cyano or $-X^2R^{12}$;

X^2 is a direct bond, -O- or –OC(O)-;

R^{12} is hydrogen or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, aryl, arylC_{1-4}alkyl, heterocyclyl and heterocyclylC_{1-4}alkyl, which group is optionally substituted by 1, 2 or 3 substituents selected from halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, $-NR^{15}R^{16}$, $-NHC(O)NR^{15}R^{16}$, $-C(O)R^{15}$ and $-C(O)OR^{15}$;

R^3 is hydrogen or $-X^3R^{13}$;

X^3 is a direct bond, $-CH_2=CH_2-$, -O-, -NH- or $-N(C_{1-6}alkyl)-$;

R^{13} is hydrogen or a group selected from C_{1-6}alkyl, aryl, arylC_{1-4}alkyl, heterocyclyl and heterocyclylC_{1-4}alkyl, which group is optionally substituted by 1 or 2 substituents independently selected from $-NR^7R^8$, $-C(O)NR^7R^8$, halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, hydroxyC_{1-4}alkylcarbonyl and C_{1-4}alkylcarbonyl;

R^7 and R^8 are independently selected from hydrogen, heterocyclyl, heterocyclylC_{1-4}alkyl, C_{1-4}alkylheterocyclylC_{1-4}alkyl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-4}alkyl, hydroxyC_{3-6}cycloalkyl, hydroxyC_{1-4}alkylC_{3-6}cycloalkyl, haloC_{1-6}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, cyanoC_{1-4}alkyl, aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkyl, bis(C_{1-4}alkyl)aminoC_{1-4}alkyl, hydroxyC_{1-4}alkoxyC_{1-4}alkyl and hydroxyC_{1-4}alkylcarbonyl; or R^7 and R^8 together with the nitrogen to which they are attached form a heterocyclic ring selected from azetidine, pyrrolidine, piperidine, morpholine, piperazine, diazepane, 1,4-diazepane and

azabicyclo[3.1.0]hexane which ring is optionally substituted on carbon or nitrogen by 1 or 2 substituents independently selected from C_{1-4}alkyl, hydroxy, hydroxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl and hydroxyC_{1-4}alkylcarbonyl, and where a ring $-CH_2-$ is optionally replaced with –C(O)-;

R^4 is hydrogen;

R^5 is aryl optionally substituted by 1 or 2 halo;

R^{15} and R^{16} are each independently hydrogen, methyl or ethyl; and

R^{19} is hydrogen, hydroxycarbonyl, C_{1-4}alkoxycarbonyl, aminocarbonyl or C_{1-4}alkanoylamino.

Another preferred class of compounds is of formula (I) wherein:

X is NH;

R^1 is hydrogen, halo or $-OR^{11}$;

R^{11} is hydrogen or a group selected from C_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-4}alkyl, which group is optionally substituted by a substituent selected from hydroxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, hydroxyC_{1-4}alkylcarbonyl, aminoC_{1-4}alkylcarbonyl, C_{1-4}alkylaminoC_{1-4}alkylcarbonyl and bis(C_{1-4}alkyl)aminoC_{1-4}alkylcarbonyl;

R^2 is hydrogen, halo, $-OR^{12}$ or $-OC(O)R^{12}$;

R^{12} is hydrogen or a group selected from C_{1-4}alkyl, aryl, heterocyclyl and heterocyclylC_{1-4}alkyl which group is optionally substituted by a substituent selected from C_{1-4}alkyl and C_{1-4}alkoxy;

R^3 is hydrogen or $-X^3R^{13}$;

X^3 is a direct bond or -O-;

R^{13} is hydrogen, methyl, ethyl, propyl or piperidinyl which methyl, ethyl or propyl are substituted by chloro, 1 or 2 hydroxy, 1 or 2 methoxy, $-NR^7R^8$ or a heterocyclyl selected from pyrrolidinyl and piperidinyl which heterocyclyl is optionally substituted by hydroxy, methyl, hydroxymethyl, 2-hydroxyethyl or glycoloyl;

R^7 and R^8 are independently selected from hydrogen, heterocyclyl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, hydroxyC_{1-4}alkylC_{3-6}cycloalkyl, C_{1-4}alkoxyC_{1-4}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-4}alkyl, haloC_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, cyanoC_{1-4}alkyl and bis(C_{1-4}alkyl)aminoC_{1-6}alkyl; or R^7 and R^8 together with the nitrogen to which they are attached form a heterocyclic ring which ring comprises 4 to 7 ring atoms of which one is nitrogen and of which another is optionally NH and which ring is optionally substituted on carbon or nitrogen by a group selected from C_{1-4}alkyl, hydroxy, hydroxyC_{1-4}alkyl hydroxyC_{1-4}alkoxyC_{1-4}alkyl and where a ring $-CH_2-$ is optionally replaced with –C(O)-;

R^4 is hydrogen;

R^5 is phenyl optionally substituted by 1 or 2 fluoro; and

R^{19} is hydrogen, hydroxycarbonyl, ethoxycarbonyl, aminocarbonyl and acetylamino.

A further preferred class of compounds is of formula (I) wherein:

X is NH;

R^1 is hydrogen, fluoro, hydroxy, methoxy, isopropoxy, pyrrolidin-2-ylmethoxy, 1-(2-hydroxyethyl)pyrrolidin-2-ylmethoxy, 1-glycoloylpyrrolidin-2-ylmethoxy, 1-(N,N-dimethylglycyl)pyrrolidin-2-ylmethoxy, 2-(5-hydroxymethyl-2-oxo-pyrrolidin-1-yl)ethoxy, 3-(5-hydroxymethyl-2-oxo-pyrrolidin-1-yl)propoxy, 2-(6-hydroxymethyl-2-oxo-piperazin-1-yl)ethoxy, 3-(6-hydroxymethyl-2-oxo-piperazin-1-yl)propoxy, 2-(5-hydroxymethyl-3-oxo-piperazin-1-yl)ethoxy or 3-(5-hydroxymethyl-3-oxo-piperazin-1-yl)propoxy;

R^2 is hydrogen, fluoro, hydroxy, methoxy, 2-methoxyethoxy, benzoyloxy, 2-morpholin-4-ylethoxy, 3-morpholin-4-ylpropoxy or 1-methylpyrrolidin-2-yloxy;

R^3 is hydrogen, hydroxy, methoxy, 3-chloropropoxy, 2-chloroethoxy, 2,2-dimethoxyethoxy, 3-[2-(hydroxymethyl)pyrrolidin-1-yl]propoxy, 3-[(2-hydroxyethyl)(isobutyl)amino]propoxy, 3-[(2-hydroxyethyl)(propyl)amino]propoxy, 3-piperidin-1-ylpropoxy, 3-pyrrolidin-1-ylpropoxy, 3-(diethylamino)propoxy, 3-piperazin-1-ylpropoxy, 3-[(2-hydroxyethyl)(methyl)amino]propoxy, 3-(cyclopropylamino)propoxy, 3-{[2-(dimethylamino)ethyl](methyl)amino}propoxy, 3-(4-methylpiperazin-1-yl)propoxy, 3-(4-hydroxypiperidin-1-yl)propoxy, 3-[bis(2-hydroxyethyl)amino]propoxy, 3-[ethyl(methyl)amino]propoxy, 3-[ethyl(2-hydroxyethyl)amino]propoxy, 3-{[2-(dimethylamino)ethyl](ethyl)amino}propoxy, 3-[2-(2-hydroxyethyl)piperidin-1-yl]propoxy, 3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy, 3-[(cyclopropylmethyl)amino]propoxy, 3-[4-(2-hydroxyethyl)piperidin-1-yl]propoxy, 3-[methyl(prop-2-yn-1-yl)amino]propoxy, 3-[allyl(methyl)amino]propoxy, 3-[isobutyl(methyl)amino]propoxy, 3-(3-hydroxypiperidin-1-yl)propoxy, 3-[4-(hydroxymethyl)piperidin-1-yl]propoxy, 3-[methyl(propyl)amino]propoxy, 3-[cyclopropylmethyl(propyl)amino]propoxy, 3-{[2-(diethylamino)ethyl](methyl)amino}propoxy, 3-{[2-(diethylamino)ethyl](ethyl)amino}propoxy, 3-(4-methyl-1,4-diazepan-1-yl)propoxy, 3-[(2-hydroxyethyl)(isopropyl)amino]propoxy, 3-[cyclopropyl(2-hydroxyethyl)amino]propoxy, 3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy, 3-[cyclobutyl(2-hydroxyethyl)amino]propoxy, 3-[cyclopropylmethyl(2-hydroxyethyl)amino]propoxy, 3-

[cyclobutylmethyl(2-hydroxyethyl)amino]propoxy, 3-[(2-hydroxy)prop-2-yn-1-lyamino]propoxy, 3-[allyl(2-hydroxyethyl)amino]propoxy, 3-[(2,2-dimethylpropyl(2-hydroxyethyl)amino]propoxy, 3-[(2-hydroxyethyl)(3,3,3-trifluoropropyl)amino]propoxy, 3-azetidin-1-ylpropoxy, 3-(dimethylamino)propoxy, 2-[(2-hydroxymethyl)pyrrolidin-1-yl]ethoxy, 2-{4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl}ethoxy, 2-[2-(2-hydroxyethyl)piperidin-1-yl]ethoxy, 2-[2-(hydroxymethyl)piperidin-1-yl]ethoxy, 2-[(2-hydroxy-1,1-dimethylethyl)amino]ethoxy, 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethoxy, 2-[(4-hydroxycyclohexyl)amino]ethoxy, 2-[3-(hydroxymethyl)piperidin-1-yl]ethoxy, 2-{[1-(hydroxymethyl)cyclopentyl]amino}ethoxy, 2-[4-(3-hydroxypropyl)piperazin-1-yl]ethoxy, 2-[cyclohexyl(2-hydroxyethyl)amino]ethoxy, 2-[(2-hydroxyethyl)(propyl)amino]ethoxy, 2-[(3-hydroxy-2,2-dimethylpropyl)amino]ethoxy, 2-tetrahydro-2*H*-pyran-4-ylamino)ethoxy, 2-[cyclobutyl(2-hydroxyethyl)amino]ethoxy, 2-[(2-hydroxyethyl)(tetrahydro-2*H*-pyran-4-yl)amino]ethoxy, 3-[cyclopentyl(2-hydroxyethyl)amino]propoxy, 3-[(3-hydroxy-1,1-dimethylpropyl)amino]propoxy, 3-[(2-cyanoethyl)(2-hydroxyethyl)amino]propoxy, 3-morpholin-4-ylpropoxy, 3-[(3-hydroxy-2,2-dimethylpropyl)amino]propoxy, 3-[(3-hydroxypropyl)amino]propoxy, 3-[(3-hydroxypropyl)(propyl)amino]propoxy, 3-[(3-hydroxypropyl)(ethyl)amino]propoxy, 3-[4-(2-hydroxyethyl)-3-oxopiperazin-1-yl]propoxy, 3-(propylamino)propoxy, 3-[glycoloyl(propyl)amino]propoxy, 3-(4-glycoloylpiperazin-1-yl)propoxy, 3-{[2-(hydroxymethyl)cyclohexyl]amino}propoxy, 3-[{1α,5α,6α)-6-(hydroxymethyl)-3-azabicyclo[3.1.0]hex-3-yl]propoxy, 3-{[2-hydroxypropyl]amino}propoxy, 3-{[2-hydroxy-1-methylethyl]amino}propoxy, 3-[(2-hydroxy-1,1-dimethylethyl)amino]propoxy, 3-[(2,3-dihydroxypropyl)amino]propoxy, 3-{[2-(2-hydroxyethoxy)ethyl]amino}propoxy, 3-(4-acetylpiperazin-1-yl)propoxy, 3-[(tetrahydrofuran-2-ylmethyl)amino]propoxy, 3-(allylamino)propoxy, 3-{[1-(hydroxymethyl)-2-methylpropyl]amino}propoxy, 3-{[(5-methylisoxazol-3-yl)methyl]amino}propoxy, 3-(tetrahydro-2*H*-pyran-4-ylamino)propoxy, 3-[3-(hydroxymethyl)pyrrolidin-1-yl]propoxy, 3-aminopropoxy, 3-[-4-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy, 2-(cyclopropylamino)ethoxy, 2-(cyclobutylamino)ethoxy, 2-(cyclopentylamino)ethoxy, 2-[{2-hydroxyethyl)(tetrahydro-2*H*-pyran-4-yl)amino]ethoxy, 2-[cyclopentyl(2-hydroxyethyl)amino]ethoxy, 2-[cyclopropyl(2-hydroxyethyl)amino]ethoxy, 2-[cyclopentyl(3-hydroxypropyl)amino]ethoxy, 2-[cyclopentyl(glycoloyl)amino]ethoxy, 2-[3-(hydroxymethyl)-4-methylpiperazin-1-yl]ethoxy, 2-[2-(hydroxymethyl)-4-methylpiperazin-1-yl]ethoxy, 2-[4-

(hydroxymethyl)piperidin-1-yl]ethoxy, 2-[4-(2-hydroxyethyl)piperidin-1-yl]ethoxy, 2-[(2-hydroxyethyl)amino]ethoxy, 2-{[2-(hydroxymethyl)cyclohexyl]amino}ethoxy, 3-[(2-hydroxyethyl)amino]propoxy, 3-[(2-hydroxyethyl)(tetrahydrofuran-3-yl)amino]propoxy, pyrrolidin-2-ylmethoxy, [1-(2-hydroxyethyl)pyrrolidin-2-yl]methoxy, [1-glycoloyopyrrolidin-2-yl]methoxy, pyrrolidin-3-ylmethoxy, [1-(2-hydroxyethyl)pyrrolidin-3-yl]methoxy, (1-glycoloylpyrrolidin-3-yl)methoxy, 3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy, (2-hydroxyethyl)amino]propoxy, 2-(5-hydroxymethyl-2-oxo-pyrrolidin-1-yl)ethoxy, 3-(5-hydroxymethyl-2-oxo-pyrrolidin-1-yl)propoxy, 2-(6-hydroxymethyl-2-oxo-piperazin-1-yl)ethoxy, 3-(6-hydroxymethyl-2-oxo-piperazin-1-yl)propoxy, 2-(5-hydroxymethyl-3-oxo-piperazin-1-yl)ethoxy, 3-(5-hydroxymethyl-3-oxo-piperazin-1-yl)propoxy, 3-(3-hydroxymethyl-4-methylpiperazin-1yl)propoxy, 3-(2-hydroxymethylmorpholin-4-yl)propoxy, 3-(glycoloylamino)propoxy or 3-(4-hydroxymethylpiperazin-1-yl)propoxy;

R^4 is hydrogen;

R^5 is 2,3-difluorophenyl, 3-fluorophenyl, 2-fluorophenyl or 2,6-difluorophenyl; and

R^{19} is hydrogen, hydroxycarbonyl, ethoxycarbonyl, aminocarbonyl and acetylamino.

A preferred class of compounds is of formula (I) wherein:

X is NR^6;

R^6 is hydrogen or methyl;

R^1 is hydrogen, halo or $-OR^{11}$;

R^{11} is hydrogen, heterocyclyl selected from piperidinyl or pyrrolidinyl, C_{1-4}alkyl optionally substituted by hydroxy, C_{1-4}alkoxy, amino, C_{1-4}alkylamino or bis(C_{1-4}alkyl)amino;

R^2 is hydrogen or $-OR^{12}$;

R^{12} is hydrogen, C_{1-4}alkyl (optionally substituted by heterocyclyl) or heterocyclyl;

R^3 is $-X^3R^{13}$;

X^3 is $-CH_2=CH_2-$, -O- or -NH-;

R^{13} is C_{1-6}alkyl substituted by $-NR^7R^8$, heterocyclyl or halo;

R^7 and R^8 are independently selected from hydrogen, heterocyclyl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, hydroxyC_{1-4}alkylC_{3-6}cycloalkyl, C_{1-3}alkoxyC_{1-4}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-3}alkyl, haloC_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, cyanoC_{1-4}alkyl and bis(C_{1-3}alkyl)aminoC_{1-6}alkyl; or R^7 and R^8 together with the nitrogen to which they are attached form a heterocyclic ring which ring comprises 4 to 7 ring atoms of which one is nitrogen and of which another is optionally NH and which ring is optionally substituted on carbon or nitrogen by a group

selected from C_{1-4}alkyl, hydroxy, hydroxyC_{1-4}alkyl and hydroxyC_{1-4}alkoxyC_{1-4}alkyl, and where a ring -CH_2- is optionally replaced with –C(O)-;

R^4 is hydrogen; and

R^5 is aryl optionally substituted by 1 or 2 halo.

A further preferred class of compounds is of formula (I) wherein:

X is NH;

R^1 is hydrogen;

R^2 is hydrogen or methoxy;

R^3 is $-X^3R^{13}$;

X^3 is -O-;

R^{13} is propyl substituted by chloro or $-NR^7R^8$;

R^7 and R^8 are independently selected from hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl, hydroxymethyl, 2-hydroxyethyl, 3-hydroxy-1,1-dimethylpropyl, methoxymethyl, 2-methoxyethyl, 2-ethoxyethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, allyl, propargyl, 2-(dimethylamino)ethyl and 2-(diethylamino)ethyl; or R^7 and R^8 together with the nitrogen to which they are attached form a heterocyclic ring selected from pyrrolidinyl, piperidinyl, piperazinyl, diazepanyl and azetidinyl where the ring is optionally substituted by hydroxy, methyl, hydroxymethyl or 2-hydroxyethyl;

R^4 is hydrogen; and

R^5 is 2,3-difluorophenyl or 3-fluorophenyl.

A preferred class of compounds is of formula (IA) wherein:

X is NR^6;

R^6 is hydrogen or methyl;

$R^{1'}$ is hydrogen, halo, or $-X^1R^{11'}$;

X^1 is a direct bond, -O-, -NH- or –N(C_{1-4}alkyl)-;

$R^{11'}$ is hydrogen, phosphonooxy or a group selected from C_{1-6}alkyl, heterocyclyl, heterocyclylC_{1-4}alkyl, heterocyclylC_{2-4}alkenyl and heterocyclylC_{2-4}alkynyl which group is optionally substituted by a substituent selected from hydroxy, phosphonooxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkyl, amino, C_{1-4}alkylamino, bis(C_{1-4}alkyl)amino, hydroxycarbonyl, C_{1-4}alkoxycarbonyl, hydroxyC_{1-4}alkylcarbonyl, phosphonooxyC_{1-}

$_4$alkylcarbonyl, C_{1-4}alkoxyC_{1-4}alkylcarbonyl, aminoC_{1-4}alkylcarbonyl, C_{1-4}alkylaminoC_{1-4}alkylcarbonyl and bis(C_{1-4}alkyl)aminoC_{1-4}alkylcarbonyl;

$R^{2'}$ is hydrogen, halo, nitro, cyano or $-X^2R^{12'}$;

X^2 is a direct bond, -O- or –OC(O)-;

$R^{12'}$ is hydrogen, phosphonooxy or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, aryl, arylC_{1-4}alkyl, heterocyclyl and heterocyclylC_{1-4}alkyl, which group is optionally substituted by 1, 2 or 3 substituents selected from halo, hydroxy, phosphonooxy, C_{1-4}alkyl, C_{1-4}alkoxy, $-NR^{15'}R^{16'}$, $-NHC(O)NR^{15'}R^{16'}$, $-C(O)R^{15'}$ and $-C(O)OR^{15'}$;

$R^{3'}$ is hydrogen, phosponooxy or $-X^3R^{13'}$;

X^3 is a direct bond, $-CH_2=CH_2-$, -O-, -NH- or $-N(C_{1-6}alkyl)-$;

$R^{13'}$ is hydrogen or a group selected from C_{1-6}alkyl, aryl, arylC_{1-4}alkyl, heterocyclyl and heterocyclylC_{1-4}alkyl, which group is optionally substituted by 1 or 2 substituents independently selected from $-NR^{7'}R^{8'}$, $-C(O)NR^{7'}R^{8'}$, halo, hydroxy, phosphonooxy, C_{1-4}alkyl, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkyl, hydroxyC_{1-4}alkylcarbonyl, phosphonooxyC_{1-4}alkylcarbonyl and C_{1-4}alkylcarbonyl;

$R^{7'}$ and $R^{8'}$ are independently selected from hydrogen, heterocyclyl, heterocyclylC_{1-4}alkyl, C_{1-4}alkylheterocyclylC_{1-4}alkyl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, phosphonooxyC_{1-6}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-4}alkyl, hydroxyC_{3-6}cycloalkyl, phosphonooxyC_{3-6}cycloalkyl, hydroxyC_{1-4}alkylC_{3-6}cycloalkyl, phosphonooxyC_{1-4}alkylC_{3-6}cycloalkyl, haloC_{1-6}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, cyanoC_{1-4}alkyl, aminoC_{1-4}alkyl, bis(C_{1-4}alkyl)aminoC_{1-4}alkyl, hydroxyC_{1-4}alkoxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkylcarbonyl and phosphonooxyC_{1-4}alkylcarbonyl; or $R^{7'}$ and $R^{8'}$ together with the nitrogen to which they are attached form a heterocyclic ring selected from azetidine, pyrrolidine, piperidine, morpholine, piperazine, diazepane, 1,4-diazepane and azabicyclo[3.1.0]hexane which ring is optionally substituted on carbon or nitrogen by 1 or 2 substituents independently selected from C_{1-4}alkyl, hydroxy, phosphonooxy, hydroxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkoxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl, hydroxyC_{1-4}alkylcarbonyl and phosphonooxyC_{1-4}alkylcarbonyl, and where a ring $-CH_2-$ is optionally replaced with –C(O)-;

R^4 is hydrogen;

R^5 is aryl optionally substituted by 1 or 2 halo;

$R^{15'}$ and $R^{16'}$ are each independently hydrogen, methyl or ethyl; and

R^{19} is hydrogen, hydroxycarbonyl, C_{1-4}alkoxycarbonyl, aminocarbonyl or C_{1-4}alkanoylamino;

provided that a compound of formula (IA) contains one phosponooxy group.

Another preferred class of compounds is of formula (IA) wherein:

X is NH;

$R^{1'}$ is hydrogen, halo or $-OR^{11'}$;

$R^{11'}$ is hydrogen, phosphonooxy or a group selected from C_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-4}alkyl, which group is optionally substituted by a substituent selected from hydroxy, phosphonooxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkyl, hydroxyC_{1-4}alkylcarbonyl, phosphonooxyC_{1-4}alkylcarbonyl, aminoC_{1-4}alkylcarbonyl, C_{1-4}alkylaminoC_{1-4}alkylcarbonyl and bis(C_{1-4}alkyl)aminoC_{1-4}alkylcarbonyl;

$R^{2'}$ is hydrogen, halo, $-OR^{12'}$ or $-OC(O)R^{12'}$;

$R^{12'}$ is hydrogen, phosphonooxy or a group selected from C_{1-4}alkyl, aryl, heterocyclyl and heterocyclylC_{1-4}alkyl which group is optionally substituted by a substituent selected from C_{1-4}alkyl and C_{1-4}alkoxy;

$R^{3'}$ is hydrogen, phosponooxy or $-X^3R^{13'}$;

X^3 is a direct bond or -O-;

$R^{13'}$ is methyl, ethyl or propyl substituted by chloro, 1 or 2 hydroxy, 1 phosphonooxy, 1 or 2 methoxy, $-NR^{7'}R^{8'}$ or a heterocyclyl selected from pyrrolidinyl and piperidinyl which heterocyclyl is optionally substituted by hydroxy, phosphonooxy, methyl, hydroxymethyl, phosphonooxymethyl, 2-hydroxyethyl, 2-phosphonooxyethyl, glycoloyl or phosphonooxymethylcarbonyl;

$R^{7'}$ and $R^{8'}$ are independently selected from hydrogen, heterocyclyl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, phosphonooxyC_{1-6}alkyl, hydroxyC_{1-4}alkylC_{3-6}cycloalkyl, phosphonooxyC_{1-4}alkylC_{3-6}cycloalkyl, C_{1-4}alkoxyC_{1-4}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-4}alkyl, haloC_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, cyanoC_{1-4}alkyl, aminoC_{1-6}alkyl, C_{1-4}alkylaminoC_{1-6}alkyl and bis(C_{1-4}alkyl)aminoC_{1-6}alkyl; or $R^{7'}$ and $R^{8'}$ together with the nitrogen to which they are attached form a heterocyclic ring which ring comprises 4 to 7 ring atoms of which one is nitrogen and of which another is optionally NH and which ring is optionally substituted on carbon or nitrogen by a group 1 or 2 substituents independently selected from C_{1-4}alkyl, hydroxy, phosphonooxy, hydroxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkyl, hydroxyC_{1-4}alkoxyC_{1-4}alkyl and phosphonooxyC_{1-4}alkoxyC_{1-4}alkyl, and where a ring $-CH_2-$ is optionally replaced with –C(O);

R^4 is hydrogen;

R^5 is phenyl optionally substituted by 1 or 2 fluoro; and

R^{19} is hydrogen, hydroxycarbonyl, ethoxycarbonyl, aminocarbonyl and acetylamino;

provided that a compound of formula (IA) contains one phosponooxy group.

A further preferred class of compounds is of formula (IA) wherein:

X is NH;

$R^{1'}$ is hydrogen, fluoro, hydroxy, phosphonooxy, methoxy, isopropoxy, pyrrolidin-2-ylmethoxy, 1-(2-hydroxyethyl)pyrrolidin-2-ylmethoxy, 1-(2-phosphonooxyethyl)pyrrolidin-2-ylmethoxy, 1-glycoloylpyrrolidin-2-ylmethoxy, 1-phosponooxymethylcarbonylpyrrolidin-2-ylmethoxy, 1-(N,N-dimethylglycyl)pyrrolidin-2-ylmethoxy, 2-(5-hydroxymethyl-2-oxo-pyrrolidin-1-yl)ethoxy, 2-(5-phosphonooxymethyl-2-oxo-pyrrolidin-1-yl)ethoxy, 3-(5-hydroxymethyl-2-oxo-pyrrolidin-1-yl)propoxy, 3-(5-phosphonooxymethyl-2-oxo-pyrrolidin-1-yl)propoxy, 2-(6-hydroxymethyl-2-oxo-piperazin-1-yl)ethoxy, 2-(6-phosphonooxymethyl-2-oxo-piperazin-1-yl)ethoxy, 3-(6-hydroxymethyl-2-oxo-piperazin-1-yl)propoxy, 3-(6-phosphonooxymethyl-2-oxo-piperazin-1-yl)propoxy, 2-(5-hydroxymethyl-3-oxo-piperazin-1-yl)ethoxy, 2-(5-phosphonooxymethyl-3-oxo-piperazin-1-yl)ethoxy, 3-(5-hydroxymethyl-3-oxo-piperazin-1-yl)propoxy or 3-(5-phosphonooxymethyl-3-oxo-piperazin-1-yl)propoxy;

$R^{2'}$ is hydrogen, fluoro, hydroxy, phosphonooxy, methoxy, 2-methoxyethoxy, benzoyloxy, 2-morpholin-4-ylethoxy, 3-morpholin-4-ylpropoxy or 1-methylpyrrolidin-2-yloxy.

$R^{3'}$ is hydrogen, phosponooxy or $-X^3R^{13'}$;

X^3 is a direct bond or -O-;

$R^{13'}$ is methyl, ethyl or propyl substituted by chloro, 1 or 2 hydroxy, 1 phosphonooxy, 1 or 2 methoxy, $-NR^{7'}R^{8'}$ or a heterocyclyl selected from pyrrolidinyl and piperidinyl which heterocyclyl is optionally substituted by hydroxy, phosphonooxy, methyl, hydroxymethyl, phosphonooxymethyl, 2-hydroxyethyl, 2-phosphonooxyethyl, glycoloyl or phosphonooxymethylcarbonyl;

$R^{7'}$ and $R^{8'}$ are independently selected from hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl, hydroxymethyl, phosphonooxymethyl, 2-hydroxyethyl, 2-phosphonooxyethyl, 2-hydroxy-1,1-dimethylethyl, 2-phosphonooxy-1,1-dimethylethyl, 3-hydroxypropyl, 3-phosphonooxypropyl, 3-hydroxy-2,2-dimethylpropyl, 3-phosphonooxy-2,2-dimethylpropyl, 3-hydroxy-1,1-dimethylpropyl, 3-phosphonooxy-1,1-dimethylpropyl, 2-hydroxypropyl, 2-phosphonooxypropyl, 2,3-dihydroxypropyl, 2-hydroxy-3-phosphonooxypropyl, 2-phosphonooxy-3-hydroxypropyl, 1-hydroxymethyl-2-methylpropyl, 1-phosphonooxymethyl-2-methylpropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-

hydroxycyclohexyl, 4-phosphonooxycyclohexyl, 1-hydroxymethylcyclopentyl, 1-phosphonooxymethylcyclopentyl, 2-hydroxymethylcyclohexyl, 2-phosphonooxymethylcyclohexyl, cyclopropylmethyl, cyclobutylmethyl, tetrahydro-2H-pyran-4-yl, tetrahydrofuran-3-yl, tetrahydrofuran-2-ylmethyl, 5-methylisoxazol-3-yl, 2-cyanoethyl, allyl, prop-2-ynyl, 2-methoxyethyl, methoxymethyl, 3,3,3-trifluoropropyl, 2-(2-hydroxyethoxy)ethyl, 2-(2-phosphonooxyethoxy)ethyl, 2-(dimethylamino)ethyl, 2-(diethylamino)ethyl, 3-aminopropyl, 3-(propylamino)propyl, glycoloyl and phosphonooxymethylcarbonyl; or $R^{7'}$ and $R^{8'}$ together with the nitrogen to which they are attached form a heterocyclic ring selected from azetidine, pyrrolidine, piperidine, morpholine, piperazine, diazepane or 1,4-diazepane which ring is optionally substituted by 1 or 2 substituents independently selected from methyl, hydroxy, phosphonooxy, hydroxymethyl, phosphonooxymethyl, 2-hydroxyethyl, 2-phosphonooxyethyl, 3-hydroxypropyl, 3-phosphonooxypropyl, 2-(2-hydroxyethoxy)ethyl, 2-(2-phosphonooxyethyl)ethyl, glycoloyl, phosphonooxymethylcarbonyl, acetyl, methoxymethyl and oxo.

R^4 is hydrogen;

R^5 is 2,3-difluorophenyl, 3-fluorophenyl, 2-fluorophenyl or 2,6-difluorophenyl; and

R^{19} is hydrogen, hydroxycarbonyl, ethoxycarbonyl, aminocarbonyl and acetylamino;

provided that a compound of formula (IA) contains one phosponooxy group.

A preferred class of compounds is of formula (IA) wherein:

X is NR^6;

R^6 is hydrogen or methyl;

R^1 is hydrogen or $-OR^{11}$;

R^{11} is hydrogen, heterocyclyl selected from piperidinyl or pyrrolidinyl, C_{1-4}alkyl optionally substituted by hydroxy, C_{1-4}alkoxy, amino, C_{1-4}alkylamino or bis(C_{1-4}alkyl)amino;

R^2 is hydrogen or $-OR^{12}$;

R^{12} is hydrogen, C_{1-4}alkyl (optionally substituted with heterocyclyl) or heterocyclyl;

$R^{3'}$ is $-X^{3'}R^{13'}$;

$X^{3'}$ is $-CH_2=CH_2-$, -O- or -NH-;

$R^{13'}$ is C_{1-6}alkyl substituted by $-NR^{7'}R^{8'}$;

$R^{7'}$ is selected from hydrogen, heterocyclyl, C_{1-6}alkyl, C_{1-3}alkoxyC_{1-6}alkyl, cyanoC_{1-4}alkyl and C_{3-6}cycloalkyl;

$R^{8'}$ is phosphonooxyC_{1-4}alkyl or phosphonooxyC_{1-4}alkylC_{3-6}cycloalkyl;

or $R^{7'}$ and $R^{8'}$ together with the nitrogen to which they are attached form a heterocyclic ring selected from pyrrolidinyl, piperidinyl and piperazinyl which ring is substituted on carbon or nitrogen by a group selected from phosphonooxy, phosponooxymethyl and 2-phoshonooxyethyl;

R^4 is hydrogen; and

R^5 is aryl optionally substituted by 1 or 2 halo.

A further preferred class of compounds is of formula (IA) wherein:

X is NH;

R^1 is hydrogen;

R^2 is hydrogen or methoxy;

$R^{3'}$ is $-X^{3'}R^{13'}$;

$X^{3'}$ is -O-;

$R^{13'}$ is propyl substituted by $-NR^{7'}R^{8'}$;

$R^{7'}$ is ethyl, propyl, cyclobutyl or 2-methoxyethyl;

$R^{8'}$ is 2-phosphonooxyethyl or 1,1-dimethyl-3-phosphonooxypropyl;

or $R^{7'}$ and $R^{8'}$ together with the nitrogen to which they are attached form a heterocyclic ring selected from pyrrolidinyl, piperidinyl and piperazinyl which ring is substituted on carbon or nitrogen by a group selected from phosphonooxy, phosponooxymethyl and 2-phoshonooxyethyl;

R^4 is hydrogen; and

R^5 is 2,3-difluorophenyl or 3-fluorophenyl.

A particular compound of formula (I) is any one of:

2-(4-{[7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide;

2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide;

2-(4-{[7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide;

2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide;

2-(4-{[7-(2-chloroethoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide;

2-(4-{[7-(2-chloroethoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(2,2-dimethoxyethoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

4-{[7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl]amino}-1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazole-3-carboxamide;

ethyl 4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazole-3-carboxylate;

2-(3-(acetylamino)-4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-[4-(quinazolin-4-ylamino)-1*H*-pyrazol-1-yl]acetamide;

2-(4-{[7-(3-chloropropoxy)-5-isopropoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide;

2-(4-{[7-(3-chloropropoxy)-5-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide;

2-(4-{[7-(3-chloropropoxy)-6-fluoroquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide;

2-(4-{[7-(3-chloropropoxy)-6-fluoroquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(isobutyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-(4-{[6-methoxy-7-(3-piperidin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(3-fluorophenyl)-2-(4-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

2-[4-({7-[3-(diethylamino)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-(4-{[6-methoxy-7-(3-piperazin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-[4-({7-[3-(cyclopropylamino)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[[2-(dimethylamino)ethyl](methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-[4-({6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-[4-({7-[3-(4-hydroxypiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

2-{4-[(7-{3-[bis(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[ethyl(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[[2-(dimethylamino)ethyl](ethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[2-(2-hydroxyethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[(cyclopropylmethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(6-methoxy-7-{3-[methyl(prop-2-yn-1-yl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[allyl(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[isobutyl(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-[4-({7-[3-(3-hydroxypiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[4-(hydroxymethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(6-methoxy-7-{3-[methyl(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[(cyclopropylmethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[[2-(diethylamino)ethyl](methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[[2-(diethylamino)ethyl](ethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-[4-({6-methoxy-7-[3-(4-methyl-1,4-diazepan-1-yl)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(isopropyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[cyclopropyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[cyclobutyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

- 2-{4-[(7-{3-[(cyclopropylmethyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[(cyclobutylmethyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(prop-2-yn-1-yl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[allyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[(2,2-dimethylpropyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(3,3,3-trifluoropropyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-(4-{[7-(3-azetidin-1-ylpropoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide;

2-{4-[(6,7-dimethoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-hydroxy-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(isobutyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-[4-({7-[3-(dimethylamino)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(2,3-difluorophenyl)-2-(4-{[6-methoxy-7-(3-piperidin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-(4-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-(4-{[6-methoxy-7-(3-piperazin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-[4-({7-[3-(cyclopropylamino)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[[2-(dimethylamino)ethyl](methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-[4-({6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-[4-({7-[3-(4-hydroxypiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

2-{4-[(7-{3-[bis(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[ethyl(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[[2-(dimethylamino)ethyl](ethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[2-(2-hydroxyethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[(cyclopropylmethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(6-methoxy-7-{3-[methyl(prop-2-yn-1-yl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[isobutyl(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-[4-({7-[3-(3-hydroxypiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(hydroxymethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(6-methoxy-7-{3-[methyl(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[(cyclopropylmethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

2-{4-[(7-{3-[[2-(diethylamino)ethyl](methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

2-{4-[(7-{3-[[2-(diethylamino)ethyl](ethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-[4-({6-methoxy-7-[3-(4-methyl-1,4-diazepan-1-yl)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(isopropyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[cyclopropyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[cyclobutyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

2-{4-[(7-{3-[(cyclopropylmethyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

2-{4-[(7-{3-[(cyclobutylmethyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(prop-2-yn-1-yl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[allyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2,2-dimethylpropyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(3,3,3-trifluoropropyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(2-{4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl}ethoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[2-(hydroxymethyl)piperidin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2-hydroxy-1,1-dimethylethyl)amino]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[4-(2-hydroxyethyl)piperazin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(*trans*-4-hydroxycyclohexyl)amino]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[3-(hydroxymethyl)piperidin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(2-{[1-(hydroxymethyl)cyclopentyl]amino}ethoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[4-(3-hydroxypropyl)piperazin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{2-[cyclohexyl(2-hydroxyethyl)amino]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2-hydroxyethyl)(propyl)amino]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(3-hydroxy-2,2-dimethylpropyl)amino]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-[4-({6-methoxy-7-[2-(tetrahydro-2*H*-pyran-4-ylamino)ethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

2-{4-[(7-{2-[cyclobutyl(2-hydroxyethyl)amino]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2-hydroxyethyl)(tetrahydro-2*H*-pyran-4-yl)amino]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2*R*)-2-(2-hydroxyethyl)piperidin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2*S*)-2-(2-hydroxyethyl)piperidin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(isobutyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[cyclopentyl(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(hydroxymethyl)piperidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3-hydroxy-1,1-dimethylpropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[(2-cyanoethyl)(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3-hydroxy-2,2-dimethylpropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3-hydroxypropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3-hydroxypropyl)(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[ethyl(3-hydroxypropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)-3-oxopiperazin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-[4-({7-[3-(propylamino)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(3-piperazin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[glycoloyl(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-[4-({7-[3-(4-glycoloylpiperazin-1-yl)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(3-{[*trans*-2-(hydroxymethyl)cyclohexyl]amino}propoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(1α,5α,6α)-6-(hydroxymethyl)-3-azabicyclo[3.1.0]hex-3-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(3-{[(2*R*)-2-hydroxypropyl]amino}propoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(3-{[(1*S*)-2-hydroxy-1-methylethyl]amino}propoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxy-1,1-dimethylethyl)amino]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2,3-dihydroxypropyl)amino]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(3-{[2-(2-hydroxyethoxy)ethyl]amino}propoxy)quinazolin-4-yl]amino}-1H-pyrazol-1-yl)acetamide;

2-[4-({7-[3-(4-acetylpiperazin-1-yl)propoxy]quinazolin-4-yl}amino)-1H-pyrazol-1-yl]-N-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(tetrahydrofuran-2-ylmethyl)amino]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

2-[4-({7-[3-(allylamino)propoxy]quinazolin-4-yl}amino)-1H-pyrazol-1-yl]-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(3-{[1-(hydroxymethyl)-2-methylpropyl]amino}propoxy)quinazolin-4-yl]amino}-1H-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(3-{[(5-methylisoxazol-3-yl)methyl]amino}propoxy)quinazolin-4-yl]amino}-1H-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-[4-({7-[3-(tetrahydro-2H-pyran-4-ylamino)propoxy]quinazolin-4-yl}amino)-1H-pyrazol-1-yl]acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3S)-3-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(3-hydroxypropoxy)quinazolin-4-yl]amino}-1H-pyrazol-1-yl)acetamide;

2-(4-{[7-(3-aminopropoxy)quinazolin-4-yl]amino}-1H-pyrazol-1-yl)-N-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2S,4R)-4-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(3-hydroxy-2,2-dimethylpropyl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{2-[cyclohexyl(2-hydroxyethyl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

2-[4-({7-[2-(cyclopropylamino)ethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(2,3-difluorophenyl)acetamide;

2-[4-({7-[2-(cyclobutylamino)ethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-[4-({7-[2-(tetrahydro-2*H*-pyran-4-ylamino)ethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

2-[4-({7-[2-(cyclopentylamino)ethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2-hydroxyethyl)(tetrahydro-2*H*-pyran-4-yl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{2-[cyclopentyl(2-hydroxyethyl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{2-[cyclopropyl(2-hydroxyethyl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

2-{4-[(7-{2-[cyclobutyl(2-hydroxyethyl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

2-{4-[(7-{2-[cyclopentyl(3-hydroxypropyl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

2-{4-[(7-{2-[cyclopentyl(glycoloyl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(3*S*)-3-(hydroxymethyl)-4-methylpiperazin-1-yl]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2*R*)-2-(hydroxymethyl)-4-methylpiperazin-1-yl]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[4-(hydroxymethyl)piperidin-1-yl]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[4-(2-hydroxyethyl)piperidin-1-yl]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2-hydroxyethyl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(2-{[*trans*-2-(hydroxymethyl)cyclohexyl]amino}ethoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(tetrahydro-2H-pyran-4-yl)amino]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2R)-2-(2-hydroxyethyl)piperidin-1-yl]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2S)-2-(2-hydroxyethyl)piperidin-1-yl]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2R)-2-(hydroxymethyl)-4-methylpiperazin-1-yl]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3S)-3-(hydroxymethyl)-4-methylpiperazin-1-yl]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2R)-2-(hydroxymethyl)morpholin-4-yl]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3S)-3-(hydroxymethyl)morpholin-4-yl]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-[4-({7-[3-(glycoloylamino)propoxy]quinazolin-4-yl}amino)-1H-pyrazol-1-yl]acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[4-(hydroxymethyl)piperidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(3-hydroxy-1,1-dimethylpropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[2-(2-hydroxyethyl)piperidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(tetrahydrofuran-3-yl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-(4-{[7-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(3-fluorophenyl)-2-[4-({7-[(2*S*)-pyrrolidin-2-ylmethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{[(2*S*)-1-(2-hydroxyethyl)pyrrolidin-2-yl]methoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{[(2*S*)-1-glycoloylpyrrolidin-2-yl]methoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-(4-{[7-(pyrrolidin-3-ylmethoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{[1-(2-hydroxyethyl)pyrrolidin-3-yl]methoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-[4-({7-[(1-glycoloylpyrrolidin-3-yl)methoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-hydroxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2-fluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2-fluorophenyl)acetamide;

2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-phenylacetamide;

2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-phenylacetamide;

N-(2,6-difluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}-6-fluoroquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[(cyclopropylmethyl)(2-hydroxyethyl)amino]propoxy}-6-fluoroquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(6-fluoro-7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(6-fluoro-7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[cyclopentyl(2-hydroxyethyl)amino]propoxy}-6-fluoroquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

2-{4-[(7-{3-[bis(2-hydroxyethyl)amino]propoxy}-5-isopropoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-5-isopropoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy}-5-isopropoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-(4-{[5-isopropoxy-7-(3-piperazin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-5-isopropoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)amino]propoxy}-5-isopropoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-[4-({7-[3-(4-glycoloylpiperazin-1-yl)propoxy]-5-isopropoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-5-methoxy-quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(5,7-dimethoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(5-hydroxy-7-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-[4-({7-methoxy-5-[(2*R*)-pyrrolidin-2-ylmethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(2,3-difluorophenyl)-2-{4-[(5-{[(2*R*)-1-glycoloylpyrrolidin-2-yl]methoxy}-7-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(5-{[(2*R*)-1-(*N*,*N*-dimethylglycyl)pyrrolidin-2-yl]methoxy}-7-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(5-{[(2*R*)-1-(2-hydroxyethyl)pyrrolidin-2-yl]methoxy}-7-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(5-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(5-fluoroquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-(4-{[7-methoxy-6-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(3-fluorophenyl)-2-[4-({7-methoxy-6-[(1-methylpyrrolidin-3-yl)oxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(3-fluorophenyl)-2-(4-{[7-methoxy-6-(2-morpholin-4-ylethoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

2-(4-{[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(6-hydroxy-7-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

4-((1-(2-((2,3-difluorophenyl)amino)-2-oxoethyl)-1*H*-pyrazol-4-yl)amino)-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-6-yl benzoate;

N-(2,3-difluorophenyl)-2-(4-((6-hydroxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-yl)amino)-1*H*-pyrazol-1-yl)acetamide;

1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-4-[(7-{3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazole-3-carboxamide;

1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazole-3-carboxamide;

2-{3-(acetylamino)-4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

ethyl 1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazole-3-carboxylate;

1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazole-3-carboxylic acid;

or a salt, ester or prodrug thereof, or more particularly a pharmaceutically acceptable salt thereof.

A further particular compound of formula (I) is any one of:

2-(4-{[7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide;

2-(4-{[7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide;

2-(4-{[7-(2-chloroethoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide;

4-{[7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl]amino}-1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazole-3-carboxamide;

2-(4-{[7-(3-chloropropoxy)-6-fluoroquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide;

2-(4-{[7-(3-chloropropoxy)-6-fluoroquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(isobutyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-(4-{[6-methoxy-7-(3-piperidin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(3-fluorophenyl)-2-(4-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

2-[4-({7-[3-(diethylamino)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-(4-{[6-methoxy-7-(3-piperazin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-[4-({7-[3-(cyclopropylamino)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[[2-(dimethylamino)ethyl](methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-[4-({6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-[4-({7-[3-(4-hydroxypiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

2-{4-[(7-{3-[bis(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[ethyl(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[[2-(dimethylamino)ethyl](ethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[2-(2-hydroxyethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[(cyclopropylmethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(6-methoxy-7-{3-[methyl(prop-2-yn-1-yl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[allyl(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[isobutyl(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-[4-({7-[3-(3-hydroxypiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[4-(hydroxymethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(6-methoxy-7-{3-[methyl(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[(cyclopropylmethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[[2-(diethylamino)ethyl](methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[[2-(diethylamino)ethyl](ethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-[4-({6-methoxy-7-[3-(4-methyl-1,4-diazepan-1-yl)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(isopropyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[cyclopropyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[cyclobutyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[(cyclopropylmethyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[(cyclobutylmethyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(prop-2-yn-1-yl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[allyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[(2,2-dimethylpropyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(3,3,3-trifluoropropyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-(4-{[7-(3-azetidin-1-ylpropoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide;

2-{4-[(6,7-dimethoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-hydroxy-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(isobutyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-[4-({7-[3-(dimethylamino)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(2,3-difluorophenyl)-2-(4-{[6-methoxy-7-(3-piperidin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-(4-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-(4-{[6-methoxy-7-(3-piperazin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-[4-({7-[3-(cyclopropylamino)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[[2-(dimethylamino)ethyl](methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-[4-({6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-[4-({7-[3-(4-hydroxypiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

2-{4-[(7-{3-[bis(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[ethyl(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[[2-(dimethylamino)ethyl](ethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[2-(2-hydroxyethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[(cyclopropylmethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(6-methoxy-7-{3-[methyl(prop-2-yn-1-yl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[isobutyl(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-[4-({7-[3-(3-hydroxypiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(hydroxymethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(6-methoxy-7-{3-[methyl(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[(cyclopropylmethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

2-{4-[(7-{3-[[2-(diethylamino)ethyl](methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

2-{4-[(7-{3-[[2-(diethylamino)ethyl](ethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-[4-({6-methoxy-7-[3-(4-methyl-1,4-diazepan-1-yl)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(isopropyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[cyclopropyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[cyclobutyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

2-{4-[(7-{3-[(cyclopropylmethyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

2-{4-[(7-{3-[(cyclobutylmethyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(prop-2-yn-1-yl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[allyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2,2-dimethylpropyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(3,3,3-trifluoropropyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(2-{4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl}ethoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[2-(hydroxymethyl)piperidin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2-hydroxy-1,1-dimethylethyl)amino]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[4-(2-hydroxyethyl)piperazin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(*trans*-4-hydroxycyclohexyl)amino]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[3-(hydroxymethyl)piperidin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(2-{[1-(hydroxymethyl)cyclopentyl]amino}ethoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[4-(3-hydroxypropyl)piperazin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{2-[cyclohexyl(2-hydroxyethyl)amino]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2-hydroxyethyl)(propyl)amino]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(3-hydroxy-2,2-dimethylpropyl)amino]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-[4-({6-methoxy-7-[2-(tetrahydro-2*H*-pyran-4-ylamino)ethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

2-{4-[(7-{2-[cyclobutyl(2-hydroxyethyl)amino]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2-hydroxyethyl)(tetrahydro-2*H*-pyran-4-yl)amino]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2*R*)-2-(2-hydroxyethyl)piperidin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2*S*)-2-(2-hydroxyethyl)piperidin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}-6-fluoroquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[(cyclopropylmethyl)(2-hydroxyethyl)amino]propoxy}-6-fluoroquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(6-fluoro-7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(6-fluoro-7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[cyclopentyl(2-hydroxyethyl)amino]propoxy}-6-fluoroquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(3-fluorophenyl)-2-(4-{[7-methoxy-6-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(3-fluorophenyl)-2-[4-({7-methoxy-6-[(1-methylpyrrolidin-3-yl)oxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(3-fluorophenyl)-2-(4-{[7-methoxy-6-(2-morpholin-4-ylethoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

2-(4-{[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(6-hydroxy-7-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

4-((1-(2-((2,3-difluorophenyl)amino)-2-oxoethyl)-1*H*-pyrazol-4-yl)amino)-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-6-yl benzoate;

N-(2,3-difluorophenyl)-2-(4-((6-hydroxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-yl)amino)-1*H*-pyrazol-1-yl)acetamide;

1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-4-[(7-{3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazole-3-carboxamide;

1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazole-3-carboxamide;

or a salt, ester or prodrug thereof, or more particularly a pharmaceutically acceptable salt thereof.

Another particular compound of formula (I) is any one of:

2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide;

2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide;

2-(4-{[7-(2-chloroethoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(2,2-dimethoxyethoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

ethyl 4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazole-3-carboxylate;

2-(3-(acetylamino)-4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-[4-(quinazolin-4-ylamino)-1*H*-pyrazol-1-yl]acetamide;

2-(4-{[7-(3-chloropropoxy)-5-isopropoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide;

2-(4-{[7-(3-chloropropoxy)-5-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(isobutyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[cyclopentyl(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(hydroxymethyl)piperidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3-hydroxy-1,1-dimethylpropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[(2-cyanoethyl)(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3-hydroxy-2,2-dimethylpropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3-hydroxypropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3-hydroxypropyl)(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[ethyl(3-hydroxypropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)-3-oxopiperazin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-[4-({7-[3-(propylamino)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(3-piperazin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[glycoloyl(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-[4-({7-[3-(4-glycoloylpiperazin-1-yl)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(3-{[*trans*-2-(hydroxymethyl)cyclohexyl]amino}propoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-l)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(1α,5α,6α)-6-(hydroxymethyl)-3-azabicyclo[3.1.0]hex-3-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(3-{[(2*R*)-2-hydroxypropyl]amino}propoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(3-{[(1*S*)-2-hydroxy-1-methylethyl]amino}propoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxy-1,1-dimethylethyl)amino]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2,3-dihydroxypropyl)amino]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(3-{[2-(2-hydroxyethoxy)ethyl]amino}propoxy)quinazolin-4-yl]amino}-1H-pyrazol-1-yl)acetamide;

2-[4-({7-[3-(4-acetylpiperazin-1-yl)propoxy]quinazolin-4-yl}amino)-1H-pyrazol-1-yl]-N-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(tetrahydrofuran-2-ylmethyl)amino]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

2-[4-({7-[3-(allylamino)propoxy]quinazolin-4-yl}amino)-1H-pyrazol-1-yl]-N-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(3-{[1-(hydroxymethyl)-2-methylpropyl]amino}propoxy)quinazolin-4-yl]amino}-1H-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(3-{[(5-methylisoxazol-3-yl)methyl]amino}propoxy)quinazolin-4-yl]amino}-1H-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-[4-({7-[3-(tetrahydro-2H-pyran-4-ylamino)propoxy]quinazolin-4-yl}amino)-1H-pyrazol-1-yl]acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3S)-3-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(3-hydroxypropoxy)quinazolin-4-yl]amino}-1H-pyrazol-1-yl)acetamide;

2-(4-{[7-(3-aminopropoxy)quinazolin-4-yl]amino}-1H-pyrazol-1-yl)-N-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2S,4R)-4-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(3-hydroxy-2,2-dimethylpropyl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{2-[cyclohexyl(2-hydroxyethyl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

2-[4-({7-[2-(cyclopropylamino)ethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(2,3-difluorophenyl)acetamide;

2-[4-({7-[2-(cyclobutylamino)ethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-[4-({7-[2-(tetrahydro-2*H*-pyran-4-ylamino)ethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

2-[4-({7-[2-(cyclopentylamino)ethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2-hydroxyethyl)(tetrahydro-2*H*-pyran-4-yl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{2-[cyclopentyl(2-hydroxyethyl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{2-[cyclopropyl(2-hydroxyethyl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

2-{4-[(7-{2-[cyclobutyl(2-hydroxyethyl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

2-{4-[(7-{2-[cyclopentyl(3-hydroxypropyl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

2-{4-[(7-{2-[cyclopentyl(glycoloyl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(3*S*)-3-(hydroxymethyl)-4-methylpiperazin-1-yl]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2*R*)-2-(hydroxymethyl)-4-methylpiperazin-1-yl]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[4-(hydroxymethyl)piperidin-1-yl]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[4-(2-hydroxyethyl)piperidin-1-yl]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2-hydroxyethyl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(2-{[*trans*-2-(hydroxymethyl)cyclohexyl]amino}ethoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

178 - N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(tetrahydro-2H-pyran-4-yl)amino]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2R)-2-(2-hydroxyethyl)piperidin-1-yl]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2S)-2-(2-hydroxyethyl)piperidin-1-yl]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2R)-2-(hydroxymethyl)-4-methylpiperazin-1-yl]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3S)-3-(hydroxymethyl)-4-methylpiperazin-1-yl]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2R)-2-(hydroxymethyl)morpholin-4-yl]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3S)-3-(hydroxymethyl)morpholin-4-yl]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-[4-({7-[3-(glycoloylamino)propoxy]quinazolin-4-yl}amino)-1H-pyrazol-1-yl]acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[4-(hydroxymethyl)piperidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(3-hydroxy-1,1-dimethylpropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[2-(2-hydroxyethyl)piperidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(tetrahydrofuran-3-yl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-(4-{[7-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(3-fluorophenyl)-2-[4-({7-[(2*S*)-pyrrolidin-2-ylmethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{[(2*S*)-1-(2-hydroxyethyl)pyrrolidin-2-yl]methoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{[(2*S*)-1-glycoloylpyrrolidin-2-yl]methoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-(4-{[7-(pyrrolidin-3-ylmethoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{[1-(2-hydroxyethyl)pyrrolidin-3-yl]methoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-[4-({7-[(1-glycoloylpyrrolidin-3-yl)methoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-hydroxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2-Fluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2-fluorophenyl)acetamide;

2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-phenylacetamide;

2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-phenylacetamide;

N-(2,6-difluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[bis(2-hydroxyethyl)amino]propoxy}-5-isopropoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-5-isopropoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy}-5-isopropoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-(4-{[5-isopropoxy-7-(3-piperazin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-5-isopropoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)amino]propoxy}-5-isopropoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-[4-({7-[3-(4-glycoloylpiperazin-1-yl)propoxy]-5-isopropoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-5-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(5,7-dimethoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(5-hydroxy-7-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-[4-({7-methoxy-5-[(2*R*)-pyrrolidin-2-ylmethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(2,3-difluorophenyl)-2-{4-[(5-{[(2*R*)-1-glycoloylpyrrolidin-2-yl]methoxy}-7-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(5-{[(2*R*)-1-(*N*,*N*-dimethylglycyl)pyrrolidin-2-yl]methoxy}-7-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(5-{[(2*R*)-1-(2-hydroxyethyl)pyrrolidin-2-yl]methoxy}-7-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(5-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(5-fluoroquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{3-(acetylamino)-4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

ethyl 1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazole-3-carboxylate;

1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazole-3-carboxylic acid;

or a salt, ester or prodrug thereof, or more particularly a pharmaceutically acceptable salt thereof.

In another aspect a particular compound of formula (IA) is any one of:

2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](propyl)amino]ethyl dihydrogen phosphate;

{(2*S*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

{(2*S*)-1-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

2-{ethyl[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate;

{(2*R*)-1-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](2-methoxyethyl)amino]ethyl dihydrogen phosphate;

{(2*S*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

{(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

{(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](ethyl)amino]ethyl dihydrogen phosphate;

2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](propyl)amino]ethyl dihydrogen phosphate;

2-{cyclobutyl[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate;

2-{cyclobutyl[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate;

2-[[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](2-methoxyethyl)amino]ethyl dihydrogen phosphate;

2-[[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](propyl)amino]ethyl dihydrogen phosphate;

2-{4-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]piperazin-1-yl}ethyl dihydrogen phosphate;

2-{ethyl[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate;

2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](ethyl)amino]ethyl dihydrogen phosphate;

3-{[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]amino}-3-methylbutyl dihydrogen phosphate;

3-{[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]amino}-3-methylbutyl dihydrogen phosphate;

{(2*R*)-1-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

2-{4-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]piperazin-1-yl}ethyl dihydrogen phosphate;

3-{[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]amino}propyl dihydrogen phosphate;

2-{[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate;

2-[[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](2-methoxyethyl)amino]ethyl dihydrogen phosphate;

3-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](ethyl)amino]propyl dihydrogen phosphate;

3-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](propyl)amino]propyl dihydrogen phosphate;

2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](propyl)amino]-2-oxoethyl dihydrogen phosphate;

2-{4-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]piperazin-1-yl}-2-oxoethyl dihydrogen phosphate;

{(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-fluoroquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

4-((1-(2-((2,3-difluorophenyl)amino)-2-oxoethyl)-1*H*-pyrazol-4-yl)amino)-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-6-yl dihydrogen phosphate;

{(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-5-isopropoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

2-{4-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-5-isopropoxyquinazolin-7-yl}oxy)propyl]piperazin-1-yl}ethyl dihydrogen phosphate;

2-{[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-5-isopropoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate;

{(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-5-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

{(2*R*)-1-[2-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)ethyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

{(2*S*)-1-[2-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)ethyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

2-[[2-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)ethyl](tetrahydro-2*H*-pyran-4-yl)amino]ethyl dihydrogen phosphate;

2-{4-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]-2-oxopiperazin-1-yl}ethyl dihydrogen phosphate;

2-[[2-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)ethyl](tetrahydro-2*H*-pyran-4-yl)amino]ethyl dihydrogen phosphate;

or a salt or ester thereof, or more particularly a pharmaceutically acceptable salt thereof.

A further particular compound of formula (IA) is any one of:

2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](propyl)amino]ethyl dihydrogen phosphate;

{(2*S*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

{(2*S*)-1-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

2-{ethyl[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate;

{(2*R*)-1-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](2-methoxyethyl)amino]ethyl dihydrogen phosphate;

{(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyqunazolin-7-yl}oxy)propyl](ethyl)amino]ethyl dihydrogen phosphate;

2-{cyclobutyl[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate;

2-{cyclobutyl[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate;

2-[[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](2-methoxyethyl)amino]ethyl dihydrogen phosphate;

{(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-fluoroquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

4-((1-(2-((2,3-difluorophenyl)amino)-2-oxoethyl)-1*H*-pyrazol-4-yl)amino)-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-6-yl dihydrogen phosphate;

{(2*R*)-1-[2-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)ethyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

{(2*S*)-1-[2-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)ethyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

2-[[2-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)ethyl](tetrahydro-2*H*-pyran-4-yl)amino]ethyl dihydrogen phosphate;

or a salt or ester thereof, or more particularly a pharmaceutically acceptable salt thereof.

Another particular compound of formula (IA) is any one of:

{(2*S*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

{(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](propyl)amino]ethyl dihydrogen phosphate;

2-[[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](propyl)amino]ethyl dihydrogen phosphate;

2-{4-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]piperazin-1-yl}ethyl dihydrogen phosphate;

2-{ethyl[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate;

2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](ethyl)amino]ethyl dihydrogen phosphate;

3-{[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]amino}-3-methylbutyl dihydrogen phosphate;

3-{[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]amino}-3-methylbutyl dihydrogen phosphate;

{(2*R*)-1-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

2-{4-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]piperazin-1-yl}ethyl dihydrogen phosphate;

3-{[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]amino}propyl dihydrogen phosphate;

2-{[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate;

2-[[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](2-methoxyethyl)amino]ethyl dihydrogen phosphate;

3-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](ethyl)amino]propyl dihydrogen phosphate;

3-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](propyl)amino]propyl dihydrogen phosphate;

2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](propyl)amino]-2-oxoethyl dihydrogen phosphate;

2-{4-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]piperazin-1-yl}-2-oxoethyl dihydrogen phosphate;

{(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-5-isopropoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

2-{4-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-5-isopropoxyquinazolin-7-yl}oxy)propyl]piperazin-1-yl}ethyl dihydrogen phosphate;

2-{[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-5-isopropoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate;

{(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-5-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

2-{4-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]-2-oxopiperazin-1-yl}ethyl dihydrogen phosphate;

2-[[2-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)ethyl](tetrahydro-2*H*-pyran-4-yl)amino]ethyl dihydrogen phosphate;

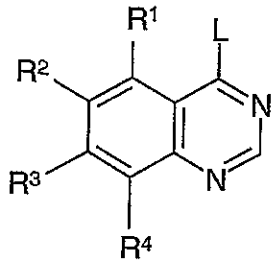
or a salt or ester thereof, or more particularly a pharmaceutically acceptable salt thereof.

In another aspect a compound of the invention is *N*-(3-fluorophenyl)-2-{4-[(7-{2-[(2-hydroxyethyl)(tetrahydro-2*H*-pyran-4-yl)amino]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide or *N*-(3-fluorophenyl)-2-{4-[(7-{2-[(2-hydroxyethyl)(tetrahydro-2*H*-pyran-4-yl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide or a salt, ester or prodrug thereof, wherein the compounds may be prepared by analogous methods to those described herein.

In a further aspect a compound of the invention is 2-[[2-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)ethyl](tetrahydro-2*H*-pyran-4-yl)amino]ethyl dihydrogen phosphate or 2-[[2-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)ethyl](tetrahydro-2*H*-pyran-4-yl)amino]ethyl dihydrogen phosphate or a sal;t or ester thereof, wherein the compounds may be prepared by analogous methods to those described herein.

Preferred compounds of formula (I) are those that are stable in mouse, rat, or human serum, preferably those that are stable in human serum.

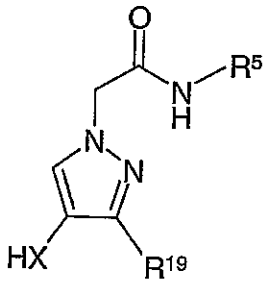
The present invention also provides a process for the preparation of a compound of formula (I) or a salt, ester or prodrug thereof, which process comprises reacting a compound of formula (II)



(II)

where L is a suitable leaving group such as chloro, bromo, SMe etc.

with a compound of formula (III)



(III)

in the presence of hydrochloric acid in dioxane under an inert atmosphere,

and thereafter if necessary:

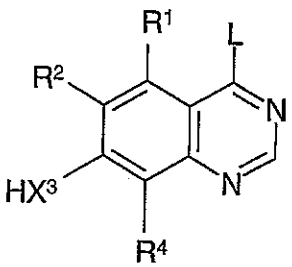
i) converting a compound of the formula (I) into another compound of the formula (I); and/or

ii) removing any protecting groups; and/or

iii) forming a salt, ester or prodrug thereof.

The reaction is suitably effected in an organic solvent such as dimethyl acetamide or isopropanol at elevated temperatures of from 80°C to 120°C for 30 minutes to 2 hours.

The process may further comprise a process for the preparation of a compound of formula (II) when R^3 is $-X^3R^{13}$, which process comprises reacting a compound of formula (IV)



(IV)

with a compound of formula (V)

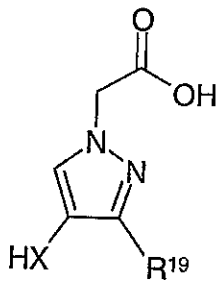
L^1-R^{13}

(V)

where L^1 is an appropriate leaving group such as chloro or L^1 is –OH which is suitably activated by a reagent such as PPh_3.

Compounds of formula (IV) and formula (V) are either known in the art or can be derived from other compounds known in the art by conventional methods which would be apparent from the literature. An analogous process exists for the preparation of a compound of formula (II) when R^1 is $-X^1R^{11}$ and/or R^2 is $-X^2R^{12}$ and/or R^4 is $-X^4R^{14}$.

The process may further comprise a process for the preparation of a compound of formula (III) which process comprises the reaction of a compound of formula (VI)



(VI)

with a compound of formula (VII)

R^5-NH_2

(VII)

The reaction is suitably effected in an organic solvent such as tetrahydrofuran (THF) or dichloromethane (DCM) at temperatures from 0°C to 25°C in the presence of a base such as pyridine under an inert atmosphere for 1 to 3 hours.

Further provided is a process for the preparation of a compound of formula (IA) or a salt or ester thereof, which process comprises phosphorylation of a suitable compound of formula (I) by reacting a compound of formula (I) and tetrazole with di-tert-butyl diethylphosphoramidite in an appropriate organic solvent such as dimethylformamide or dimethylacetamide under an inert atmosphere, followed by (after 1 to 5 hours) the addition of hydrogen peroxide and sodium metabisulphite. Deprotection of the phosphate group then yields a compound of formula (IA). Deprotection is suitably effected with hydrochloric acid in dioxane or dichloromethane (DCM) at ambient temperature for 6 to 30 hours.

Suitable reaction conditions are illustrated herein.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogen group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are 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). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an

arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound formula (I), or a pharmaceutically acceptable salt, ester or prodrug thereof, as defined herein in association with a pharmaceutically acceptable diluent or carrier.

Also provided is a pharmaceutical composition which comprises a compound of formula (IA), or a pharmaceutically acceptable salt or ester thereof, as defined herein in association with a pharmaceutically acceptable diluent or carrier.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for

example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal track, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, soya bean oil, coconut oil, or preferably olive oil, or any other acceptable vehicle.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxyethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or

condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible or lyophilised powders and granules suitable for preparation of an aqueous suspension or solution by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, solutions, emulsions or particular systems, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable

preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in polyethylene glycol.

Suppository formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedure well known in the art.

Compositions for administration by insufflation may be in the form of a finely divided powder containing particles of average diameter of, for example, 30μm or much less preferably 5μm or less and more preferably between 5μm and 1μm, the powder itself comprising either active ingredient alone or diluted with one or more physiologically acceptable carriers such as lactose. The powder for insufflation is then conveniently retained in a capsule containing, for example, 1 to 50mg of active ingredient for use with a turbo-inhaler device, such as is used for insufflation of the known agent sodium cromoglycate.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

Therefore in a further aspect of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt, ester or prodrug thereof, for use in therapy. In addition a compound of formula (IA) or a pharmaceutically acceptable salt or ester thereof is provided for use in therapy.

Further provided is a compound of formula (I), or a pharmaceutically acceptable salt, ester or prodrug thereof, for use as a medicament and also provided is a compound of formula (IA), or a pharmaceutically acceptable salt or ester thereof, for use as a medicament.

Additionally a compound of formula (I), or a pharmaceutically acceptable salt, ester or prodrug thereof is provided for use in a method of treatment of a warm-blooded animal such as man by therapy. A compound of formula (IA) or a pharmaceutically acceptable salt or ester thereof is also provided for use in a method of treatment of a warm-blooded animal such as man by therapy.

In another aspect of the invention, there is provided a compound of formula (I) or a pharmaceutically acceptable salt, ester or prodrug thereof, in the preparation of a medicament for the treatment of a disease where the inhibition of one or more Aurora kinase(s) is beneficial. A compound of formula (IA) or a pharmaceutically acceptable salt thereof is also provided for use in the preparation of a medicament for the treatment of a disease where the inhibition of one or more Aurora kinase(s) is beneficial is also provided. In particular it is envisaged that inhibition of Aurora-A kinase and/or Aurora-B kinase may be beneficial.

In another aspect of the invention, there is provided a compound of formula (I) or a pharmaceutically acceptable salt, ester or prodrug thereof, for use in the preparation of a medicament for the treatment of hyperproliferative diseases such as cancer and in particular colorectal, breast, lung, prostate, bladder, renal or pancreatic cancer or leukaemia or lymphoma. Also provided is a compound of formula (IA) or a pharmaceutically acceptable salt or ester thereof for use in the preparation of a medicament for the treatment of hyperproliferative diseases such as cancer and in particular colorectal, breast, lung, prostate, bladder, renal or pancreatic cancer or leukaemia or lymphoma.

In another aspect of the invention, there is provided the use of a compound of formula (I) or a pharmaceutically acceptable salt, ester or prodrug thereof, in the preparation of a medicament for the treatment of a disease where the inhibition of one or more Aurora kinase(s) is beneficial. The use of a compound of formula (IA) or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of a disease where the inhibition of one or more Aurora kinase(s) is beneficial is also provided. In particular it is envisaged that inhibition of Aurora-A kinase and/or Aurora-B kinase may be beneficial.

In another aspect of the invention, there is provided the use of a compound of formula (I) or a pharmaceutically acceptable salt, ester or prodrug thereof, in the preparation of a medicament for the treatment of hyperproliferative diseases such as cancer and in particular colorectal, breast, lung, prostate, bladder, renal or pancreatic cancer or leukaemia or lymphoma. Also provided is the use of a compound of formula (IA) or a pharmaceutically acceptable salt or ester thereof in the preparation of a medicament for the treatment of

hyperproliferative diseases such as cancer and in particular colorectal, breast, lung, prostate, bladder, renal or pancreatic cancer or leukaemia or lymphoma.

According to yet another aspect, there is provided a compound of formula (I) or a pharmaceutically acceptable salt ester or prodrug thereof for use in a method of treating a human suffering from a disease in which the inhibition of one or more Aurora kinases is beneficial, comprising the steps of administering to a person in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, ester or prodrug thereof. Further provided is a compound of formula (IA) or a pharmaceutically acceptable salt or ester thereof for use in a method of treating a human suffering from a disease in which the inhibition of one or more Aurora kinases is beneficial, comprising the steps of administering to a person in need thereof a therapeutically effective amount of a compound of formula (IA) or a pharmaceutically acceptable salt or ester thereof. In particular it is envisaged that inhibition of Aurora-A kinase and/or Aurora-B kinase may be beneficial.

Further provided is a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in a method of treating a human suffering from a hyperproliferative disease such as cancer and in particular colorectal, breast, lung, prostate, bladder, renal or pancreatic cancer or leukaemia or lymphoma, comprising the steps of administering to a person in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, ester or prodrug thereof. A compound of formula (IA) is also provided for use in a method of treating a human suffering from a hyperproliferative disease such as cancer and in particular colorectal, breast, lung, prostate, bladder, renal or pancreatic cancer or leukaemia or lymphoma, comprising the steps of administering to a person in need thereof a therapeutically effective amount of a compound of formula (IA) or a pharmaceutically acceptable salt or ester thereof.

Also provided is a method of treating a human suffering from a disease in which the inhibition of one or more Aurora kinases is beneficial, comprising the steps of administering to a person in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, ester or prodrug thereof. Further provided is a method of treating a human suffering from a disease in which the inhibition of one or more Aurora kinases is beneficial, comprising the steps of administering to a person in need thereof a therapeutically effective amount of a compound of formula (IA) or a pharmaceutically acceptable salt or ester thereof. In particular it is envisaged that inhibition of Aurora-A kinase and/or Aurora-B kinase may be beneficial.

Additionally provided is a method of treating a human suffering from a hyperproliferative disease such as cancer and in particular colorectal, breast, lung, prostate, bladder, renal or pancreatic cancer or leukaemia or lymphoma, comprising the steps of administering to a person in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, ester or prodrug thereof. Another aspect provides a method of treating a human suffering from a hyperproliferative disease such as cancer and in particular colorectal, breast, lung, prostate, bladder, renal or pancreatic cancer or leukaemia or lymphoma, comprising the steps of administering to a person in need thereof a therapeutically effective amount of a compound of formula (IA) or a pharmaceutically acceptable salt or ester thereof.

For the above mentioned therapeutic uses the dose administered will vary with the compound employed, the mode of administration, the treatment desired, the disorder indicated and the age and sex of the animal or patient. The size of the dose would thus be calculated according to well known principles of medicine.

In using a compound of formula (I) or formula (IA) for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.05 mg/kg to 50 mg/kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.05 mg/kg to 25 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.05 mg/kg to 25 mg/kg body weight will be used.

The treatment defined herein may be applied as a sole therapy or may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents :-

(i) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside and hydroxyurea; antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and

taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and iodoxyfene), oestrogen receptor down regulators (for example fulvestratrant), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5α-reductase such as finasteride;

(iii) Agents which inhibit cancer cell invasion (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);

(iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies (for example the anti-erbb2 antibody trastuzumab [Herceptin™] and the anti-erbb1 antibody cetuximab [C225]) , farnesyl transferase inhibitors, tyrosine kinase inhibitors and serine-threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-*N*-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, (for example the anti-vascular endothelial cell growth factor antibody bevacizumab [Avastin™], compounds such as those disclosed in International Patent Applications WO97/22596, WO97/30035, WO97/32856 and WO98/13354) and compounds that work by other mechanisms (for example linomide, inhibitors of integrin αvβ3 function and angiostatin);

(vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO99/02166, WO00/40529, WO00/41669, WO01/92224, WO02/04434 and WO02/08213;

(vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

(ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

In addition a compound of the invention may be used in combination with one or more cell cycle inhibitors. In particular with cell cycle inhibitors which inhibit bub1, bubR1 or CDK.

Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically-active agent within its approved dosage range.

In addition to their use in therapeutic medicine, a compound of formula (I) or a salt, ester or prodrug thereof or a compound of formula (IA) or a salt or ester thereof are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of cell cycle activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

The compounds of the invention inhibit the serine-threonine kinase activity of the Aurora kinases, in particular Aurora-A kinase and/or Aurora-B kinase and thus inhibit the cell cycle and cell proliferation. These properties may be assessed for example, using one or more of the procedures set out below.

(a) In Vitro Aurora-A kinase inhibition test

This assay determines the ability of a test compound to inhibit serine-threonine kinase activity. DNA encoding Aurora-A may be obtained by total gene synthesis or by cloning. This DNA may then be expressed in a suitable expression system to obtain polypeptide with serine-threonine kinase activity. In the case of Aurora-A, the coding sequence was isolated from cDNA by polymerase chain reaction (PCR) and cloned into the BamH1 and Not1 restriction endonuclease sites of the baculovirus expression vector pFastBac HTc (GibcoBRL/Life technologies). The 5' PCR primer contained a recognition sequence for the restriction endonuclease BamH1 5' to the Aurora-A coding sequence. This allowed the insertion of the Aurora-A gene in frame with the 6 histidine residues, spacer region and rTEV protease cleavage site encoded by the pFastBac HTc vector. The 3' PCR primer replaced the Aurora-A stop codon with additional coding sequence followed by a stop codon and a recognition sequence for the restriction endonuclease Not1. This additional coding sequence (5' TAC CCA TAC GAT GTT CCA GAT TAC GCT TCT TAA 3') encoded for the polypeptide sequence YPYDVPDYAS. This sequence, derived from the influenza hemagglutin protein, is frequently used as a tag epitope sequence that can be identified using specific monoclonal antibodies. The recombinant pFastBac vector therefore encoded for an N-terminally 6 his tagged, C terminally influenza hemagglutin epitope tagged Aurora-A protein. Details of the methods for the assembly of recombinant DNA molecules can be found in standard texts, for example Sambrook et al. 1989, Molecular Cloning - A Laboratory Manual, 2nd Edition, Cold Spring Harbor Laboratory press and Ausubel et al. 1999, Current Protocols in Molecular Biology, John Wiley and Sons Inc.

Production of recombinant virus can be performed following manufacturer's protocol from GibcoBRL. Briefly, the pFastBac-1 vector carrying the Aurora-A gene was transformed into E. coli DH10Bac cells containing the baculovirus genome (bacmid DNA) and via a transposition event in the cells, a region of the pFastBac vector containing gentamycin resistance gene and the Aurora-A gene including the baculovirus polyhedrin promoter was transposed directly into the bacmid DNA. By selection on gentamycin, kanamycin, tetracycline and X-gal, resultant white colonies should contain recombinant bacmid DNA encoding Aurora-A. Bacmid DNA was extracted from a small scale culture of several BH10Bac white colonies and transfected into Spodoptera frugiperda Sf21 cells grown in TC100 medium (GibcoBRL) containing 10% serum using CellFECTIN reagent (GibcoBRL)

following manufacturer's instructions. Virus particles were harvested by collecting cell culture medium 72 hrs post transfection. 0.5 mls of medium was used to infect 100 ml suspension culture of Sf21s containing 1 x 10^7 cells/ml. Cell culture medium was harvested 48 hrs post infection and virus titre determined using a standard plaque assay procedure. Virus stocks were used to infect Sf9 and "High 5" cells at a multiplicity of infection (MOI) of 3 to ascertain expression of recombinant Aurora-A protein.

For the large scale expression of Aurora-A kinase activity, Sf21 insect cells were grown at 28°C in TC100 medium supplemented with 10% foetal calf serum (Viralex) and 0.2% F68 Pluronic (Sigma) on a Wheaton roller rig at 3 r.p.m. When the cell density reached $1.2x10^6$ cells ml^{-1} they were infected with plaque-pure Aurora-A recombinant virus at a multiplicity of infection of 1 and harvested 48 hours later. All subsequent purification steps were performed at 4°C. Frozen insect cell pellets containing a total of 2.0 x 10^8 cells were thawed and diluted with lysis buffer (25 mM HEPES (N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulphonic acid]) pH7.4 at 4°C , 100 mM KCl, 25 mM NaF, 1 mM Na_3VO_4, 1 mM PMSF (phenylmethylsulphonyl fluoride), 2 mM 2-mercaptoethanol, 2 mM imidazole, 1 μg/ml aprotinin, 1 μg/ml pepstatin, 1 μg/ml leupeptin), using 1.0 ml per 3 x 10^7 cells. Lysis was achieved using a dounce homogeniser, following which the lysate was centrifuged at 41,000*g* for 35 minutes. Aspirated supernatant was pumped onto a 5 mm diameter chromatography column containing 500 μl Ni NTA (nitrilo-tri-acetic acid) agarose (Qiagen, product no. 30250) which had been equilibrated in lysis buffer. A baseline level of UV absorbance for the eluent was reached after washing the column with 12 ml of lysis buffer followed by 7 ml of wash buffer (25 mM HEPES pH7.4 at 4°C , 100 mM KCl, 20 mM imidazole, 2 mM 2-mercaptoethanol). Bound Aurora-A protein was eluted from the column using elution buffer (25 mM HEPES pH7.4 at 4°C , 100 mM KCl, 400 mM imidazole, 2 mM 2-mercaptoethanol). An elution fraction (2.5 ml) corresponding to the peak in UV absorbance was collected. The elution fraction, containing active Aurora-A kinase, was dialysed exhaustively against dialysis buffer (25 mM HEPES pH7.4 at 4°C , 45% glycerol (v/v), 100 mM KCl, 0.25% Nonidet P40 (v/v), 1 mM dithiothreitol).

Each new batch of Aurora-A enzyme was titrated in the assay by dilution with enzyme diluent (25mM Tris-HCl pH7.5, 12.5mM KCl, 0.6mM DTT). For a typical batch, stock enzyme is diluted 1 in 666 with enzyme diluent & 20µl of dilute enzyme is used for each assay well. Test compounds (at 10mM in dimethylsulphoxide (DMSO) were diluted with

water & 10µl of diluted compound was transferred to wells in the assay plates. "Total" & "blank" control wells contained 2.5% DMSO instead of compound. Twenty microlitres of freshly diluted enzyme was added to all wells, apart from "blank" wells. Twenty microlitres of enzyme diluent was added to "blank" wells. Twenty microlitres of reaction mix (25mM Tris-HCl, 78.4mM KCl, 2.5mM NaF, 0.6mM dithiothreitol, 6.25mM $MnCl_2$, 6.25mM ATP, 7.5µM peptide substrate [biotin-LRRWSLGLRRWSLGLRRWSLGLRRWSLG]) containing 0.2µCi [γ^{33}P]ATP (Amersham Pharmacia, specific activity ≥2500Ci/mmol) was then added to all test wells to start the reaction. The plates were incubated at room temperature for 60 minutes. To stop the reaction 100µl 20% v/v orthophosphoric acid was added to all wells. The peptide substrate was captured on positively-charged nitrocellulose P30 filtermat (Whatman) using a 96-well plate harvester (TomTek) & then assayed for incorporation of ^{33}P with a Beta plate counter. "Blank" (no enzyme) and "total" (no compound) control values were used to determine the dilution range of test compound which gave 50% inhibition of enzyme activity. In this test, the compounds of the invention generally give 50% inhibition of enzyme activity at concentrations of 1nM to 1000nM and in particular compound 27 in Table 2 gave 50% inhibition of enzyme activity at a concentration of 34nM, compound 60 in Table 3 gave 50% inhibition of enzyme activity at a concentration of 10nM and compound 187 in Table 5 gave 50% inhibition of enzyme activity at a concentration of 0.5µM

(b) <u>In Vitro Aurora-B kinase inhibition test</u>

This assay determines the ability of a test compound to inhibit serine-threonine kinase activity. DNA encoding Aurora-B may be obtained by total gene synthesis or by cloning. This DNA may then be expressed in a suitable expression system to obtain polypeptide with serine-threonine kinase activity. In the case of Aurora-B, the coding sequence was isolated from cDNA by polymerase chain reaction (PCR) and cloned into the pFastBac system in a manner similar to that described above for Aurora-A (i.e. to direct expression of a 6-histidine tagged Aurora-B protein).

For the large scale expression of Aurora-B kinase activity, Sf21 insect cells were grown at 28°C in TC100 medium supplemented with 10% foetal calf serum (Viralex) and 0.2% F68 Pluronic (Sigma) on a Wheaton roller rig at 3 r.p.m. When the cell density reached $1.2x10^6$ cells ml^{-1} they were infected with plaque-pure Aurora-B recombinant virus at a multiplicity of infection of 1 and harvested 48 hours later. All subsequent purification steps

were performed at 4°C. Frozen insect cell pellets containing a total of 2.0 x 10^8 cells were thawed and diluted with lysis buffer (50 mM HEPES (N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulphonic acid]) pH7.5 at 4°C , 1 mM Na_3VO_4, 1 mM PMSF (phenylmethylsulphonyl fluoride), 1 mM dithiothreitol, 1 μg/ml aprotinin, 1 μg/ml pepstatin, 1 μg/ml leupeptin), using 1.0 ml per 2 x 10^7 cells. Lysis was achieved using a sonication homogeniser, following which the lysate was centrifuged at 41,000*g* for 35 minutes. Aspirated supernatant was pumped onto a 5 mm diameter chromatography column containing 1.0 ml CM sepharose Fast Flow (Amersham Pharmacia Biotech) which had been equilibrated in lysis buffer. A baseline level of UV absorbance for the eluent was reached after washing the column with 12 ml of lysis buffer followed by 7 ml of wash buffer (50 mM HEPES pH7.4 at 4°C , 1 mM dithiothreitol). Bound Aurora-B B protein was eluted from the column using a gradient of elution buffer (50 mM HEPES pH7.4 at 4°C , 0.6 M NaCl, 1 mM dithiothreitol, running from 0% elution buffer to 100% elution buffer over 15 minutes at a flowrate of 0.5 ml/min). Elution fractions (1.0 ml) corresponding to the peak in UV absorbance was collected. Elution fractions were dialysed exhaustively against dialysis buffer (25 mM HEPES pH7.4 at 4°C , 45% glycerol (v/v), 100 mM KCl, 0.05% (v/v) IGEPAL CA630 (Sigma Aldrich), 1 mM dithiothreitol). Dialysed fractions were assayed for Aurora-B kinase activity.

Each new batch of Aurora-B enzyme was titrated in the assay by dilution with enzyme diluent (25mM Tris-HCl pH7.5, 12.5mM KCl, 0.6mM DTT). For a typical batch, stock enzyme is diluted 1 in 40 with enzyme diluent & 20μl of dilute enzyme is used for each assay well. Test compounds (at 10mM in dimethylsulphoxide (DMSO) were diluted with water & 10μl of diluted compound was transferred to wells in the assay plates. "Total" & "blank" control wells contained 2.5% DMSO instead of compound. Twenty microlitres of freshly diluted enzyme was added to all wells, apart from "blank" wells. Twenty microlitres of enzyme diluent was added to "blank" wells. Twenty microlitres of reaction mix (25mM Tris-HCl, 78.4mM KCl, 2.5mM NaF, 0.6mM dithiothreitol, 6.25mM $MnCl_2$, 37.5mM ATP, 25μM peptide substrate [biotin-LRRWSLGLRRWSLGLRRWSLGLRRWSLG]) containing 0.2μCi [γ^{33}P]ATP (Amersham Pharmacia, specific activity ≥2500Ci/mmol) was then added to all test wells to start the reaction. The plates were incubated at room temperature for 60 minutes. To stop the reaction 100μl 20% v/v orthophosphoric acid was added to all wells. The peptide substrate was captured on positively-charged nitrocellulose P30 filtermat (Whatman) using a 96-well plate harvester (TomTek) & then assayed for incorporation of ^{33}P with a Beta plate

counter. "Blank" (no enzyme) and "total" (no compound) control values were used to determine the dilution range of test compound which gave 50% inhibition of enzyme activity. In this test, the compounds of the invention generally give 50% inhibition of enzyme activity at concentrations of 1nM to 1000nM and in particular compound 27 in Table 2 gave 50% inhibition of enzyme activity at a concentration of 5nM, compound 60 in Table 3 gave 50% inhibition of enzyme activity at a concentration of 8nM and compound 187 in Table 5 gave 50% inhibition of enzyme activity at a concentration of 9nM.

(c) In Vitro cell proliferation assay

This and other assays can be used to determine the ability of a test compound to inhibit the growth of adherent mammalian cell lines, for example the human tumour cell line SW620 (ATCC CCL-227). This assay determines the ability of at test compound to inhibit the incorporation of the thymidine analogue, 5'-bromo-2'-deoxy-uridine (BrdU) into cellular DNA. SW620 or other adherent cells were typically seeded at $1x10^5$ cells per well in L-15 media (GIBCO) plus 5% foetal calf serum, 1% L-glutamine (100µl / well) in 96 well tissue culture treated 96 well plates (Costar) and allowed to adhere overnight. The following day the cells were dosed with compound (diluted from 10mM stock in DMSO using L-15 (with 5% FCS, 1% L-glutamine). Untreated control wells and wells containing a compound known to give 100% inhibition of BrdU incorporation were included on each plate. After 48 hours in the presence / absence of test compound the ability of the cells to incorporate BrdU over a 2 hour labelling period was determined using a Boehringer (Roche) Cell Proliferation BrdU ELISA kit (cat. No. 1 647 229) according to manufacturers directions. Briefly, 15µl of BrdU labelling reagent (diluted 1:100 in media – L-15, 5% FCS, 1% L-glutamine) was added to each well and the plate returned to a humidified (+5% CO_2) 37°C incubator for 2 hours. After 2 hours the labelling reagent was removed by decanting and tapping the plate on a paper towel. FixDenat solution (50µl per well) was added and the plates incubated at room temperature for 45mins with shaking. The FixDenat solution was removed by decanting and tapping the inverted plate on a paper towel. The plate was then washed once with phosphate buffered saline (PBS) and 100µl /well of Anti-BrdU-POD antibody solution (diluted 1:100 in antibody dilution buffer) added. The plate was then incubated at room temperature with shaking for 90min. Unbound Anti-BrdU-POD antibody was removed by decanting and washing the plate 4 times with PBS before being blotted dry. TMB substrate solution was

added (100µl/well) and incubated for approximately 10 minutes at room temperature with shaking until a colour change was apparent. The optical density of the wells was then determined at 690nm wavelength using a Titertek Multiscan plate reader. The values from compound treated, untreated and 100% inhibition controls were used to determine the dilution range of a test compound that gave 50% inhibition of BrdU incorporation. The compounds of the invention are generally active at 1nM to 100µM in this test and in particular compound 27 in Table 2 gave 50% inhibition of enzyme activity at a concentration of 10nM, compound 60 in Table 3 gave 50% inhibition of enzyme activity at a concentration of 1nM and compound 187 in Table 5 gave 50% inhibition of enzyme activity at a concentration of 1nM.

(d) In Vitro cell cycle analysis assay

This assay determines the ability of a test compound to arrest cells in specific phases of the cell cycle. Many different mammalian cell lines could be used in this assay and SW620 cells are included here as an example. SW620 cells were seeded at 7 x 10^5 cells per T25 flask (Costar) in 5 ml L-15 (5% FCS, 1% L-glutamine). Flasks were then incubated overnight in a humidified 37^{0}C incubator with 5% CO_2. The following day, 5µl of L-15 (5% FCS, 1% L-glutamine) carrying the appropriate concentration of test compound solubilised in DMSO was added to the flask. A no compound control treatment was also included (0.5% DMSO). The cells were then incubated for a defined time (24 hours) with compound. After this time the media was aspirated from the cells and they were washed with 5ml of prewarmed (37^{0}C) sterile PBSA, then detached from the flask by brief incubation with trypsin and followed by resuspension in 5ml of 1% Bovine Serum Albumin (BSA, Sigma-Aldrich Co.) in sterile PBSA. The samples were then centrifuged at 2200rpm for 10 min. The supernatant was aspirated to leave 200µl of the PBS/BSA solution. The pellet was resuspended in this 200µl of solution by pipetting 10 times to create a single cell suspension. One ml of ice-cold 80% ethanol was slowly added to each cell suspension and the samples stored at -20°C overnight or until required for staining. Cells were pelleted by centrifugation, ethanol aspirated off and pellets resuspended in 200µl PBS containing 100µg/ml RNAse (Sigma Aldrich) & 10µg/ml Propidium Iodide (Sigma Aldrich). Cell suspensions were incubated at 37°C for 30min, a further 200µl PBS added and samples stored in the dark at 4°C overnight.

Each sample was then syringed 10 times using 21-guage needle. The samples were then transferred to LPS tubes and DNA content per cell analysed by Fluorescence activated

cell sorting (FACS) using a FACScan flow cytometer (Becton Dickinson). Typically 30,000 events were counted and recorded using CellQuest v1.1 software (Verity Software). Cell cycle distribution of the population was calculated using Modfit software (Verity Software) and expressed as percentage of cells with 2N (G0/G1), 2N-4N (S phase) and with 4N (G2/M) DNA content.

The compounds of the invention are generally active in this test at 1nM to 10μM and in particular compound 27 in Table 2 gave 50% inhibition of enzyme activity at a concentration of 7nM, compound 60 in Table 3 gave 50% inhibition of enzyme activity at a concentration of 3nM and compound 187 in Table 5 gave 50% inhibition of enzyme activity at a concentration of 21nM.

The invention will now be illustrated in the following non limiting examples, in which standard techniques known to the skilled chemist and techniques analogous to those described in these examples may be used where appropriate, and 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) operations were carried out at ambient temperature, typically in the range 18-25°C and in air unless stated, or unless the skilled person would otherwise operate under an atmosphere of an inert gas such as argon;

(iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385);

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

(v) the structures of the end products of the formula (I) were generally confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured in deuterated dimethyl sulphoxide (DMSO d_6) (unless otherwise stated) on the delta scale (ppm downfield from tetramethylsilane) using one of the following four instruments

- Varian Gemini 2000 spectrometer operating at a field strength of 300 MHz
- Bruker DPX300 spectrometer operating at a field strength of 300MHz
- JEOL EX 400 spectrometer operating at a field strength of 400 MHz
- Bruker Avance 500 spectrometer operating at a field strength of 500MHz

Peak multiplicities are shown as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; qu, quintet; m, multiplet; br s, broad singlet;

(vi) robotic synthesis was carried out using a Zymate XP robot, with solution additions via a Zymate Master Laboratory Station and stirred via a Stem RS5000 Reacto-Station at 25°C;

(vii) work up and purification of reaction mixtures from robotic synthesis was carried out as follows: evaporations were carried out *in vacuo* using a Genevac HT 4; column chromatography was performed using either an Anachem Sympur MPLC system on silica using 27 mm diameter columns filled with Merck silica (60 μm, 25 g); the structures of the final products were confirmed by LCMS on a Waters 2890 / ZMD micromass system using the following and are quoted as retention time (RT) in minutes:

Column:	waters symmetry C18 3.5 μm 4.6x50 mm
Solvent A:	H_2O
Solvent B:	CH_3CN
Solvent C :	MeOH + 5% HCOOH
Flow rate:	2.5 ml / min
Run time:	5 minutes with a 4.5 minute gradient from 0-100% C
Wavelength:	254 nm, bandwidth 10 nm
Mass detector:	ZMD micromass
Injection volume	0.005 ml

(viii) Analytical LCMS for compounds which had not been prepared by robotic synthesis was performed on a Waters Alliance HT system using the following and are quoted as retention time (RT) in minutes:

Column:	2.0 mm x 5 cm Phenomenex Max-RP 80A
Solvent A:	Water
Solvent B:	Acetonitrile
Solvent C:	Methanol / 1% formic acid or Water / 1% formic acid
Flow rate:	1.1 ml / min
Run time:	5 minutes with a 4.5 minute gradient from 0-95% B + constant 5% solvent C
Wavelength:	254 nm, bandwidth 10 nm
Injection volume	0.005 ml
Mass detector:	Micromass ZMD

(ix) Preparative high performance liquid chromatography (HPLC) was performed on either

- Waters preparative LCMS instrument, with retention time (RT) measured in minutes:

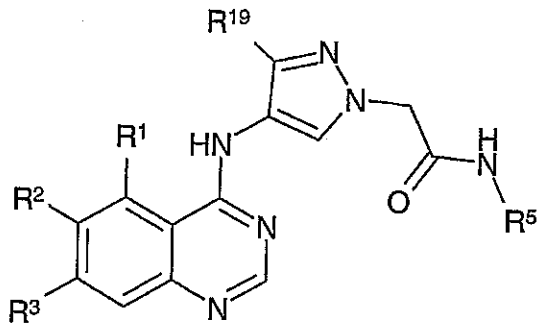
Column:	β-basic Hypercil (21x100 mm) 5μm
Solvent A:	Water / 0.1% Ammonium carbonate
Solvent B:	Acetonitrile
Flow rate:	25 ml / min
Run time:	10 minutes with a 7.5 minute gradient from 0-100% B
Wavelength:	254 nm, bandwidth 10 nm
Injection volume	1 - 1.5 ml
Mass detector :	Micromass ZMD

- Gilson preparative HPLC instrument, with retention time (RT) measured in minutes:

Column:	21 mm x 15 cm Phenomenex Luna2 C18
Solvent A:	Water + 0.1% trifluoracetic acid,
Solvent B:	Acetonitrile + 0.1% trifluoracetic acid
Flow rate:	21 ml / min
Run time:	20 minutes with various 10 minute gradients from 5-100% B
Wavelength:	254 nm, bandwidth 10 nm
Injection volume	0.1-4.0 ml

(x) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), HPLC, infra-red (IR), MS or NMR analysis.

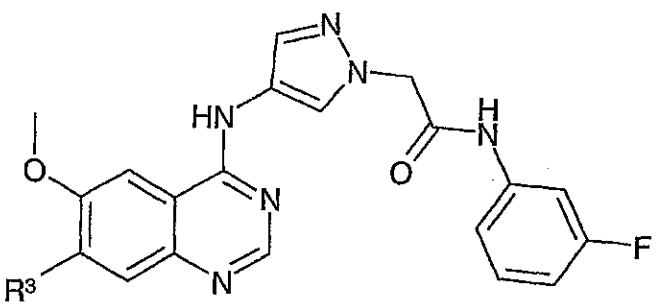
Table 1



Compound	R^1	R^2	R^3	R^5	R^{19}
1	H	OMe	3-chloropropoxy	3-fluorophenyl	H
2	H	H	3-	2,3-	H

			chloropropoxy	difluorophenyl	
3	H	OMe	3-chloropropoxy	2,3-difluorophenyl	H
4	H	H	3-chloropropoxy	3-fluorophenyl	H
5	H	H	2-chloroethoxy	2,3-difluorophenyl	H
6	H	OMe	2-chloroethoxy	2,3-difluorophenyl	H
7	H	H	2,2-dimethoxyethoxy	2,3-difluorophenyl	H
8	H	OMe	3-chloropropoxy	3-fluorophenyl	carboxamide
9	H	H	3-chloropropoxy	3-fluorophenyl	ethyl carboxylate
10	H	H	3-chloropropoxy	3-fluorophenyl	acetylamino
11	H	H	H	2,3-difluorophenyl	H
12	isopropoxy	H	3-chloropropoxy	2,3-difluorophenyl	H
13	OMe	H	3-chloropropoxy	2,3-difluorophenyl	H
14	H	F	3-chloropropoxy	2,3-difluorophenyl	H
15	H	F	3-chloropropoxy	3-fluorophenyl	H

Table 2

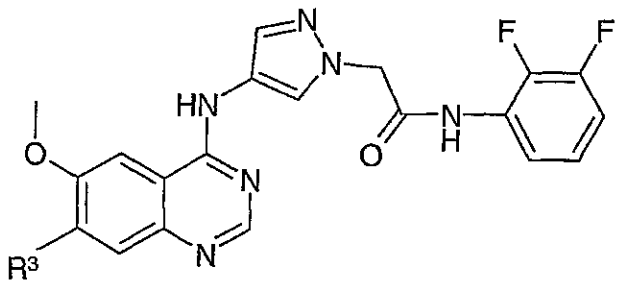


Compound	R^3
16	3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy
17	3-[(2-hydroxyethyl)(isobutyl)amino]propoxy

18	3-[(2-hydroxyethyl)(propyl)amino]propoxy
19	3-piperidin-1-ylpropoxy
20	3-pyrrolidin-1-ylpropoxy
21	3-(diethylamino)propoxy
22	3-piperazin-1-ylpropoxy
23	3-[(2-hydroxyethyl)(methyl)amino]propoxy
24	3-(cyclopropylamino)propoxy
25	3-[[2-(dimethylamino)ethyl](methyl)amino]propoxy
26	3-(4-methylpiperazin-1-yl)propoxy
27	3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy
28	3-(4-hydroxypiperidin-1-yl)propoxy
29	3-[bis(2-hydroxyethyl)amino]propoxy
30	3-[ethyl(methyl)amino]propoxy
31	3-[ethyl(2-hydroxyethyl)amino]propoxy
32	3-[[2-(dimethylamino)ethyl](ethyl)amino]propoxy
33	3-[2-(2-hydroxyethyl)piperidin-1-yl]propoxy
34	3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy
35	3-[(cyclopropylmethyl)amino]propoxy
36	3-[4-(2-hydroxyethyl)piperidin-1-yl]propoxy
37	3-[methyl(prop-2-yn-1-yl)amino]propoxy
38	3-[allyl(methyl)amino]propoxy
39	3-[isobutyl(methyl)amino]propoxy
40	3-(3-hydroxypiperidin-1-yl)propoxy
41	3-[4-(hydroxymethyl)piperidin-1-yl]propoxy
42	3-[methyl(propyl)amino]propoxy
43	3-[(cyclopropylmethyl)(propyl)amino]propoxy
44	3-[[2-(diethylamino)ethyl](methyl)amino]propoxy
45	3-[[2-(diethylamino)ethyl](ethyl)amino]propoxy
46	3-(4-methyl-1,4-diazepan-1-yl)propoxy
47	3-[(2-hydroxyethyl)(isopropyl)amino]propoxy
48	3-[cyclopropyl(2-hydroxyethyl)amino]propoxy

49	3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy
50	3-[cyclobutyl(2-hydroxyethyl)amino]propoxy
51	3-[(cyclopropylmethyl)(2-hydroxyethyl)amino]propoxy
52	3-[(cyclobutylmethyl)(2-hydroxyethyl)amino]propoxy
53	3-[(2-hydroxyethyl)(prop-2-yn-1-yl)amino]propoxy
54	3-[allyl(2-hydroxyethyl)amino]propoxy
55	3-[(2,2-dimethylpropyl)(2-hydroxyethyl)amino]propoxy
56	3-[(2-hydroxyethyl)(3,3,3-trifluoropropyl)amino]propoxy
57	3-azetidin-1-ylpropoxy
58	methoxy
59	hydroxy

Table 3

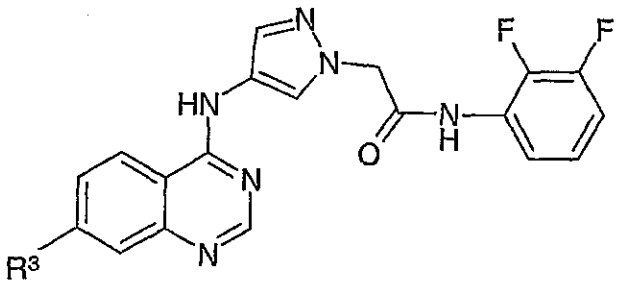


Compound	R^3
60	3-[(2-hydroxyethyl)(isobutyl)amino]propoxy
61	3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy
62	3-[(2-hydroxyethyl)(propyl)amino]propoxy
63	3-(dimethylamino)propoxy
64	3-piperidin-1-ylpropoxy
65	3-pyrrolidin-1-ylpropoxy
66	3-piperazin-1-ylpropoxy
67	3-[(2-hydroxyethyl)(methyl)amino]propoxy

68	3-(cyclopropylamino)propoxy
69	3-[[2-(dimethylamino)ethyl](methyl)amino]propoxy
70	3-(4-methylpiperazin-1-yl)propoxy
71	3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy
72	3-(4-hydroxypiperidin-1-yl)propoxy
73	3-[bis(2-hydroxyethyl)amino]propoxy
74	3-[ethyl(methyl)amino]propoxy
75	3-[ethyl(2-hydroxyethyl)amino]propoxy
76	3-[[2-(dimethylamino)ethyl](ethyl)amino]propoxy
77	3-[2-(2-hydroxyethyl)piperidin-1-yl]propoxy
78	3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy
79	3-[(cyclopropylmethyl)amino]propoxy
80	3-[4-(2-hydroxyethyl)piperidin-1-yl]propoxy
81	3-[methyl(prop-2-yn-1-yl)amino]propoxy
82	3-[isobutyl(methyl)amino]propoxy
83	3-(3-hydroxypiperidin-1-yl)propoxy
84	3-[4-(hydroxymethyl)piperidin-1-yl]propoxy
85	3-[methyl(propyl)amino]propoxy
86	3-[(cyclopropylmethyl)(propyl)amino]propoxy
87	3-[[2-(diethylamino)ethyl](methyl)amino]propoxy
88	3-[[2-(diethylamino)ethyl](ethyl)amino]propoxy
89	3-(4-methyl-1,4-diazepan-1-yl)propoxy
90	3-[(2-hydroxyethyl)(isopropyl)amino]propoxy
91	3-[cyclopropyl(2-hydroxyethyl)amino]propoxy
92	3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy
93	3-[cyclobutyl(2-hydroxyethyl)amino]propoxy
94	3-[(cyclopropylmethyl)(2-hydroxyethyl)amino]propoxy
95	3-[(cyclobutylmethyl)(2-hydroxyethyl)amino]propoxy
96	3-[(2-hydroxyethyl)(prop-2-yn-1-yl)amino]propoxy
97	3-[allyl(2-hydroxyethyl)amino]propoxy
98	3-[(2,2-dimethylpropyl)(2-hydroxyethyl)amino]propoxy

99	3-[(2-hydroxyethyl)(3,3,3-trifluoropropyl)amino]propoxy
100	2-[(2*R*)-(2-hydroxymethyl)pyrrolidin-1-yl]ethoxy
101	2-{4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl}ethoxy
102	2-[2-(hydroxymethyl)piperidin-1-yl]ethoxy
103	2-[(2-hydroxy-1,1-dimethylethyl)amino]ethoxy
104	2-[4-(2-hydroxyethyl)piperazin-1-yl]ethoxy
105	2-[(*trans*-4-hydroxycyclohexyl)amino]ethoxy
106	2-[3-(hydroxymethyl)piperidin-1-yl]ethoxy
107	2-{[1-(hydroxymethyl)cyclopentyl]amino}ethoxy
108	2-[4-(3-hydroxypropyl)piperazin-1-yl]ethoxy
109	2-[cyclohexyl(2-hydroxyethyl)amino]ethoxy
110	2-[(2-hydroxyethyl)(propyl)amino]ethoxy
111	2-[(3-hydroxy-2,2-dimethylpropyl)amino]ethoxy
112	2-(tetrahydro-2*H*-pyran-4-ylamino)ethoxy
113	2-[cyclobutyl(2-hydroxyethyl)amino]ethoxy
114	2-[(2-hydroxyethyl)(tetrahydro-2*H*-pyran-4-yl)amino]ethoxy
115	2-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]ethoxy
116	2-[(2*R*)-2-(2-hydroxyethyl)piperidine-1-yl]ethoxy
117	2-[(2*S*)-2-(2-hydroxyethyl)piperidine-1-yl]ethoxy

Table 4



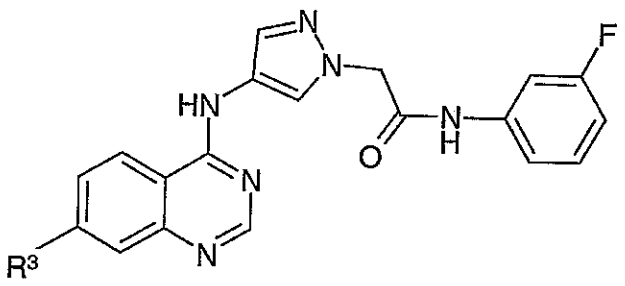
Compound	R^3
118	3-[(2-hydroxyethyl)(propyl)amino]propoxy

119	3-[(2-hydroxyethyl)(isobutyl)amino]propoxy
120	3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy
121	3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy
122	3-[(2-hydroxyethyl)(cyclopentyl)amino]propoxy
123	3-[(2-hydroxyethyl)(ethyl)amino]propoxy
124	3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy
125	3-[4-(hydroxymethyl)piperidin-1-yl]propoxy
126	3-[(3-hydroxy-1,1 dimethylpropyl)amino]propoxy
127	3-[(2-cyanoethyl)(2-hydroxyethyl)amino]propoxy
128	3-morpholin-4-ylpropoxy
129	3-[(3-hydroxy-2,2-dimethylpropyl)amino]propoxy
130	3-[(3-hydroxypropyl)amino]propoxy
131	3-[(3-hydroxypropyl)(propyl)amino]propoxy
132	3-[ethyl(3-hydroxypropyl)amino]propoxy
133	3-[4-(2-hydroxyethyl)-3-oxopiperazin-1-yl]propoxy
134	3-(propylamino)propoxy
135	3-piperazin-1-ylpropoxy
136	3-[glycoloyl(propyl)amino]propoxy
137	3-(4-glycoloylpiperazin-1-yl)propoxy
138	3-{[trans-2-(hydroxymethyl)cyclohexyl]amino}propoxy
139	3-[(1α,5α,6α)-6-(hydroxymethyl)-3-azabicyclo[3.1.0]hex-3-yl]propoxy
140	3-{[(2R)-2-hydroxypropyl]amino}propoxy
141	3-{[(1S)-2-hydroxy-1-methylethyl]amino}propoxy
142	3-[(2-hydroxy-1,1-dimethylethyl)amino]propoxy
143	3-[(2,3-dihydroxypropyl)amino]propoxy
144	3-{[2-(2-hydroxyethoxy)ethyl]amino}propoxy
145	3-(4-acetylpiperazin-1-yl)propoxy
146	3-[(tetrahydrofuran-2-ylmethyl)amino]propoxy
147	3-(allylamino)propoxy
148	3-{[1-(hydroxymethyl)-2-methylpropyl]amino}propoxy

149	3-{[(5-methylisoxazol-3-yl)methyl]amino}propoxy
150	3-(tetrahydro-2H-pyran-4-ylamino)propoxy
151	3-[(3S)-3-(hydroxymethyl)pyrrolidin-1-yl]propoxy
152	3-hydroxypropoxy
153	3-aminopropoxy
154	3-[(2S,4R)-4-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy
155	2-[(3-hydroxy-2,2-dimethylpropyl)amino]ethoxy
156	2-[cyclohexyl(2-hydroxyethyl)amino]ethoxy
157	2-(cyclopropylamino)ethoxy
158	2-(cyclobutylamino)ethoxy
159	2-(tetrahydro-2H-pyran-4-ylamino)ethoxy
160	2-(cyclopentylamino)ethoxy
161	2-[(2-hydroxyethyl)(tetrahydro-2H-pyran-4-yl)amino]ethoxy
162	2-[cyclopentyl(2-hydroxyethyl)amino]ethoxy
163	2-[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]ethoxy
164	2-[cyclopropyl(2-hydroxyethyl)amino]ethoxy
165	2-[cyclobutyl(2-hydroxyethyl)amino]ethoxy
166	2-[cyclopentyl(3-hydroxypropyl)amino]ethoxy
167	2-[cyclopentyl(glycoloyl)amino]ethoxy
168	2-[(3S)-3-(hydroxymethyl)-4-methylpiperazin-1-yl]ethoxy
169	2-[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]ethoxy
170	2-[(2R)-2-(hydroxymethyl)-4-methylpiperazin-1-yl]ethoxy
171	2-[4-(hydroxymethyl)piperidin-1-yl]ethoxy
172	2-[4-(2-hydroxyethyl)piperidin-1-yl]ethoxy
173	2-[(2-hydroxyethyl)amino]ethoxy
174	2-{[trans-2-(hydroxymethyl)cyclohexyl]amino}ethoxy
175	3-[(2-hydroxyethyl)amino]propoxy
176	3-pyrrolidin-1-ylpropoxy
177	methoxy
178	3-[(2-hydroxyethyl)(tetrahydro-2H-pyran-4-yl)amino]propoxy
179	3-[(2*R*)-2-(2-hydroxyethyl)piperidin-1-yl]propoxy

180	3-[(2*S*)-2-(2-hydroxyethyl)piperidin-1-yl]propoxy
181	3-[(2*R*)-2-(hydroxymethyl)-4-methylpiperazin-1-yl]propoxy}
182	3-[(3*S*)-3-(hydroxymethyl)-4-methylpiperazin-1-yl]propoxy
183	3-[(2*R*)-2-(hydroxymethyl)morpholin-4-yl]propoxy
184	3-[(3*S*)-3-(hydroxymethyl)morpholin-4-yl]propoxy
185	3-(glycoloylamino)propoxy

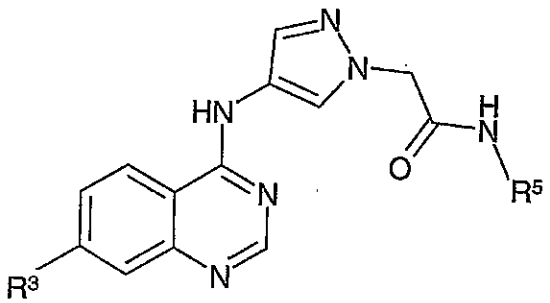
Table 5



Compound	R^3
186	3-[(2-hydroxyethyl)(propyl)amino]propoxy
187	3-[(2-hydroxyethyl)(ethyl)amino]propoxy
188	3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy
189	3-[4-(hydroxymethyl)piperidin-1-yl]propoxy
190	3-[(3-hydroxy-1,1 dimethylpropyl)amino]propoxy
191	3-[2-(2-hydroxyethyl)piperidin-1-yl]propoxy
192	3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy
193	3-[(2-hydroxyethyl)(tetrahydrofuran-3-yl)amino]propoxy
194	3-morpholin-4-ylpropoxy
195	(2*S*)-pyrrolidin-2-ylmethoxy
196	[(2*S*)-1-(2-hydroxyethyl)pyrrolidin-2-yl]methoxy
197	[(2*S*)-1-glycoloylpyrrolidin-2-yl]methoxy
198	(pyrrolidin-3-yl)methoxy
199	[1-(2-hydroxyethyl)pyrrolidin-3-yl]methoxy

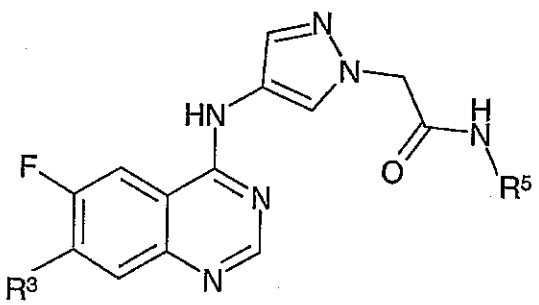
200	(1-glycoloylpyrrolidin-3-yl)methoxy
201	3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy
202	hydroxy

Table 6



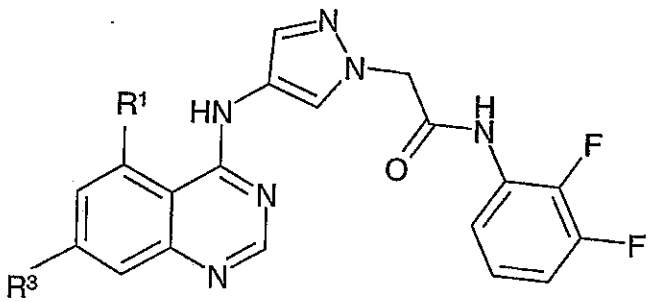
Compound	R^3	R^5
203	3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy	2-fluorophenyl
204	3-[ethyl(2-hydroxyethyl)amino]propoxy	2-fluorophenyl
205	3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy	phenyl
206	3-[ethyl(2-hydroxyethyl)amino]propoxy	phenyl
207	3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy	2,6-difluorophenyl

Table 7



Compound	R^3	R^5
208	3-[ethyl(2-hydroxyethyl)amino]propoxy	3-fluorophenyl
209	3-[(cyclopropylmethyl)(2-hydroxyethyl)amino]propoxy	2,3-difluorophenyl
210	3-[(2-hydroxyethyl)(propyl)amino]propoxy	2,3-difluorophenyl
211	3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy	2,3-difluorophenyl
212	3-[cyclopentyl(2-hydroxyethyl)amino]propoxy	2,3-difluorophenyl

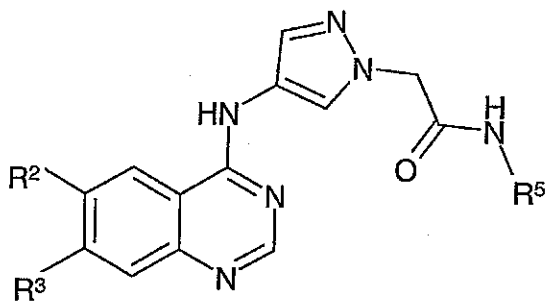
Table 8



Compound	R^1	R^3
213	isopropoxy	3-[bis(2-hydroxyethyl)amino]propoxy
214	isopropoxy	3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy
215	isopropoxy	3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy
216	isopropoxy	3-piperazin-1-ylpropoxy
217	isopropoxy	3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl
218	isopropoxy	(2-hydroxyethyl)amino]propoxy
219	isopropoxy	3-(4-glycoloylpiperazin-1-yl)propoxy
220	OMe	3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-

		yl]propoxy
221	OMe	OMe
222	OH	OMe
223	(2*R*)-pyrrolidin-2-ylmethoxy	OMe
224	[(2*R*)-1-glycoloylpyrrolidin-2-yl]methoxy	OMe
225	[(2*R*)-1-(*N*,*N*-dimethylglycyl)pyrrolidin-2-yl]methoxy}-	OMe
226	[(2*R*)-1-(2-hydroxyethyl)pyrrolidin-2-yl]methoxy	OMe
227	OMe	H
228	F	H

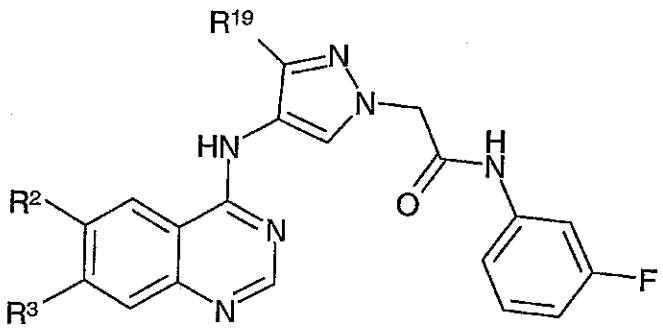
Table 9



Compound	R^2	R^3	R^5
229	3-morpholin-4-ylpropoxy	OMe	3-fluorophenyl
230	(1-methylpyrrolidin-3-yl)oxy	OMe	3-fluorophenyl
231	2-morpholin-4-ylethoxy	OMe	3-fluorophenyl
232	2-methoxyethoxy	2-methoxyethoxy	2,3-difluorophenyl
233	OH	OMe	3-fluorophenyl

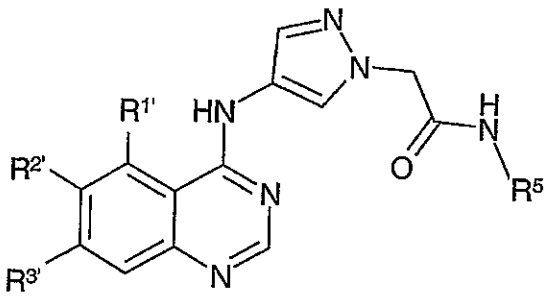
234	benzoate	(1-methylpiperidin-4-yl)methoxy	2,3-difluorophenyl
235	OH	(1-methylpiperidin-4-yl)methoxy	2,3-difluorophenyl

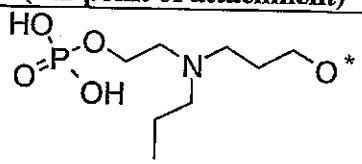
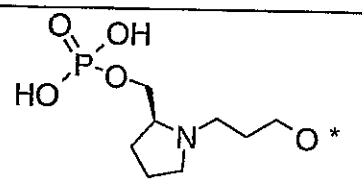
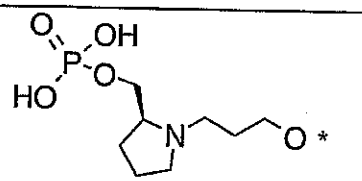
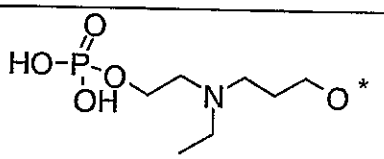
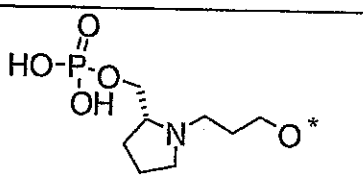
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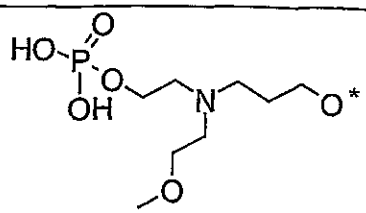
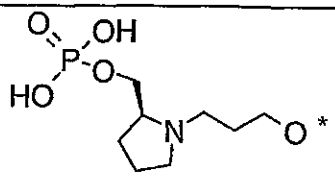
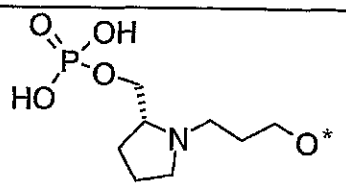
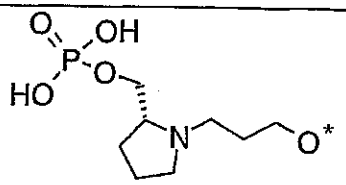
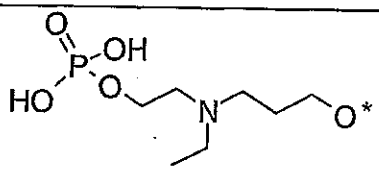
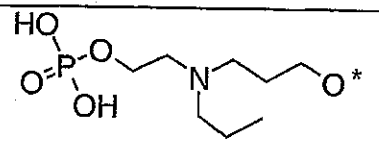
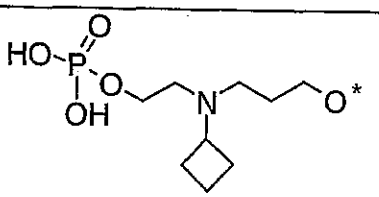
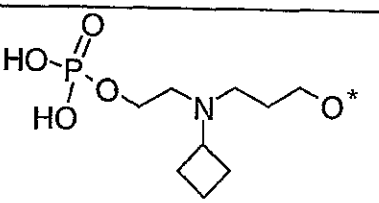


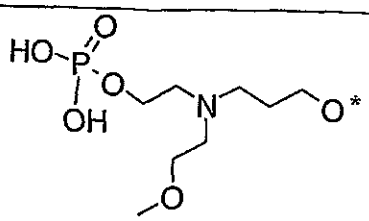
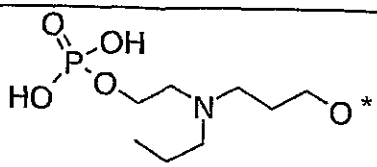
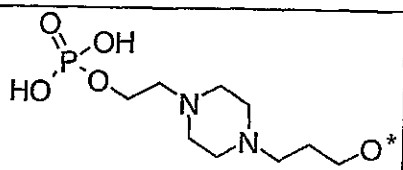
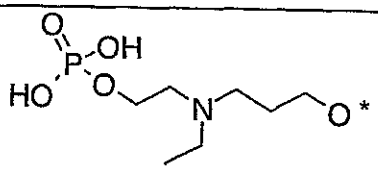
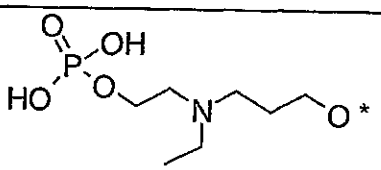
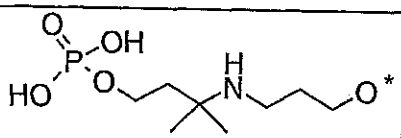
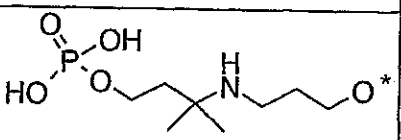
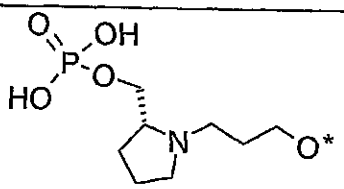
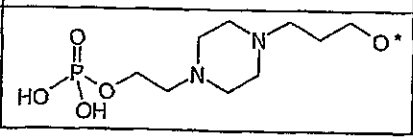
Compound	R^2	R^3	R^{19}
236	OMe	3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy	carboxamide
237	OMe	3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy	carboxamide
238	H	3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy	acetylamino
239	H	3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy	ethyl carboxylate
240	H	3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy	carboxylic acid

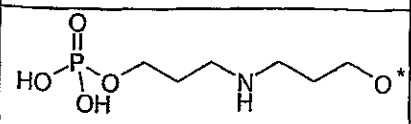
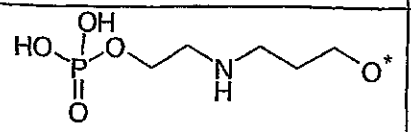
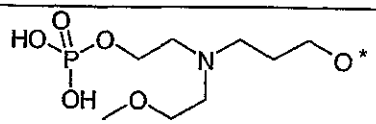
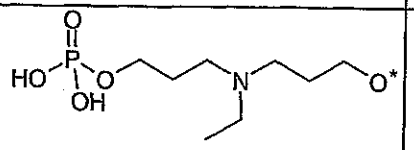
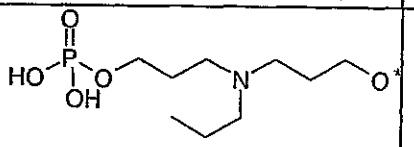
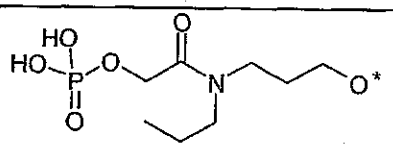
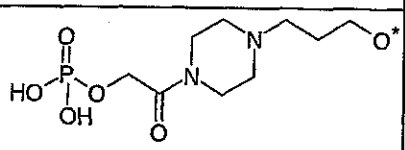
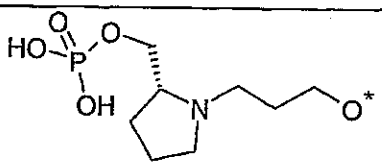
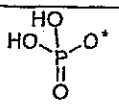
Table 11

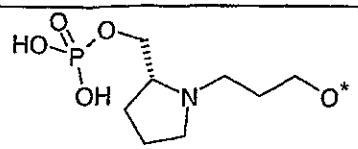
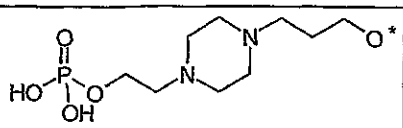
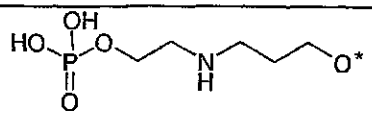
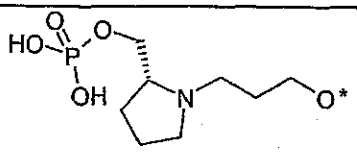
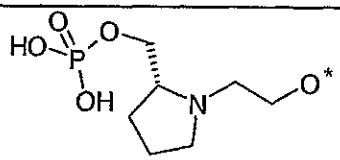
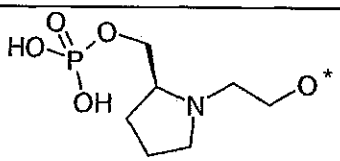
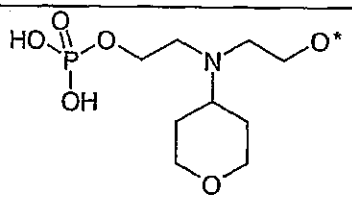
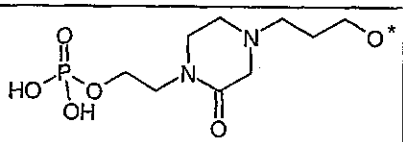
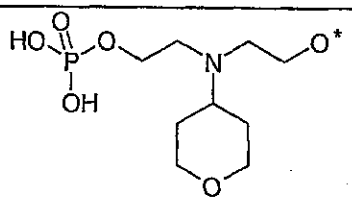


Compound	$R^{1'}$	$R^{2'}$	$R^{3'}$ (* is point of attachment)	R^5
241	H	OMe		2,3-difluorophenyl
242	H	OMe		2,3-difluorophenyl
243	H	OMe		3-fluorophenyl
244	H	OMe		3-fluorophenyl
245	H	OMe		3-fluorophenyl

246	H	OMe		2,3-difluorophenyl
247	H	H		2,3-difluorophenyl
248	H	H		2,3-difluorophenyl
249	H	OMe		2,3-difluorophenyl
250	H	OMe		2,3-difluorophenyl
251	H	H		2,3-difluorophenyl
252	H	OMe		2,3-difluorophenyl
253	H	OMe		3-fluorophenyl

254	H	OMe		3-fluorophenyl
255	H	H		3-fluorophenyl
256	H	H		2,3-difluorophenyl
257	H	H		3-fluorophenyl
258	H	H		2,3-difluorophenyl
259	H	H		3-fluorophenyl
260	H	H		2,3-difluorophenyl
261	H	H		3-fluorophenyl
262	H	H		3-fluorophenyl

263	H	H		2,3-difluorophenyl
264	H	H		2,3-difluorophenyl
265	H	H		3-fluorophenyl
266	H	H		2,3-difluorophenyl
267	H	H		2,3-difluorophenyl
268	H	H		2,3-difluorophenyl
269	H	H		2,3-difluorophenyl
270	H	F		2,3-difluorophenyl
271	H		(1-methylpiperidin-4-yl)methoxy	2,3-difluorophenyl

272	isopropoxy	H		2,3-difluorophenyl
273	isopropoxy	H		2,3-difluorophenyl
274	isopropoxy	H		2,3-difluorophenyl
275	OMe	H		2,3-difluorophenyl
276	H	OMe		2,3-difluorophenyl
277	H	OMe		2,3-difluorophenyl
278	H	OMe		2,3-difluorophenyl
279	H	H		2,3-difluorophenyl
280	H	H		2,3-difluorophenyl

Example 1 - Preparation of compound 1 in table 1 - 2-(4-{[7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide

A solution of 4.0 N hydrochloric acid in dioxane (250 μl) was added to a suspension of 2-(4-amino-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide (234 mg, 1 mmol) and 4-chloro-7-(3-chloropropoxy)-6-methoxyquinazoline (287 mg, 1 mmol) in dimethylacetamide (5 ml) and reaction mixture heated at 90 °C under argon for 0.5 hours. The mixture was cooled to ambient temperature, diluted with dichloromethane (16 ml) and the resultant precipitate filtered. The solid was washed with dichloromethane, diethyl ether and dried *in vacuo* to yield compound 1 in table 1 (495 mg, 95 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.96 (s, 1H), 8.39 (s, 1H), 8.09 (s, 1H), 7.95 (s, 1H), 7.61 (d, 1H), 7.38 (m, 2H), 7.33 (s, 1H), 6.92 (t, 1H), 5.15 (s, 2H), 4.33 (t, 2H), 4.03 (s, 3H), 3.84 (t, 2H), 2.32 (m, 2H).

MS (+ve ESI): 485.1, 487.2 $(M+H)^+$

2-(4-amino-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide used as starting material, was obtained as follows:

a) A solution of phosphorus oxychloride (668 mg, 4.40 mmol) in tetrahydrofuran (4 ml) was added to a mixture of (4-nitro-1H-pyrazol-1-yl)acetic acid (684 mg, 4.00 mmol), 3-fluoroaniline (500 mg, 4.5 mmol) and pyridine (1.26 g, 16 mmol) in tetrahydrofuran (20 ml) at 0 °C under argon. The resulting mixture was stirred for 1 hour and an aqueous solution of sodium bicarbonate (20 ml) added. The mixture was further diluted with water and extracted with ethyl acetate (3 x 50 ml). The organic phase was recovered, dried and concentrated to give an oil which was triturated with diethyl ether : petroleum ether (1:1) to yield *N*-(3-fluorophenyl)-2-(4-nitro-1*H*-pyrazol-1-yl)acetamide (695 mg, 65 % yield):

^{1}H-NMR (DMSO d_6): 8.93 (s, 1H), 8.33 (s, 1H), 7.51 (dd, 1H), 7.38 (q, 1H), 7.31 (d, 1H), 6.95 (t, 1H), 5.17 (s, 2H).

MS (+ve ESI): 265.2 $(M+H)^+$.

b) A solution of *N*-(3-fluorophenyl)-2-(4-nitro-1*H*-pyrazol-1-yl)acetamide (634 mg, 2.40 mmol) and platinum oxide (126 mg) in ethanol : ethyl acetate (1:4, 50 ml) was stirred under an atmosphere of hydrogen (80 psi) for 3 hours. The catalyst was removed by filtration and the residue purified by silica gel chromatography. Elution with dichloromethane : methanol (9:1 to 8:2) followed by dichloromethane : methanolic ammonia (3 N) (9:1) gave an oil which was

triturated with diethyl ether to yield 2-(4-amino-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide (350 mg, 62 % yield):

^{1}H-NMR (DMSO d_6): 7.57 (d, 1H), 7.35 (q, 1H), 7.29 (d, 1H), 7.09 (s, 1H), 6.96 (s, 1H), 6.91 (t, 1H), 5.77 (s, 2H), 4.82 (br s, 2H).

MS (+ve ESI): 235.3 $(M+H)^+$.

4-chloro-7-(3-chloropropoxy)-6-methoxyquinazoline used as starting material, was obtained as follows:

a) Palladium on carbon (3.3g of a 10 % mixture) was added to a solution of 7-(benzyloxy)-6-methoxyquinazolin-4-(3H)-one (20 g, 71 mmol) (prepared according to *J. Med. Chem.* **1999**, *42*, 5369-5389) was suspended in dimethylformamide (530 ml). Ammonium formate (45 g, 710 mmol) was then added portion wise over 1.25 hours. The reaction mixture was stirred for an additional 0.5 hours and the catalyst was removed by filtration. The solvent was removed *in vacuo* to yield 7-hydroxy-6-methoxyquinazolin-4-(3H)-one (8.65 g, 64 % yield):

^{1}H-NMR (DMSO d_6): 7.91 (s, 1H), 7.45 (s, 1H), 7.01 (s, 1H), 3.90 (s, 3H).

b) A mixture of 7-hydroxy-6-methoxyquinazolin-4-(3H)-one (8.0 g, 41.6 mmol), pyridine (7.5 ml) and acetic anhydride (63 ml) was heated at 100 °C for 4.5 hours and left to cool to ambient temperature 18 hours. The reaction mixture was poured into ice/water (400 ml) and the resultant precipitate collected by filtration and dried *in vacuo*. Analysis revealed that hydrolysis of the acetate group on the 4 position of the quinazoline was incomplete. The mixture was therefore treated with water (150 ml) and pyridine (0.5 ml) at 90 °C for 15 minutes. The reaction was cooled and the solid was collected by filtration, washed with water and dried *in vacuo* to yield 7-(acetoxy)-6-methoxyquinazolin-4-(3H)-one (7.4 g, 76 % yield):

^{1}H-NMR (DMSO d_6): 8.05 (s, 1H), 7.65 (s, 1H), 7.45 (s, 1H), 3.90 (s, 3H), 2.31 (s, 3H).

c) Dimethylformamide (0.5 ml) was added to a solution of 7-(acetoxy)-6-methoxyquinazolin-4-(3H)-one (2.0 g, 8.5 mmol) in thionyl chloride (32 ml) and the reaction mixture was heated at reflux for 1.5 hours. Upon cooling to ambient temperature, the thionyl chloride was removed *in vacuo* and azeotroped twice with toluene. The residue was diluted with dichloromethane (15 ml), a solution of 10 % ammonia in methanol (80 ml) added and the mixture heated at 80 °C for 10 minutes. Upon cooling to ambient temperature, the solvent was evaporated to almost complete dryness, water was added and the pH adjusted to 7 with dilute

hydrochloric acid. The resultant precipitate was collected by filtration and dried *in vacuo* at 35 °C for 18 hours to yield 4-chloro-7-hydroxy-6-methoxyquinazoline (1.65 g, 92 % yield):
^{1}H-NMR (DMSO d_6): 8.81 (s, 1H), 7.40 (s, 1H), 7.25 (s, 1H), 4.00 (s, 3H).

d) Triphenylphosphine (2.6 g, 10.1 mmol) and 3-chloropropanol (0.69 ml, 8.2 mmol) were added to a suspension of 4-chloro-7-hydroxy-6-methoxyquinazoline (1.65 g, 7.8 mmol) in dichloromethane (100 ml) under argon. The flask was placed in a water bath at 20 °C and di-*tert*butyl azodicarboxylate (2.30 g, 10.1 mmol) added portion wise over a few minutes. The reaction mixture was stirred at ambient temperature for 2 hours. The reaction mixture was concentrated and the solution loaded directly onto a silica chromatography column. Elution with ethyl acetate : petroleum ether (3:7), yielded 4-chloro-7-(3-chloropropoxy)-6-methoxyquinazoline (2.0 g, 91 % yield):
^{1}H-NMR (DMSO d_6): 8.90 (s, 1H), 7.55 (s, 1H), 7.45 (s, 1H), 4.42 (m, 2H), 4.05 (s, 3H), 3.80 (m, 2H), 2.31 (m, 2H).

Example 2 - Preparation of compound 2 in table 1 - 2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide

Di-*tert*butyl azodicarboxylate (805 mg, 3.50 mmol) in dichloromethane (5 ml) was slowly added to a mixture of *N*-(2,3-difluorophenyl)-2-{4-[(7-hydroxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (554 mg, 1.40 mmol), triphenyl phosphine (917 mg, 3.5 mmol) and 3-chloro-1-propanol (172 mg, 1.82 mmol) in dichloromethane (10 ml) and tetrahydrofuran (25 ml) at ambient temperature under argon. The mixture was stirred at ambient temperature for 18 hours and concentrated *in vacuo*. The residual oil was dissolved in dichloromethane and 4.0 N hydrochloric acid in dioxane (2 ml) added. Diethyl ether (10 ml) was added and the resultant precipitate was recovered by filtration, washed with diethyl ether and dried. The solid was dissolved in dichloromethane and treated with an aqueous solution of sodium bicarbonate. The aqueous phase was extracted with dichloromethane (2 x 15 ml) and the combined organic phases were dried and concentrated to yield compound 2 in table 1 (400 mg, 60 % yield):
^{1}H-NMR (DMSO d_6, TFA): 8.98 (s, 1H), 8.62 (d, 1H), 8.41 (s, 1H), 7.98 (s, 1H), 7.75 (t, 1H), 7.56 (d, 1H), 7.28 (s, 1H), 7.21 (m, 2H), 5.26 (s, 2H), 4.32 (t, 2H), 3.85 (t, 2H), 2.30 (t, 2H).
MS (+ve ESI): 473 $(M+H)^+$.

N-(2,3-difluorophenyl)-2-{4-[(7-hydroxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide used as starting material, was obtained as follows:

a) 2-Amino-4-fluorobenzoic acid (7.75 g, 50 mmol) was heated in formamide (50 ml) at 150 °C for 8 hours. Water (50 ml) was added to the reaction mixture and the solid recovered by filtration, washed with water and dried *in vacuo* (50 °C, 0.1 mm Hg) to yield 7-fluoroquinazolin-4-(3H)-one (7.3 g, 89 % yield):

^{1}H-NMR (DMSO d_6): 8.21 (m, 1H), 8.15 (s, 1H), 7.45 (m, 1H), 7.38 (m, 1H).

b) Sodium (10.3 g, 0.45 mol) was added to benzyl alcohol (200 ml, 1.94 mol) under argon and the mixture heated at 120 °C for 4 hours. 7-Fluoroquinazolin-4-(3H)-one (15 g, 90 mmol) was added to the mixture and the reaction heated at 120 °C for 18 hours. The mixture was cooled, poured into water (800 ml) and the pH adjusted to 4 with hydrochloric acid (2 N, 150 ml). The resultant precipitate was collected by filtration, washed with water, pentane and diethyl ether to yield 7-(benzyloxy)quinazolin-4-(3H)-one (22.3 g, 98 % yield):

^{1}H-NMR (DMSO d_6): 8.05 (s, 1H), 8.02 (d, 1H), 7.48 (m, 2H), 7.41 (t, 2H), 7.36 (d, 1H), 7.17 (m, 2H), 5.26 (s, 2H).

c) Dimethylformamide (0.5 ml) was added to a suspension of 7-(benzyloxy)quinazolin-4-(3H)-one (5.04 g, 20 mmol) in thionyl chloride (50 ml) and the mixture heated at reflux for 2 hours. The thionyl chloride was removed *in vacuo* and the residual oil dissolved in dichloromethane (100 ml). This solution was slowly added to an aqueous saturated solution of sodium bicarbonate (100 ml) and the organic phase recovered. The aqueous phase was extracted with dichloromethane (2 x 50 ml) and the combined organics dried and concentrated to yield 7-(benzyloxy)-4-chloroquinazoline (4.68 g, 86.5 % yield):

^{1}H-NMR (DMSO d_6, TFA): 9.15 (s, 1H), 8.15 (d, 1H), 7.51 (m, 2H), 7.43 (m, 2H), 7.38 (m, 2H), 7.30 (m, 1H), 5.32 (s, 2H).

d) 2-(4-amino-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide (504 mg, 2 mmol) was added to a solution of 7-(benzyloxy)-4-chloroquinazoline (541 mg, 2 mmol) in dimethylacetamide (10 ml) under argon. A solution of 4.0 N hydrochloric acid in dioxane (500 μl, 2 mmol) was added and the mixture was heated at 90 °C for 1.5 hours. The mixture was cooled, diluted with dichloromethane and the resultant precipitate recovered by filtration. The solid was washed with dichloromethane and diethyl ether and dried *in vacuo* to yield 2-(4-{[7-(benzyloxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide (850 mg, 81 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.97 (s, 1H), 8.68 (d, 1H), 8.41 (s, 1H), 8.00 (s, 1H), 7.75 (t, 1H), 7.61 (d, 1H), 7.53 (m, 2H), 7.45 (m, 2H), 7.42 (d, 1H), 7.36 (m, 1H), 7.20 (m, 2H), 5.38 (s, 2H), 5.25 (s, 2H).

MS (+ve ESI): 487.1 $(M+H)^+$.

e) 2-(4-{[7-(benzyloxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide (836 mg, 1.60 mmol) was dissolved in trifluoroacetic acid (8 ml) and heated under reflux for 2.5 hours. The solution was concentrated and the residual oil was dissolved in methanol and neutralised with an aqueous solution of sodium bicarbonate. Water was added to the mixture and the solid recovered by filtration and dried *in vacuo* to yield *N*-(2,3-difluorophenyl)-2-{4-[(7-hydroxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (633 mg, 100 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.92 (s, 1H), 8.51 (d, 1H), 8.36 (s, 1H), 7.92 (s, 1H), 7.70 (t, 1H), 7.32 (d, 1H), 7.21 (m, 2H), 7.13 (s, 1H), 5.22 (s, 2H).

MS (+ve ESI): 397 $(M+H)^+$.

2-(4-amino-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide, used as starting material was prepared as follows:

a) An analogous reaction to that described in example 1a, but starting 2,3-difluoroaniline (1.55 g, 120 mmol) yielded N-(2,3-difluorophenyl)-2-(4-nitro-1*H*-pyrazol-1-yl)acetamide (1.13 g, 40 % yield):

^{1}H-NMR (DMSO d_6): 10.43 (br s, 1H), 8.90 (s, 1H), 8.30 (s, 1H), 7.69 (m, 1H), 7.19 (m, 2H), 5.23 (s, 2H).

b) An analogous reaction to that described in example 1b, but starting with N-(2,3-difluorophenyl)-2-(4-nitro-1*H*-pyrazol-1-yl)acetamide (5.22 g, 185 mmol) yielded 2-(4-amino-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide (4.2 g, 90 % yield):

^{1}H-NMR (DMSO d_6): 7.68 (m, 1H), 7.17 (m, 2H), 7.09 (s, 1H), 6.97 (s, 1H), 4.90 (s, 2H), 3.85 (br s, 2H).

MS (+ve ESI) : 253 $(M+H)^+$.

Example 3 - Preparation of compound 3 in table 1 - 2-(4-{[7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide

4 N hydrochloric acid in dioxane (250 μl, 1 mmol) was added to a solution of 2-(4-amino-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide (293 mg, 1 mmol) and 4-chloro-7-

(3-chloropropoxy)-6-methoxyquinazoline (287 mg, 1 mmol) in dimethylacetamide (8 ml) and the mixture heated under argon at 90 °C for 1 hour. The reaction was cooled, diluted with dichloromethane (20 ml) and the resultant precipitate recovered by filtration. The solid was washed with dichloromethane, diethyl ether and dried *in vacuo* to yield compound 3 in table 1 (480 mg, 90 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.94 (s, 1H), 8.41 (s, 1H), 8.13 (s, 1H), 7.98 (s, 1H), 7.74 (m, 1H), 7.34 (s, 1H), 7.21 (m, 2H), 5.24 (s, 2H), 4.33 (t, 2H), 4.03 (s, 3H), 3.83 (t, 2H), 2.32 (t, 2H).

MS (+ve ESI): 503 $(M+H)^+$.

Example 4 - Preparation of compound 4 in table 1 - 2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 3 but starting with 2-(4-amino-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide (312 mg, 1.34 mmol) and 4-chloro-7-(3-chloropropoxy)quinazoline (344 mg, 1.34 mmol) yielded compound 4 in table 1 (624 mg, 95 % yield):

^{1}H-NMR (DMSO d_6): 11.84 (s, 1H), 10.81 (s, 1H), 8.94 (s, 1H), 8.82 (m, 1H), 8.42 (s, 1H), 8.02 (s, 1H), 7.60 (m, 1H), 7.49 (m, 1H), 7.36 (m, 3H), 6.92 (m, 1H), 5.15 (s, 2H), 4.13 (t, 2H), 3.85 (t, 2H), 2.28 (t, 2H).

MS (+ve ESI) : 455 $(M+H)^+$.

4-chloro-7-(3-chloropropoxy)quinazoline, used as the starting material was obtained as follows:

a) Formamidine acetate (20.13 g, 193.4 mmol) was added to a solution of 2-amino-4-fluorobenzoic acid (15 g, 96.7 mmol) in 2-methoxyethanol (97 ml) and the mixture heated to reflux for 18 hours. The reaction was cooled, concentrated and the residue stirred in aqueous ammonium hydroxide (0.01 M, 250 ml) for 1 hour. The suspension was filtered, washed with water and dried over phosphorus pentoxide to yield 7-fluoroquinazolin-4-ol as an off-white solid (10.35 g, 65 % yield):

^{1}H-NMR (DMSO d_6): 12.32 (br s, 1H), 8.19 (dd, 1H), 8.14 (s, 1H), 7.45 (m, 1H), 7.39 (m, 1H).

^{19}F-NMR (DMSO d_6): -105 (m)

MS (-ve ESI): 163 $(M-H)^-$,

MS (+ve ESI): 165 $(M+H)^+$.

b) Sodium hydride (14.6 g, 365 mmol) was added at 0 °C to a solution of 1,3-propanediol (27.8 g, 365 mmol) in dimethylformamide (70 ml). 7-Fluoroquinazolin-4-ol (10 g, 60.9 mmol) was added portion wise and the reaction mixture heated at 60 °C, then at 110 °C for 3 hours. The reaction was cooled to 0 °C, quenched with water (280 ml) and adjusted to pH 5.9. The resulting suspension was filtered, washed with water then diethyl ether and dried over phosphorus pentoxide to yield 7-(3-hydroxypropoxy)quinazolin-4-ol as a white powder (12.41 g, 92 % yield):

^{1}H-NMR (DMSO d_6): 11.90 (br s, 1H), 8.04 (s, 1H), 8.00 (d, 1H), 7.10 (m, 2H), 4.17 (t, 2H), 3.58 (t, 2H), 1.92 (m, 2H).

MS (+ve ESI): 221 $(M+H)^+$.

c) Dimethylformamide (1 ml) was added to a mixture of 7-(3-hydroxypropoxy)quinazolin-4-ol (10.5 g, 47.7 mmol) and thionyl chloride (100 ml, 137 mmol) and the reaction mixture heated to 85 °C for 1 hour. The mixture was cooled to ambient temperature, diluted with toluene and evaporated to dryness. This was repeated until all thionyl chloride was removed. The residue was dissolved in dichloromethane and washed with a saturated sodium bicarbonate solution. The aqueous layer was extracted with dichloromethane and the combined organics were dried (magnesium sulphate) and concentrated to leave a yellow solid. Trituration with diethyl ether removed a less soluble impurity and the diethyl ether filtrate was concentrated to yield 4-chloro-7-(3-chloropropoxy)quinazoline as an off-white solid (8.5 g, 70 % yield):

^{1}H-NMR (DMSO d_6): 13.25 (br s, 1H), 8.34 (s, 1H), 8.06 (d, 1H), 7.17 (m, 2H), 4.21 (t, 2H), 3.83 (t, 2H), 2.23 (m, 2H).

MS (+ve ESI): 257, 259 $(M+H)^+$.

Example 5 – Preparation of compound 5 in table 1 - 2-(4-{[7-(2-chloroethoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide

A mixture of 4-chloro-7-(2-chloroethoxy)quinazoline (1.65 g, 6.8 mmol), 2-(4-amino-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide (1.7 g, 6.8 mmol) and hydrogen chloride (1.57 ml of a 4M solution in 1,4-dioxane, 6.3 mmol) in dimethylacetamide (30 ml) was heated at 90°C for 1 hour and then allowed to cool to room temperature. The mixture was diluted with diethyl ether and the resultant precipitate filtered to give compound 5 in table 1 as the hydrochloride salt (4.3 g, 100% yield):

^{1}H-NMR (DMSO d_6): 11.74 (br s, 1H), 10.02 (s, 1H), 8.89 (s, 1H), 8.87 (d, 1H), 8.42 (s, 1H), 8.05 (s, 1H), 7.68 (m, 1H), 7.45 (m, 2H), 7.15 (m, 2H), 5.17 (s, 2H), 4.52 (t, 2H), 4.00 (t, 2H).

MS (+ve ESI): 459 $(M+H)^+$

MS (-ve ESI): 457 $(M-H)^-$.

4-chloro-7-(2-chloroethoxy)quinazoline used as starting material, was prepared as follows:

a) A mixture of sodium hydride (60% in oil, 7.67 g, 189.6 mmol) and dimethylacetamide (160 ml) were cooled in an ice-bath under a nitrogen atmosphere and then ethylene glycol (18.2 g, 284 mmol) was slowly added. The reaction mixture was warmed to 60°C for 10 minutes and then 7-fluoroquinazolin-4-ol (7.75 g, 47.3 mmol) was slowly added. The reaction mixture was heated to 110°C for 16 hours and then the mixture was concentrated to approximately half volume. The mixture was poured into water and the pH of the solution was adjusted to 5 with dilute hydrochloric acid. The resultant precipitate was filtered and then dried in a vacuum oven at 65°C for 16 hours. The residue was triturated with diethyl ether to give 7-(2-hydroxyethoxy)quinazolin-4-ol (4.4 g) as an off white solid which was used in subsequent steps without further purification:

MS (+ve ESI): 207 $(M+H)^+$

MS (-ve ESI): 205 $(M-H)^-$.

b) A mixture of 7-(2-hydroxyethoxy)quinazolin-4-ol (4.4 g, ~21mmol), thionyl chloride (40 ml) and dimethylformamide (0.4 ml) was heated at reflux for 2 hours. The mixture was evaporated under reduced pressure and then co-evaporated twice with toluene. The residue was partitioned between dichloromethane and aqueous ammonia solution and the organic layer was separated, dried over magnesium sulphate and then evaporated under reduced pressure. The residue was purified by silica gel chromatography eluting with a 0 to 8% mixture of methanol (containing 10% 7N ammonia in methanol) in dichloromethane to give 4-chloro-7-(2-chloroethoxy)quinazoline (4g, 65% yield):

^{1}H-NMR ($CDCl_3$): 8.95 (s, 1H), 8.17 (d, 1H), 7.37 (dd, 1H), 7.30 (d, 1H), 4.43 (t, 2H), 3.93 (t, 2H).

MS (+ve ESI): 243, 244, 246$(M+H)^+$.

Example 6 – Preparation of compound 6 in table 1 - 2-(4-{[7-(2-chloroethoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide

A mixture of 4-chloro-6-methoxyquinazolin-7-ol (5.0 g, 24 mmol), potassium carbonate (9.94 g, 72 mmol) and 1-bromo-2-chloroethane (7.98 ml, 96 mmol) in dimethyl acetamide (50 ml) was heated at 90°C for 3 hours. The reaction mixture was allowed to cool to room temperature and then filtered. The filtrate was purified directly by silica gel chromatography eluting with a 20 to 80% mixture of ethyl acetate in *iso*-hexane. The obtained product was triturated with diethyl ether to give a 3 : 1 mixture of 4-chloro-7-(2-chloroethoxy)-6-methoxyquinazoline : 4-chloro-7-(2-bromoethoxy)-6-methoxyquinazoline (4.77 g, 73% yield) as a white solid:

^{1}H-NMR (DMSO d_6 data for 4-chloro-7-(2-chloroethoxy)-6-methoxyquinazoline): 8.90 (s, 1H), 7.53 (s, 1H), 7.41 (s, 1H), 4.54 (t, 2H), 4.09 (t, 2H), 4.02 (s, 3H).

MS (+ve ESI, data for 4-chloro-7-(2-chloroethoxy)-6-methoxyquinazoline): 273, 275, 277 $(M+H)^+$

b) A 3 : 1 mixture of 4-chloro-7-(2-chloroethoxy)-6-methoxyquinazoline : 4-chloro-7-(2-bromoethoxy)-6-methoxyquinazoline (1.3 g, 4.5 mmol), 2-(4-amino-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide (1.4 g, 5.5 mmol) and hydrogen chloride (1.06 ml of a 4M solution in 1,4-dioxane) in dimethyl acetamide (20 ml) was heated at 90°C for 1 hour. The mixture was allowed to cool to room temperature and then diluted with diethyl ether and filtered to leave compound 6 in table 1 as a 2 : 1 mixture of 2-(4-{[7-(2-chloroethoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide : 2-(4-{[7-(2-bromoethoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide as the hydrochloride salt (2.5 g):

MS (+ve ESI data for 2-(4-{[7-(2-chloroethoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide): 489, 491 $(M+H)^+$.

Example 7 – Preparation of compound 7 in table 1 - *N*-(2,3-difluorophenyl)-2-(4-{[7-(2,2-dimethoxyethoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide

Bromoacetaldehyde dimethyl acetal (1.3 ml, 11.0 mmol) was added to a solution of *N*-(2,3-difluorophenyl)-2-{4-[(7-hydroxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide trifluoroacetate (4.37 g, 10.5 mmol), cesium carbonate (13.21 g, 40.5 mmol) and potassium iodide (1.86 g, 11.2 mmol) in dimethylacetamide (35 ml) heated at 106°C and the mixture was stirred at this temperature for 3.5 hours. The mixture was allowed to cool to room

temperature and then a dilute solution of hydrochloric acid (2M, 27.5 ml) was added to pH 7. The solution was diluted with water (100 ml) and the resultant precipitate was filtered. The filtered solid was washed with water (2 x 30 ml) and then with diethylether (2 x 50 ml) to give compound 7 in table 1 (1.76 g, 34% yield) which was used in subsequent steps without further purification:

^{1}H-NMR (DMSO d_6): 10.27 (s, 1H), 9.93 (s, 1H), 8.54 (s, 1H), 8.36 (d, 1H), 8.33 (s, 1H), 7.77 (s, 1H), 7.68-7.74 (m, 1H), 7.25 (dd, 1H), 7.13-7.22 (m, 3H), 5.14 (s, 2H), 4.75 (t, 1H), 4.15 (d, 2H), 3.37 (s, 6H);

MS (+ve ESI): 485 $(M+H)^+$.

N-(2,3-difluorophenyl)-2-{4-[(7-hydroxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide trifluoroacetate used as starting material, was prepared as follows:

a) A solution of 2-(4-{[7-(benzyloxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide (0.977 g, 1.87 mmol) in trifluoroacetic acid (20 ml) was heated at reflux for 4.5 hours. The mixture was evaporated under reduced pressure and the resultant residue was triturated with diethyl ether to give *N*-(2,3-difluorophenyl)-2-{4-[(7-hydroxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide as the trifluoroacetate salt (0.944 g, 99% yield):

^{1}H-NMR (DMSO d_6): 11.43 (br s, 1H), 10.39 (br s, 1H), 8.90 (s, 1H), 8.50 (d, 1H), 8.34 (s, 1H), 7.92 (s, 1H), 7.67-7.73 (m, 1H), 7.29 (dd, 1H), 7.16-7.23 (m, 2H), 7.11 (d, 1H), 5.21 (s, 2H);

MS (+ve ESI): 397 $(M+H)^+$.

Example 8 – Preparation of compound 8 in table 1 – 4-{[7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl]amino}-1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazole-3-carboxamide

A solution of 4-chloro-7-(3-chloropropoxy)-6-methoxyquinazoline (327 mg, 1 mmol) and 4-amino-1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazole-3-carboxamide (280 mg, 1 mmol) in dimethylacetamide (5 ml) and a solution of hydrogen chloride in dioxane (4M, 0.25 ml) was heated at 85°C for 1 hour. The mixture was evaporated and the residue was triturated with dichloromethane and diethylether and then dried *in vacuo* at 50°C to yield compound 8 in table 1 (580 mg, 100% yield):

^{1}H-NMR (DMSOd_6): 11.72 (s, 1H), 10.92 (s, 1H), 8.97 (s, 1H), 8.58 (s, 1H), 8.07 (s, 1H), 7.81 (s, 1H), 7.6 (d, 1H), 7.51 (s, 1H), 7.45 (s, 1H), 7.37 (m, 2H), 6.93 (m, 1H), 5.28 (s, 2H), 4.33 (t, 2H), 4.02 (s, 3H), 3.85 (t, 2H), 2.32 (m, 2H);

MS (+ve ESI): 528.06 $(M+H)^+$.

4-amino-1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazole-3-carboxamide used as starting material, was prepared as follows:

a) Ethyl 4-nitro-1H-pyrazole-3-carboxylate (741 mg, 4 mmol) was heated at 90°C with a concentrated solution of aqueous ammonia (28%, 20 ml) in a sealed vessel for 3 hours. The mixture was evaporated and the residue was triturated with diethyl ether to give 4-nitro-1H-pyrazole-3-carboxamide (0.54 g, 86% yield) as a white solid:

^{1}H-NMR (DMSO d_6): 8.70 (s, 1H), 8.06 (s, 1H), 7.83 (s, 1H);

MS (+ve ESI): 157.13 $(M+H)^+$.

b) A mixture of 2-chloro-*N*-(3-fluorophenyl)acetamide (0.65 g, 3.46 mmol), 4-nitro-1H-pyrazole-3-carboxamide (0.54 g, 3.46 mmol) and potassium carbonate (0.57 g, 4.13 mmol) in dimethylformamide (10 ml) was stirred at room temperature for 48 hours. The mixture was evaporated and the residue partitioned between ethyl acetate and water. The organic phase was separated, washed, dried and then concentrated to yield 1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-4-nitro-1*H*-pyrazole-3-carboxamide (730 mg, 69% yield).

^{1}HNMR (DMSO d_6): 10.68 (s, 1H), 8.9 (s, 1H), 8.05 (s, 1H), 7.78 (s, 1H), 7.55 (m, 1H), 7.38 (m, 1H), 7.29 (d, 1H), 6.94 (m, 1H), 5.15 (s, 2H);

MS (+ve ESI): 308.08 $(M+H)^+$.

c) Hydrazine hydrate (0.4 ml, 8.26 mmol) was slowly added to a mixture of 1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-4-nitro-1*H*-pyrazole-3-carboxamide (580 mg, 1.89 mmol) and Raney nickel (0.25 g) in ethanol (40 ml) at 50°C, and the mixture was stirred for 1 hour. Dimethylformamide was added to the mixture to solubilize the precipitated solid. The mixture was filtered, the filtrate was evaporated and the residue triturated with a mixture of dichloromethane and diethyl ether to yield 4-amino-1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazole-3-carboxamide (430 mg, 81% yield):

^{1}H-NMR (DMSO d_6): 10.49 (s, 1H), 7.55 (d, 1H), 7.37 (q, 1H), 7.29 (d, 1H), 7.16 (s, 1H), 7.14 (s, 1H), 7.0 (s, 1H), 6.91 (m, 1H), 4.92 (s, 2H), 4.68 (s, 2H);

MS (+ve ESI): 278.19 $(M+H)^+$.

Example 9 – Preparation of compound 9 in table 1 – ethyl 4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazole-3-carboxylate

A mixture of ethyl 4-amino-1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazole-3-carboxylate (0.123 g, 0.4 mmol) and 4-chloro-7-(3-chloropropoxy)quinazoline (0.102 g, 0.4 mmol) in dimethyl acetamide (2ml) was heated at 80°C for 0.5 hour. The reaction mixture was allowed to cool and then diluted with diethyl ether. The precipitated solid was filtered and then washed with a mixture of diethyl ether : dichloromethane 1 : 1 to give compound 9 in table 1 (0.219 g, 92% yield):

^{1}H-NMR (DMSO d_6 TFA): 9.0 (s, 1H), 8.49 (m, 2H), 7.59 (m, 2H), 7.37 (m, 3H), 6.92 (t, 1H), 5.3 (s, 2H), 4.38 (t, 2H), 4.29 (q, 2H), 3.87 (t, 2H), 2.32 (t, 2H), 1.2 (t, 3H).

MS (+ ve ESI): 527.22 $(M+H)^+$

Ethyl 4-amino-1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazole-3-carboxylate used as starting material, was prepared as follows:

a) A mixture of ethyl 4-nitro-1H-pyrazole-3-carboxylate (0.685 g, 3.7 mmol) and 2-chloro-*N*-(3-fluorophenyl) acetamide (0.694 g, 3.7 mmol) and potassium carbonate (0.613 g, 4.44 mmol) in dimethyl formamide (10 ml) was stirred at room temperature for 20 hours. The mixture was evaporated and the residue was purified by silica gel chromatography eluting with a 8 to 10% mixture of ethyl acetate in dichloromethane to give ethyl 1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-4-nitro-1*H*-pyrazole-3-carboxylate (0.920 g, 74% yield):

^{1}H-NMR (DMSO d_6 TFA): 9.02 (s, 1H), 7.57 (d, 1H), 7.39 (q, 1H), 7.32 (d, 1H), 6.93 (t, 1H), 5.24 (s, 2H), 4.38 (q, 2H), 1.31 (t, 3H);

MS (+ ve ESI): 337.17 $(M+H)^+$.

b) A mixture of ethyl 1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-4-nitro-1*H*-pyrazole-3-carboxylate (0.168 g, 0.5 mmol) was hydrogenated over 10% palladium on carbon (0.034 g) in a mixture of methanol (6 ml) and dichloromethane (3 ml) for 3 hours. The mixture was filtered through Celite and the filtrate was evaporated to leave ethyl 4-amino-1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazole-3-carboxylate (0.135 g, 88% yield):

^{1}H-NMR (DMSO d_6): 10.57 (s, 1H), 7.56 (d, 1H), 7.37 (q, 1H), 7.29 (d, 1H), 7.23 (s, 1H), 6.91 (t, 1H), 4.96 (s, 2H), 4.71 (s, 2H), 4.23 (q, 2H), 1.27 (t, 3H).

MS (+ ve ESI): 307.27 $(M+H)^+$

Example 10– Preparation of compound 10 in table 1 - 2-(3-(acetylamino)-4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide

2-[3-(Acetylamino)-4-amino-1*H*-pyrazol-1-yl]-*N*-(3-fluorophenyl)acetamide (0.160 g, 0.55 mmol) and 4-chloro-7-(3-chloropropoxy)quinazoline (0.141 g, 0.55 mmol) were dissolved in dimethyl acetamide (2 ml). Dioxane hydrochloric acid (4 M, 0.055 ml) was added and the mixture was heated at 80°C for 20 minutes. The reaction mixture was allowed to cool and then diluted with diethyl ether. The resultant solid was filtered and then dried *in vacuo* at 50°C to leave compound 10 in table 1 (0.280 g, 89% yield):

^{1}H-NMR (DMSO d_6): 10.66 (s, 1H), 8.95 (s, 1H), 8.56 (s, 1H), 8.19 (d, 1H), 7.57 (d, 1H), 7.52 (d, 1H), 7.34 (m, 2H), 7.29 (s, 1H), 6.88 (t, 1H), 5.06 (s, 2H), 4.3 (t, 2H), 3.82 (t, 2H), 2.27 (t, 2H), 2.15 (s, 3H);

MS (+ve ESI): 512.25, 514.25 $(M+H)^+$.

2-[3-(Acetylamino)-4-amino-1*H*-pyrazol-1-yl]-*N*-(3-fluorophenyl)acetamide used as starting material, was prepared as follows:

a) A solution of *N*-1H-pyrazol-3-ylacetamide (*Liebigs annalen der chemie.*, **1967**, *707*, 147; 0.500 g, 4.0 mmol) was stirred in a mixture of nitric acid (d = 1.52, 0.2 ml, 4.8 mmol) and sulphuric acid (d = 1.83, 2 ml) at 0°C for 2.5 hours. The mixture was poured onto ice and the resultant precipitate was filtered, washed with water and then a 2 : 1 mixture of diethyl ether : methanol and then with diethyl ether. The residue was dried *in vacuo* to give *N*-(4-nitro-1*H*-pyrazol-3-yl)acetamide (0.44 g, 65% yield):

^{1}H-NMR (DMSO d_6 TFA): 8.33 (s, 1H), 2.18 (s, 3H);

MS (- ve ESI): 169.2 $(M-H)^-$.

b) A mixture of *N*-(4-nitro-1*H*-pyrazol-3-yl)acetamide (0.380 g, 2.25 mmol), 2-chloro-*N*-(3-fluorophenyl)acetamide (0.420 g, 2.25 mmol) and potassium carbonate (00.370 g, 2.7 mmol) in dimethyl formamide (10 ml) was heated at 50°C for 1 hour. The mixture was filtered and the filtrate was evaporated. The residue was triturated with a mixture of 2% methanol in dichloromethane and then with diethyl ether to give 2-[3-(acetylamino)-4-nitro-1*H*-pyrazol-1-yl]-*N*-(3-fluorophenyl)acetamide

(0.400 g, 55% yield):

^{1}H-NMR (DMSO d_6 TFA): 8.85 (s, 1H), 7.56 (d, 1H), 7.37 (q, 1H), 7.31 (d, 1H), 6.93 (t, 1H), 5.08 (s, 2H), 2.06 (s, 3H);

MS (+ ve ESI): 322.21 $(M+H)^+$.

c) Hydrazine hydrate (43.6 μl, 0.9 mmol) was slowly added to a solution of 2-[3-(acetylamino)-4-nitro-1*H*-pyrazol-1-yl]-*N*-(3-fluorophenyl)acetamide (0.145 g, 0.45 mmol) in a mixture of dimethylacetamide (3 ml) and methanol (3 ml) in the presence of 10% palladium on carbon (0.030 g). The mixture was stirred at 75°C for 20 minutes and then allowed to cool. The mixture was filtered through Celite and the residue washed with methanol. The filtrate was evaporated and the residue triturated with a 1 : 2 mixture of dichloromethane : diethyl ether to give 2-[3-(acetylamino)-4-amino-1*H*-pyrazol-1-yl]-*N*-(3-fluorophenyl)acetamide (0.125 g, 95% yield):

^{1}H-NMR (DMSO d_6 TFA): 7.99 (s, 1H), 7.58 (d, 1H), 7.37 (q, 1H), 7.30 (d, 1H), 6.92 (t, 1H), 5.02 (s, 2H), 2.09 (s, 3H);

MS (+ ve ESI): 292.27 $(M+H)^+$.

Example 11 – Preparation of compound 11 in table 1 - *N*-(2,3-difluorophenyl)-2-[4-(quinazolin-4-ylamino)-1*H*-pyrazol-1-yl]acetamide

A mixture of quinazolin-4(3*H*)-one (0.146 g, 1.0 mmol) and 1 drop of dimethylformamide in thionyl chloride (3 ml) was heated at 70°C for 1 hour. The mixture was evaporated under reduced pressure and the residue suspended in dimethylacetamide (5 ml). 2-(4-Amino-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide (0.252 g, 1.0 mmol) was added and the mixture was then heated at 80°C for 1 hour. The reaction mixture was allowed to cool to room temperature and then acetonitrile (20 ml) was added and the resultant solid filtered to leave compound 11 in table 1 (0.220 g, 58% yield):

^{1}H-NMR (DMSO d_6): 11.82 (br s, 1H), 10.39 (br s, 1H), 9.00 (s, 1H), 8.78 (d, 1H), 8.42 (s, 1H), 8.10 (d, 1H), 8.04 (s, 1H), 7.84 (m, 2H), 7.65 (m, 1H), 7.20 (m, 2H), 5.22 (s, 2H);

MS (+ve ESI): 381 $(M+H)^+$.

Example 12 – Preparation of compound 12 in table 1 – 2-(4-{[7-(3-chloropropoxy)-5-isopropoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide

1-Bromo-3-chloropropane (0.6 ml, 6 mmol) was added to a solution of *N*-(2,3-difluorophenyl)-2-{4-[(7-hydroxy-5-isopropoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (2.7 g, 6.0 mmol) and potassium carbonate (0.90 g, 6.0 mmol) in dimethylacetamide (60 ml) and the mixture was heated at 70°C for 1 hour. The mixture was evaporated under reduced pressure and the residue was purified by silica gel chromatography eluting with a 0 to 10% mixture of methanol (containing 10% 7N ammonia in methanol) in dichloromethane to give compound 12 in table 1 (1.5 g, 46% yield) as a white solid:

^{1}H-NMR (DMSO d_6): 10.68 (br s, 1H), 9.8 (s, 1H), 8.42 (s, 1H), 8.34 (s, 1H), 7.70 (s, 2H), 7.19 (m, 2H), 6.78 (d, 1H), 6.70 (d, 1H), 5.15 (s, 2H), 4.96 (septet, 1H), 4.20 (m, 2H), 3.80 (t, 2H), 2.22 (t, 2H), 1.42 (d, 6H);

MS (+ve ESI): 532 $(M+H)^+$

MS (-ve ESI): 529 $(M-H)^-$.

N-(2,3-difluorophenyl)-2-{4-[(7-hydroxy-5-isopropoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide used as starting material, was prepared as follows:

a) Isopropanol (1.5 ml, 18.7 mmol) was added to a solution of [7-(benzyloxy)-5-hydroxy-4-oxoquinazolin-3(4*H*)-yl]methyl pivalate (see WO01/094341, 6.5 g, 17.0 mmol) and triphenylphosphine (6.2 g, 23.8 mmol) in dichloromethane (300 ml). The reaction mixture was cooled to 0°C and then a solution of di-*tert*-butylazodicarboxylate (4.7 g, 20.4 mmol) in dichloromethane (25 ml) was added dropwise over 30 minutes. The mixture was allowed to warm to room temperature and then stirred for 2 hours. The mixture was evaporated under reduced pressure to afford crude [7-(benzyloxy)-5-isopropoxy-4-oxoquinazolin-3(4*H*)-yl]methyl pivalate which was used in the next stage without further purification.

b) [7-(benzyloxy)-5-isopropoxy-4-oxoquinazolin-3(4*H*)-yl]methyl pivalate was stirred in a 7N solution of ammonia in methanol (250 ml) at room temperature for 24 hours. The mixture was evaporated under reduced pressure and the residue purified by silica gel chromatography eluting with a 0 to 10% mixture of methanol in dichloromethane to give 7-(benzyloxy)-5-isopropoxyquinazolin-4(3*H*)-one (4.6 g, 87% yield over 2 steps) as a white solid:

^{1}H-NMR (DMSO d_6): 11.63 (br s, 1H), 7.88 (s, 1H), 7.40 (m, 5H), 6.74 (d, 1H), 6.60 (d, 1H), 5.20 (s, 2H), 4.63 (septet, 1H), 1.26 (d, 6H);

MS (+ve ESI): 311 $(M+H)^+$

MS (-ve ESI): 309 $(M-H)^-$.

c) Ammonium formate (9.5 g, 150 mmol) and 10% palladium on carbon (500 mg) were added to a solution of 7-(benzyloxy)-5-isopropoxyquinazolin-4(3*H*)-one (4.6 g, 15.0 mmol) in dimethylformamide (40 ml) and the mixture stirred at ambient temperature for 4 hours. The mixture was filtered through Celite and then evaporated under reduced pressure. The residue was stirred in water (100 ml) for 30 minutes and then filtered and washed with water (25 ml) and then dried to leave 7-hydroxy-5-isopropoxyquinazolin-4(3*H*)-one (3.3 g, 100% yield) as a white solid:

^{1}H-NMR (DMSO d_6): 11.47 (br s, 1H), 10.29 (br s, 1H), 7.88 (s, 1H), 6.48 (d, 1H), 6.40 (d, 1H), 4.56 (septet, 1H), 1.26 (d, 6H);

MS (+ve ESI): 221 $(M+H)^+$

MS (-ve ESI): 219 $(M-H)^-$.

d) Pyridine (0.18 ml, 1.5 mmol) was added to a suspension of 7-hydroxy-5-isopropoxyquinazolin-4(3*H*)-one (3.3 g, 15 mmol) in acetic anhydride (10 ml, 75 mmol) and the mixture was stirred at 75°C for 45 minutes. The mixture was evaporated under reduced pressure and the residue obtained was stirred in water (50 ml) at 75°C for 1 hour and then cooled to ambient temperature and filtered to afford 5-isopropoxy-4-oxo-3,4-dihydroquinazolin-7-yl acetate (2.6 g, 65% yield) as a white solid:

^{1}H-NMR (DMSO d_6): 11.85 (br s, 1H), 7.96 (s, 1H), 6.89 (d, 1H), 6.82 (d, 1H), 4.62 (septet, 1H), 2.25 (s, 3H), 1.28 (d, 6H);

MS (+ve ESI): 263 $(M+H)^+$

MS (-ve ESI): 261 $(M-H)^-$.

e) Phosphoryl chloride (3.7 ml, 40 mmol) was added to a solution of 5-isopropoxy-4-oxo-3,4-dihydroquinazolin-7-yl acetate (2.6 g, 10 mmol) and di-*iso*-propylethylamine (14 ml, 80 mmol) in 1,2-dichloroethane (75 ml) and the reaction was heated at 80°C for 1 hour. The mixture was evaporated under reduced pressure and the residue suspended in dimethylacetamide (30 ml). 2-(4-Amino-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide (2.5 g, 10 mmol) was added and the mixture was then heated at 90°C for 1 hour. The mixture was evaporated under reduced pressure and the residue stirred in a 7N solution of ammonia in methanol (100 ml) at ambient temperature for 2 hours. The mixture was evaporated under reduced pressure to leave a yellow solid which was stirred in water (50 ml) for 1 hour, then filtered and the residue purified by silica gel chromatography eluting with a 0 to 10% mixture

of methanol in dichloromethane to give *N*-(2,3-difluorophenyl)-2-{4-[(7-hydroxy-5-isopropoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (2.7 g, 60% yield):
^{1}H-NMR (DMSO d_6): 10.27 (br s, 1H), 9.8 (s, 1H), 8.38 (s, 1H), 8.34 (s, 1H), 7.70 (s, 2H), 7.19 (m, 2H), 6.60 (s, 1H), 5.12 (s, 2H), 4.84 (septet, 1H), 1.42 (d, 6H);
MS (+ve ESI): 455 $(M+H)^+$
MS (-ve ESI): 453 $(M-H)^-$.

Example 13 – Preparation of compound 13 in table 1 - 2-(4-{[7-(3-chloropropoxy)-5-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide

Phosphoryl chloride (0.21 ml, 2.3 mmol) was added to a solution of 7-(3-chloropropoxy)-5-methoxyquinazolin-4(3*H*)-one (0.180 g, 0.67 mmol) and di-*iso*-propylethylamine (0.75 ml, 4.3 mmol) in 1,2-dichloroethane (10 ml) and the mixture was heated at 80°C for 3 hours. The mixture was evaporated under reduced pressure and the residue suspended in dimethylacetamide (10 ml). 2-(4-Amino-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide (0.169 g, 0.67 mmol) was added and the mixture was heated at 90°C for 1 hour. The mixture was evaporated under reduced pressure and the residue triturated with methanol to give compound 13 in table 1 (0.250 g, 74% yield):
^{1}H-NMR (DMSO d_6): 8.80 (s, 1H), 8.35 (s, 1H), 7.95 (s, 1H), 7.70 (m, 1H), 7.20 (m, 2H), 6.92 (s, 1H), 6.80 (s, 1H), 5.20 (s, 2H), 4.30 (t, 2H), 4.15 (s, 3H), 3.81 (t, 2H), 2.20 (m, 2H);
MS (+ve ESI): 503 $(M+H)^+$.

7-(3-chloropropoxy)-5-methoxyquinazolin-4(3*H*)-one used as starting material, was prepared as follows:

a) Potassium carbonate (5.4 g, 41.6 mmol) was added to a solution of [7-(benzyloxy)-5-hydroxy-4-oxoquinazolin-3(4*H*)-yl]methyl pivalate (see WO01/094341, 4.0 g, 10.4 mmol) in dimethylformamide (200 ml) and the mixture was stirred at 0°C for 5 minutes. Dimethyl sulphate (2.0 ml, 20.8 mmol) was added and the reaction mixture stirred at 0°C for a further 5 minutes and then warmed to room temperature and stirred for 1 hour. The reaction mixture was evaporated under reduced pressure and the residue dissolved in dichloromethane (100 ml) and washed with water (2 x 50 ml). The organics were dried over magnesium sulphate, filtered and evaporated under reduced pressure to give 7-(benzyloxy)-5-methoxy-4-oxoquinazolin-3(4*H*)-yl]methyl pivalate which was used in the next stage without further purification.

b) 7-(benzyloxy)-5-methoxy-4-oxoquinazolin-3(4*H*)-yl]methyl pivalate in trifluoroacetic acid (50 ml) was heated at 70°C for 3 hours. The mixture was evaporated under reduced pressure and purified by reverse phase chromatography eluting with 0.2% aqueous trifluoroacetic acid in acetonitrile using a 5 to 50% gradient over 25 minutes to give 7-hydroxy-5-methoxy-4-oxoquinazolin-3(4*H*)-yl)methyl pivalate (1.68 g, 53 % yield over 2 steps) as a white solid:

^{1}H-NMR (DMSO d_6): 10.82 (br s, 1H), 8.20 (s, 1H), 6.50 (s, 1H), 6.45 (s, 1H), 5.78 (s, 2H), 3.78 (s, 3H), 1.15 (s, 9H);

MS (+ve ESI): 307 $(M+H)^+$.

c) 1-Bromo-3-chloropropane (0.44 ml, 4.4 mmol) was added to a solution of 7-hydroxy-5-methoxy-4-oxoquinazolin-3(4H)-yl)methyl pivalate (1.68 g, 4.4 mmol) and potassium carbonate (1.2 g, 8.8 mmol) in dimethylacetamide (40 ml) and the mixture was heated at 70°C for 3 hours. The mixture was evaporated under reduced pressure and the residue purified by reverse phase chromatography eluting with 0.2% aqueous trifluoroacetic acid in acetonitrile using a 5 to 50% gradient over 25 minutes. The fractions containing product were concentrated under reduced pressure and then basified with aqueous sodium carbonate. The resultant solid was filtered and washed with water to give 7-(3-chloropropoxy)-5-methoxy-4-oxoquinazolin-3(4H)-yl]methyl pivalate (0.380 g, 36 % yield):

^{1}H-NMR (DMSO d_6): 8.35 (s, 1H), 6.70 (d, 1H), 6.60 (d, 1H), 5.80 (s, 2H), 4.23 (t, 2H), 3.82 (s, 3H), 3.78 (t, 2H), 2.20 (m, 2H), 1.15 (s, 9H);

MS (+ve ESI): 383 $(M+H)^+$.

d) 7-(3-chloropropoxy)-5-methoxy-4-oxoquinazolin-3(4H)-yl]methyl pivalate (0.380 g, 1.0 mmol) was stirred in a 7N solution of ammonia in methanol (50 ml) at room temperature for 24 hours. The volatiles were removed by evaporation under reduced pressure and the residue purified by reverse phase chromatography eluting with 0.2% aqueous trifluoroacetic acid in acetonitrile using a 5 to 50% gradient over 25 minutes. The fractions containing product were concentrated under reduced pressure and then basified with aqueous sodium carbonate. The resultant solid was filtered and washed with water to give 7-(3-chloropropoxy)-5-methoxyquinazolin-4(3*H*)-one (0.180 g, 67% yield):

^{1}H-NMR (DMSO d_6): 8.35 (s, 1H), 6.70 (d, 1H), 6.60 (d, 1H), 5.80 (s, 2H), 4.23 (t, 2H), 3.82 (s, 3H), 3.78 (t, 2H), 2.20 (m, 2H), 1.15 (s, 9H);

MS (+ve ESI): 383 $(M+H)^+$.

Example 14 – Preparation of compound 14 in table 1 - 2-(4-{[7-(3-chloropropoxy)-6-fluoroquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide

A mixture of 2-{4-[(6-fluoro-7-hydroxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide trifluoroacetate (1.89 g, 3.58 mmol), 1-bromo-3-chloropropane (0.68 g, 4.32 mmol) and cesium carbonate (2.5 g, 7.67 mmol) in dimethylformamide (20 ml) was heated at 70°C for 90 minutes. The mixture was allowed to cool to room temperature and then poured into water and the resultant precipitate filtered to give compound 14 in table 1 (1.59 g, 90% yield):

MS (+ve ESI): 491 $(M+H)^+$.

2-{4-[(6-fluoro-7-hydroxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide trifluoroacetate used as starting material, was prepared as follows:

a) Benzyl alcohol (4.27 g, 39.5 mmol) was added dropwise to a stirred suspension of sodium hydride (1.6 g of a 60 % dispersion in mineral oil, 40.0 mmol) in dimethylformamide (50 ml) at 0 °C. The reaction was stirred at 0 °C for 1 hour before addition of 6,7-difluoroquinazolin-4(1*H*)-one (3.60 g, 19.8 mmol) whereupon the reaction was heated to 60 °C for 2 hours. The reaction was cooled to ambient temperature, poured into water (200 ml) and the resultant solid collected by suction filtration. Drying of the solid *in vacuo* yielded 7-(benzyloxy)-6-fluoroquinazolin-4(1*H*)-one (4.45 g, 83 % yield) as a pale brown solid : ^{1}H-NMR (DMSO d_6) : 12.24 (br s, 1H), 8.05 (s, 1H), 7.80 (d, 1H), 7.52 (m, 2H), 7.44 (m, 3H), 7.38 (t, 1H), 5.35 (s, 2H).

b) 7-(Benzyloxy)-6-fluoroquinazolin-4(1*H*)-one (2.00 g, 7.41 mmol) was taken up in phosphorus oxychloride (20 ml) and the reaction heated at reflux for 90 minutes. The reaction was cooled, azeotroped with toluene (2 x 50 ml) and taken up in dichloromethane (5 ml) The organic phase was washed with saturated aqueous sodium hydrogen carbonate solution and then dried over magnesium sulphate. Solvent evaporation *in vacuo* followed by drying of the solid *in vacuo* yielded 7-(benzyloxy)-4-chloro-6-fluoroquinazoline (1.50 g, 71 % yield) as a pale yellow solid :

^{1}H-NMR ($CDCl_3$) : 8.93 (s, 1H), 7.89 (d, 1H), 7.51 (m, 3H), 7.35-7.46 (m, 3H), 5.32 (s, 2H).

c) A mixture of 7-(benzyloxy)-4-chloro-6-fluoroquinazoline (1.20 g, 4.16 mmol) and 2-(4-amino-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide (1.05 g, 4.16 mmol) in isopropanol (20 ml) was heated at 80°C for 10 minutes and then allowed to cool to room temperature. The mixture was diluted with diethyl ether and then filtered to give 2-(4-{[7-

(benzyloxy)-6-fluoroquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide hydrochloride (1.96 g, 87% yield) as a yellow solid:

^{1}H-NMR (DMSO-d_6): 11.80 (s,1H), 10.40 (s, 1H), 8.94 (s, 1H), 8.90 (d, 1H), 8.42 (s, 1H), 8.03 (s, 1H), 7.71 (m, 1H), 7.61 (m, 1H), 7.55 (m, 2H), 7.45 (m, 3H), 7.20 (m, 2H), 5.41 (s, 2H), 5.22 (s, 2H);

MS (+ve ESI): 505 $(M+H)^+$.

d) A solution of 2-(4-{[7-(benzyloxy)-6-fluoroquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide hydrochloride (1.90 g, 3.51 mmol) in trifluoroacetic acid (20 ml) was heated at 70°C for 4 hours. The mixture was evaporated and the residue triturated with diethyl ether to give 2-{4-[(6-fluoro-7-hydroxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide as the trifluoroacetic acid salt (1.89 g, 100% yield) as a pale yellow solid:

MS (+ve ESI): 415 $(M+H)^+$.

Example 15 – Preparation of compound 15 in table 1 - 2-(4-{[7-(3-chloropropoxy)-6-fluoroquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide

A mixture of 2-{4-[(6-fluoro-7-hydroxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide trifluoroacetate (0.496 g, 0.97 mmol), 1-bromo-3-chloropropane (0.184 g, 1.17 mmol) and cesium carbonate (0.634 g, 1.94 mmol) in dimethylformamide (5 ml) was heated at 90°C for 30 minutes. The mixture was allowed to cool to room temperature and then poured into water and the resultant precipitate filtered to give compound 15 in table 1 (0.402 g, 88% yield) as a pale brown solid:

^{1}H-NMR (DMSO-d_6): 10.51 (s, 1H), 9.84 (s, 1H), 8.57 (s, 1H), 8.34 (m, 2H), 7.77 (s, 1H), 7.59 (d, 1H), 7.39 (m, 2H), 7.32 (m, 1H), 6.91 (m, 1H), 5.07 (s, 2H), 4.37 (t, 2H), 3.83 (t, 2H), 2.29 (quintet, 2H).

2-{4-[(6-fluoro-7-hydroxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide trifluoroacetate used as starting material, was prepared as follows:

a) A mixture of 7-(benzyloxy)-4-chloro-6-fluoroquinazoline (0.288 g, 1.0 mmol) and 2-(4-amino-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide (0.234 g, 1.0 mmol) in isopropanol (5 ml) was heated at 80°C for 10 minutes. The mixture was allowed to cool to room temperature and then diluted with diethyl ether. The resultant solid was filtered to give 2-(4-

{[7-(benzyloxy)-6-fluoroquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide hydrochloride (0.499 g, 95% yield) as a yellow solid:
MS (+ve ESI): 487 $(M+H)^+$.

b) A solution of 2-(4-{[7-(benzyloxy)-6-fluoroquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide hydrochloride (0.499 g, 1.18 mmol) in trifluoroacetic acid (5 ml) was heated at 70°C for 4 hours. The mixture was evaporated and the residue triturated with diethyl ether to give 2-{4-[(6-fluoro-7-hydroxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide as the trifluoroacetate salt (0.496 g, 97% yield) as a pale yellow solid:
MS (+ve ESI): 397 $(M+H)^+$.

Example 16 - Preparation of compound 16 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

(2S)-Pyrrolidin-2-ylmethanol (80 mg, 0.8 mmol) was added to a solution of 2-(4-{[7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide (104 mg, 0.2 mmol) and potassium iodide (66 mg, 0.4 mmol) in dimethylacetamide (0.5 ml) and the mixture heated under argon at 90 °C for 3 hours. The solvent was evaporated, and the residue purified by preparative LCMS (Waters symmetry 5 μm column, 19 x 100 mm) to yield compound 16 in table 2 (100 mg, 91 % yield):
^{1}H-NMR (DMSO d_6, TFA): 8.97 (s, 1H), 8.41 (s, 1H), 8.09 (s, 1H), 7.96 (s, 1H), 7.61 (d, 1H), 7.34 (m, 3H), 6.91 (t, 1H), 5.15 (s, 2H), 4.30 (t, 2H), 4.03 (s, 3H), 3.78 (m, 1H), 3.62 (m, 4H), 3.25 (m, 2H), 2.38 (m, 2H), 2.14 (m, 1H), 2.05 (m, 1H), 1.91 (m, 1H), 1.81 (m, 1H);
MS (+ve ESI): 550.3 $(M+H)^+$.

Example 17 - Preparation of compound 17 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(isobutyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 16 but starting with 2-(isobutyl amino)ethanol (94 mg, 0.8 mmol) yielded compound 17 in table 2 (75 mg, 66 % yield):
^{1}H-NMR (DMSO d_6, TFA): 8.98 (s, 1H), 8.42 (s, 1H), 8.09 (s, 1H), 7.95 (s, 1H), 7.61 (d, 1H), 7.36 (m, 3H), 6.92 (t, 1H), 5.15 (s, 2H), 4.30 (m, 2H), 4.03 (s, 3H), 3.80 (m, 2H), 3.38 (m, 2H), 3.29 (m, 2H), 3.12 (m, 1H), 3.08 (m, 1H), 2.31 (m, 2H), 1.10 (t, 1H), 1.01 (d, 6H);
MS (+ve ESI): 566.2 $(M+H)^+$.

Example 18 - Preparation of compound 18 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 16 but starting with 2-(propylamino)ethanol (82 mg, 0.8 mmol) yielded compound 18 in table 2 (85 mg, 77 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.97 (s, 1H), 8.39 (s, 1H), 8.08 (s, 1H), 7.95 (s, 1H), 7.60 (m, 1H), 7.38 (m, 1H), 7.32 (m, 2H), 6.92 (m, 1H), 5.15 (s, 2H), 4.29 (t, 2H), 4.02 (s, 3H), 3.77 (t, 2H), 3.39 (m, 2H), 3.28 (t, 2H), 3.15 (m, 2H), 2.28 (m, 2H), 1.71 (m, 2H), 0.95 (t, 3H);
MS (+ve ESI): 552.2 $(M+H)^+$.

Example 19 - Preparation of compound 19 in table 2 - *N*-(3-fluorophenyl)-2-(4-{[6-methoxy-7-(3-piperidin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide

An analogous reaction to that described in example 16 but starting with piperidine (55 mg, 0.65 mmol) yielded compound 19 in table 2 (78 mg, 73 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.59 (m, 1H), 7.37 (m, 1H), 7.34 (m, 1H), 7.31 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.16 (t, 2H), 3.96 (s, 3H), 2.41 (t, 2H), 2.35 (m, 4H), 1.94 (m, 2H), 1.51 (m, 4H), 1.39 (m, 2H);
MS (+ve ESI): 534.2 $(M+H)^+$.

Example 20 - Preparation of compound 20 in table 2 - *N*-(3-fluorophenyl)-2-(4-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide

An analogous reaction to that described in example 16 but starting with pyrrolidine (46 mg, 0.65 mmol) yielded compound 20 in table 2 (71 mg, 69 % yield):

^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.42 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.75 (s, 1H), 7.59 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.83 (m, 1H), 5.06 (s, 2H), 4.17 (t, 2H), 3.96 (s, 3H), 2.54 (t, 2H), 2.45 (m, 4H), 1.96 (m, 2H), 1.69 (m, 4H);
MS (+ve ESI): 520.2 $(M+H)^+$.

Example 21 - Preparation of compound 21 in table 2 - 2-[4-({7-[3-(diethylamino)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 16 but starting with diethyl amine (48 mg, 0.65 mmol) yielded compound 21 in table 2 (62 mg, 59 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.34 (s, 1H), 7.81 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.14 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.16 (t, 2H), 3.96 (s, 3H), 2.52 (t, 2H), 2.46 (m, 4H), 1.89 (m, 2H), 0.95 (t, 6H);

MS (+ve ESI): 522.1 $(M+H)^+$.

Example 22 - Preparation of compound 22 in table 2 - *N*-(3-fluorophenyl)-2-(4-{[6-methoxy-7-(3-piperazin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide

An analogous reaction to that described in example 16 but starting with piperazine (56 mg, 0.65 mmol) yielded compound 22 in table 2 (54 mg, 51 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.34 (s, 1H), 7.78 (s, 1H), 7.75 (s, 1H), 7.58 (m, 1H), 7.39 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.16 (t, 2H), 3.96 (s, 3H), 2.69 (m, 4H), 2.41 (t, 2H), 2.31 (m, 4H), 1.94 (m, 2H);

MS (+ve ESI): 535.1 $(M+H)^+$.

Example 23 - Preparation of compound 23 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 16 but starting 2-(methylamino)ethanol (49 mg, 0.65 mmol) yielded compound 23 in table 2 (67 mg, 64 % yield):

^{1}H-NMR (DMSO d_6): 9.18 (s, 1H), 8.42 (s, 1H), 8.35 (s, 1H), 7.81 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.16 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.36 (t, 1H), 4.17 (t, 2H), 3.96 (s, 3H), 3.47 (m, 2H), 2.5 (m, 2H), 2.42 (t, 2H), 2.2 (s, 3H), 1.92 (m, 2H);

MS (+ve ESI): 524.1 $(M+H)^+$.

Example 24 - Preparation of compound 24 in table 2 - 2-[4-({7-[3-(cyclopropylamino)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 16 but starting with cyclopropylamine (37 mg, 0.65 mmol) yielded compound 24 in table 2 (51 mg, 51 % yield):
^{1}H-NMR (DMSO d_6): 9.71 (s, 1H), 8.50 (s, 1H), 8.37 (s, 1H), 7.80 (s, 1H), 7.78 (s, 1H), 7.61 (m, 1H), 7.39 (m, 1H), 7.34 (m, 1H), 7.18 (s, 1H), 6.95 (m, 1H), 5.09 (s, 2H), 4.19 (t, 2H), 3.98 (s, 3H), 2.77 (t, 2H), 2.09 (m, 1H), 1.94 (m, 2H), 0.37 (m, 2H), 0.23 (m, 2H);
MS (+ve ESI): 506.1 $(M+H)^+$.

Example 25 - Preparation of compound 25 in table 2 - 2-{4-[(7-{3-[[2-(dimethylamino)ethyl](methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 16 but starting with N,N,N'-trimethylethane-1,2-diamine (66 mg, 0.65 mmol) yielded compound 25 in table 2 (49 mg, 45 % yield):
^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.59 (m, 1H), 7.37 (m, 1H), 7.31 (m, 1H), 7.14 (s, 1H), 6.93 (m, 1H), 5.06 (s, 2H), 4.15 (t, 2H), 3.96 (s, 3H), 2.50 (m, 2H), 2.41 (m, 2H), 2.29 (m, 2H), 2.19 (s, 3H), 2.11 (s, 6H), 1.91 (m, 2H);
MS (+ve ESI): 551.1 $(M+H)^+$.

Example 26 - Preparation of compound 26 in table 2 - *N*-(3-fluorophenyl)-2-[4-({6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide

An analogous reaction to that described in example 16 but starting with 1-methylpiperazine (65 mg, 0.65 mmol) yielded compound 26 in table 2 (80 mg, 73 % yield):
^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.59 (m, 1H), 7.38 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.90 (m, 1H), 5.06 (s, 2H), 4.16 (t, 2H), 3.96 (s, 3H), 2.44 (t, 2H), 2.11-2.60 (m, 8H), 2.14 (s, 3H), 1.94 (m, 2H);
MS (+ve ESI): 549.1 $(M+H)^+$.

Example 27 - Preparation of compound 27 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 16 but starting with (2R)-pyrrolidin-2-ylmethanol (66 mg, 0.65 mmol) yielded compound 27 in table 2 (74 mg, 67 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.31 (m, 1H), 7.16 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.34 (t, 1H), 4.17 (t, 2H), 3.96 (s, 3H), 3.17 (m, 1H), 3.07 (m, 1H), 2.96 (m, 1H), 2.41 (m, 3H), 2.15 (m, 1H), 1.94 (m, 2H), 1.80 (m, 1H), 1.65 (m, 2H), 1.56 (m, 1H);

MS (+ve ESI): 550.1 $(M+H)^+$.

Example 28 - Preparation of compound 28 in table 2 - *N*-(3-fluorophenyl)-2-[4-({7-[3-(4-hydroxypiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide

An analogous reaction to that described in example 16 but starting with 4-piperidinol (66 mg, 0.65 mmol) yielded compound 28 in table 2 (110 mg, 100 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.97 (s, 1H), 8.48 (s, 1H), 8.14 (s, 1H), 7.98 (s, 1H), 7.61 (m, 1H), 7.38 (m, 2H), 7.36 (s, 1H), 6.91 (m, 1H), 5.16 (s, 2H), 4.31 (t, 2H), 4.04 (s, 3H), 3.70 (m, 1H), 3.57 (d, 1H), 3.41 (d, 1H), 3.30 (m, 3H), 3.04 (t, 1H), 2.32 (m, 2H), 2.02 (m, 1H), 1.89 (m, 2H), 1.61 (m, 1H);

MS (+ve ESI): 550.1 $(M+H)^+$.

Example 29 - Preparation of compound 29 in table 2 - 2-{4-[(7-{3-[bis(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 16 but starting with 2,2'-iminodiethanol (68 mg, 0.65 mmol) yielded compound 29 in table 2 (53 mg, 48 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.34 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.38 (m, 1H), 7.32 (m, 1H), 7.17 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.35 (t, 2H), 4.18 (t, 2H), 3.96 (s, 3H), 3.42 (m, 4H), 2.64 (m, 2H), 2.54 (m, 4H), 1.90 (m, 2H);

MS (+ve ESI): 554.2 $(M+H)^+$.

Example 30 - Preparation of compound 30 in table 2 - 2-{4-[(7-{3-[ethyl(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 16 but starting with ethyl (methyl)amine (38 mg, 0.65 mmol) yielded compound 30 in table 2 (67 mg, 66 % yield):
^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.31 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.16 (t, 2H), 3.96 (s, 3H), 2.46 (t, 2H), 2.36 (q, 2H), 2.16 (s, 3H), 1.92 (m, 2H), 0.98 (t, 3H);
MS (+ve ESI): 508.1 $(M+H)^+$.

Example 31 - Preparation of compound 31 in table 2 - 2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 16 but starting with 2-(ethylamino)ethanol (58 mg, 0.65 mmol) yielded compound 31 in table 2 (63 mg, 58 % yield):
^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.33 (t, 1H), 4.17 (t, 2H), 3.96 (s, 3H), 3.42 (m, 2H), 2.61 (t, 2H), 2.50 (m, 4H), 1.89 (m, 2H), 0.96 (t, 3H);
MS (+ve ESI): 538.1 $(M+H)^+$.

Example 32 - Preparation of compound 32 in table 2 - 2-{4-[(7-{3-[[2-(dimethylamino)ethyl](ethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 16 but starting with N'-ethyl-N,N-dimethylethane-1,2-diamine (76 mg, 0.65 mmol) yielded compound 32 in table 2 (33 mg, 29 % yield):
^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.14 (s, 1H), 6.92 (m, 1H), 5.06 (s, 1H), 4.17 (t, 2H), 3.96 (s, 3H), 2.57 (t, 2H), 2.48 (m, 4H), 2.27 (t, 2H), 2.09 (s, 6H), 1.88 (m, 2H), 0.95 (t, 3H);
MS (+ve ESI): 565.1 $(M+H)^+$.

Example 33 - Preparation of compound 33 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[2-(2-hydroxyethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 16 but starting with 2-piperidin-2-ylethanol (84 mg, 0.65 mmol) yielded compound 33 in table 2 (67 mg, 58 % yield):
^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.38 (t, 1H), 4.15 (t, 2H), 3.96 (s, 3H), 3.44 (m, 2H), 2.76 (m, 2H), 2.46 (m, 2H), 2.23 (m, 1H), 1.91 (m, 2H), 1.74 (m, 1H), 1.59 (m, 2H), 1.46 (m, 3H), 1.28 (m, 2H);
MS (+ve ESI): 578.2 $(M+H)^+$.

Example 34 - Preparation of compound 34 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 16 but starting with 2-piperazin-1-ylethanol (85 mg, 0.65 mmol) yielded compound 34 in table 2 (85 mg, 74 % yield):
^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.36 (t, 1H), 4.16 (t, 2H), 3.96 (s, 3H), 3.47 (m, 2H), 2.35-2.45 (m, 12H), 1.94 (m, 2H);
MS (+ve ESI): 579.2 $(M+H)^+$.

Example 35 - Preparation of compound 35 in table 2 - 2-{4-[(7-{3-[(cyclopropylmethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 16 but starting with (cyclopropylmethyl)amine (46 mg, 0.65 mmol) yielded compound 35 in table 2 (53 mg, 51 % yield):
^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.59 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.16 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.19 (t, 2H), 3.96 (s, 3H), 2.71 (t, 2H), 2.39 (d, 2H), 1.93 (m, 2H), 0.88 (m, 1H), 0.39 (m, 2H), 0.11 (m, 2H);
MS (+ve ESI): 520.1 $(M+H)^+$.

Example 36 - Preparation of compound 36 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 16 but starting with 2-piperidin-4-ylethanol (84 mg, 0.65 mmol) yielded compound 36 in table 2 (101 mg, 88 % yield):
^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.32 (t, 1H), 4.15 (t, 2H), 3.96 (s, 3H), 3.43 (m, 2H), 2.85 (m, 2H), 2.42 (t, 2H), 1.94 (m, 2H), 1.85 (t, 2H), 1.61 (d, 2H), 1.35 (t, 3H), 1.13 (m, 2H);
MS (+ve ESI): 578.1 $(M+H)^+$.

Example 37 - Preparation of compound 37 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(6-methoxy-7-{3-[methyl(prop-2-yn-1-yl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 16 but starting with N-methylprop-2-yn-1-amine (45 mg, 0.65 mmol) yielded compound 37 in table 2 (58 mg, 56 % yield):
^{1}H-NMR (DMSO d_6): 8.61 (s, 1H), 8.37 (s, 1H), 7.99 (s, 1H), 7.86 (s, 1H), 7.61 (m, 1H), 7.37 (m, 1H), 7.33 (m, 1H), 7.23 (s, 1H), 6.92 (m, 1H), 5.09 (s, 2H), 4.24 (t, 2H), 3.99 (s, 3H), 3.71 (m, 1H), 3.08 (m, 2H), 2.74 (m, 2H), 2.17 (m, 2H);
MS (+ve ESI): 518.1 $(M+H)^+$.

Example 38 - Preparation of compound 38 in table 2 - 2-{4-[(7-{3-[allyl(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 16 but starting with N-methylprop-2-en-1-amine (46 mg, 0.65 mmol) yielded compound 38 in table 2 (79 mg, 76 % yield):
^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.83 (m, 1H), 5.18 (d, 1H), 5.07 (d, 1H), 5.06 (s, 2H), 4.16 (t, 2H), 3.96 (s, 3H), 2.98 (d, 2H), 2.48 (m, 2H), 2.16 (s, 3H), 1.94 (m, 2H);
MS (+ve ESI): 520.1 $(M+H)^+$.

Example 39 - Preparation of compound 39 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[isobutyl(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 16 but starting with isobutyl(methyl)amine (57 mg, 0.65 mmol) yielded compound 39 in table 2 (64 mg, 60 % yield):

^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.38 (m, 1H), 7.32 (m, 1H), 7.13 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.17 (t, 2H), 3.96 (s, 3H), 2.45 (t, 2H), 2.15 (s, 3H), 2.04 (d, 2H), 1.92 (m, 2H), 1.72 (m, 1H), 0.82 (d, 6H);
MS (+ve ESI): 536.2 $(M+H)^+$.

Example 40 - Preparation of compound 40 in table 2 - *N*-(3-fluorophenyl)-2-[4-({7-[3-(3-hydroxypiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide

An analogous reaction to that described in example 16 but starting with piperidin-3-ol (66 mg, 0.65 mmol) yielded compound 40 in table 2 (78 mg, 71 % yield):

^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.16 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.59 (d, 1H), 4.16 (t, 2H), 3.96 (s, 3H), 3.48 (m, 2H), 2.83 (m, 1H), 2.67 (m, 1H), 2.46 (m, 2H), 1.94 (m, 2H), 1.85 (m, 1H), 1.76 (m, 2H), 1.61 (m, 1H), 1.42 (m, 1H);
MS (+ve ESI): 550.1 $(M+H)^+$.

Example 41 - Preparation of compound 41 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[4-(hydroxymethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 16 but starting with piperidin-4-ylmethanol (75 mg, 0.65 mmol) yielded compound 41 in table 2 (88 mg, 78 % yield):

^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.40 (t, 1H), 4.15 (t, 2H), 3.96 (s, 3H), 3.23 (m, 2H), 2.87 (d, 2H), 2.43 (t, 2H), 1.94 (m, 2H), 1.85 (t, 2H), 1.63 (d, 2H), 1.33 (m, 1H), 1.13 (m, 2H);
MS (+ve ESI): 564.2 $(M+H)^+$.

Example 42 - Preparation of compound 42 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(6-methoxy-7-{3-[methyl(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 16 but starting with methyl(propyl)amine (48 mg, 0.65 mmol) yielded compound 42 in table 2 (68 mg, 66 % yield):

^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.14 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.16 (t, 2H), 3.96 (s, 3H), 2.46 (t, 2H), 2.26 (t, 2H), 2.16 (s, 3H), 1.92 (m, 2H), 1.42 (m, 2H), 0.83 (t, 3H);
MS (+ve ESI): 522.1 $(M+H)^+$.

Example 43 - Preparation of compound 43 in table 2 - 2-{4-[(7-{3-[(cyclopropylmethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 16 but starting with (cyclopropylmethyl)propylamine (74 mg, 0.65 mmol) yielded compound 43 in table 2 (3 mg, 3 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.34 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.38 (m, 1H), 7.32 (m, 1H), 7.14 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.18 (t, 2H), 3.95 (s, 3H), 2.64 (m, 2H), 2.43 (m, 2H), 2.31 (d, 2H), 1.90 (m, 2H), 1.42 (m, 2H), 0.83 (m, 4H), 0.40 (m, 2H), 0.06 (m, 2H);
MS (+ve ESI): 562.2 $(M+H)^+$.

Example 44 - Preparation of compound 44 in table 2 - 2-{4-[(7-{3-[[2-(diethylamino)ethyl](methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 16 but starting with N,N-diethyl-N'-methylethane-1,2-diamine (85 mg, 0.65 mmol) yielded compound 44 in table 2 (83 mg, 71 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.14 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.16 (t, 2H), 3.96 (s, 3H), 2.41 (m, 10H), 2.19 (s, 3H), 1.91 (m, 2H), 0.90 (t, 6H);

MS (+ve ESI): 579.2 $(M+H)^+$.

Example 45 - Preparation of compound 45 in table 2 - 2-{4-[(7-{3-[[2-(diethylamino)ethyl](ethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 16 but starting with N,N,N'-triethylethane-1,2-diamine (94 mg, 0.65 mmol) yielded compound 45 in table 2 (70 mg, 59 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.14 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.17 (t, 2H), 3.96 (s, 3H), 2.58 (m, 2H), 2.42 (m, 10H), 1.88 (m, 2H), 0.96 (t, 3H), 0.91 (t, 6H);

MS (+ve ESI): 593.2 $(M+H)^+$.

Example 46 - Preparation of compound 46 in table 2 - *N*-(3-fluorophenyl)-2-[4-({6-methoxy-7-[3-(4-methyl-1,4-diazepan-1-yl)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide

An analogous reaction to that described in example 16 but starting with 1-methyl-1,4-diazepane (74 mg, 0.65 mmol) yielded compound 46 in table 2 (55 mg, 49 % yield):

^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.16 (t, 2H), 3.95 (s, 3H), 2.63 (m, 10H), 2.23 (s, 3H), 1.91 (m, 2H), 1.71 (m, 2H);

MS (+ve ESI): 563.2 $(M+H)^+$.

Example 47 - Preparation of compound 47 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(isopropyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 16 but starting with 2-(isopropylamino)ethanol (67 mg, 0.65 mmol) yielded compound 47 in table 2 (82 mg, 74 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.34 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.27 (t, 1H), 4.16 (t, 2H), 3.97 (s, 3H), 3.35 (m, 2H), 2.89 (m, 1H), 2.54 (m, 2H), 2.45 (m, 2H), 1.86 (m, 2H), 0.92 (d, 6H);

MS (+ve ESI): 552.2 $(M+H)^+$.

Example 48 - Preparation of compound 48 in table 2 - 2-{4-[(7-{3-[cyclopropyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 16 but starting with 2-(cyclopropylamino)ethanol (66 mg, 0.65 mmol) yielded compound 48 in table 2 (73 mg, 66 % yield):

^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.32 (m, 1H), 4.15 (t, 2H), 3.96 (s, 3H), 3.5 (m, 2H), 2.76 (t, 2H), 2.65 (t, 2H), 1.95 (m, 2H), 1.82 (m, 1H), 0.43 (m, 2H), 0.31 (m, 2H);

MS (+ve ESI): 550.1 $(M+H)^+$.

Example 49 - Preparation of compound 49 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 16 but starting with 2-((2-methoxyethyl)amino)ethanol (77 mg, 0.65 mmol) yielded compound 49 in table 2 (97 mg, 85 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.59 (m, 1H), 7.38 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.31 (t, 1H),

4.17 (t, 2H), 3.96 (s, 3H), 3.43 (m, 2H), 3.37 (m, 2H), 3.20 (s, 3H), 2.64 (m, 4H), 2.53 (t, 2H), 1.91 (m, 2H);

MS (+ve ESI): 568.1 $(M+H)^+$.

Example 50 - Preparation of compound 50 in table 2 - 2-{4-[(7-{3-[cyclobutyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 16 but starting with 2-(cyclobutylamino)ethanol (75 mg, 0.65 mmol) yielded compound 50 in table 2 (106 mg, 94 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.34 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.53 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.35 (t, 1H), 4.15 (t, 2H), 3.96 (s, 3H), 3.42 (m, 2H), 3.12 (m, 1H), 2.56 (t, 2H), 2.46 (t, 2H), 1.94 (m, 2H), 1.88 (m, 2H), 1.75 (m, 2H), 1.54 (m, 2H);

MS (+ve ESI): 564.1 $(M+H)^+$.

Example 51 - Preparation of compound 51 in table 2 - 2-{4-[(7-{3-[(cyclopropylmethyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 16 but starting with 2-((cyclopropylmethyl)amino)ethanol (75 mg, 0.65 mmol) yielded compound 51 in table 2 (75 mg, 66 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 3H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.38 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.32 (t, 1H), 4.18 (t, 2H), 3.96 (s, 3H), 3.46 (m, 2H), 2.69 (t, 2H), 2.58 (t, 2H), 2.35 (d, 2H), 1.91 (m, 2H), 0.83 (m, 1H), 0.41 (m, 2H), 0.08 (m, 2H);

MS (+ve ESI): 564.1 $(M+H)^+$.

Example 52 - Preparation of compound 52 in table 2 - 2-{4-[(7-{3-[(cyclobutylmethyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 16 but starting with 2-((cyclobutylmethyl)amino)ethanol (84 mg, 0.65 mmol) yielded compound 52 in table 2 (90 mg, 78 % yield):

^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.14 (s, 1H), 6.92 (m, 1H), 5.07 (s, 2H), 4.29 (t, 1H), 4.15 (t, 2H), 3.97 (s, 3H), 3.42 (m, 2H), 2.57 (t, 2H), 2.47 (m, 4H), 1.93 (m, 3H), 1.89 (t, 2H), 1.76 (m, 2H), 1.59 (m, 2H);

MS (+ve ESI): 578.2 $(M+H)^+$.

Example 53 - Preparation of compound 53 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(prop-2-yn-1-yl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 16 but starting with 2-(prop-2-yn-1-ylamino)ethanol (64 mg, 0.65 mmol) yielded compound 53 in table 2 (69 mg, 63 % yield):

^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.59 (m, 1H), 7.38 (m, 1H), 7.32 (m, 1H), 7.16 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.43 (t, 1H), 4.17 (t, 2H), 3.96 (s, 3H), 3.46 (m, 2H), 3.41 (d, 2H), 3.09 (t, 1H), 2.63 (t, 2H), 2.54 (t, 2H), 1.92 (m, 2H);

MS (+ve ESI): 548.1 $(M+H)^+$.

Example 54 - Preparation of compound 54 in table 2 - 2-{4-[(7-{3-[allyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 16 but starting with 2-(allylamino)ethanol (66 mg, 0.65 mmol) yielded compound 54 in table 2 (100 mg, 91 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.83 (m, 1H), 5.18 (dd, 1H), 5.09 (dd, 1H), 5.06 (s, 2H), 4.36 (t, 1H), 4.16 (t, 2H), 3.96 (s, 3H), 3.45 (m, 1H), 3.11 (d, 2H), 2.61 (t, 2H), 1.92 (m, 2H);

MS (+ve ESI): 550.1 $(M+H)^+$.

Example 55 - Preparation of compound 55 in table 2 - 2-{4-[(7-{3-[(2,2-dimethylpropyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 16 but starting with 2-((2,2-dimethylpropyl)amino)ethanol (85 mg, 0.65 mmol) yielded compound 55 in table 2 (85 mg, 66 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.34 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.14 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.33 (t, 1H), 4.17 (t, 2H), 3.95 (s, 3H), 3.44 (m, 2H), 2.64 (t, 2H), 2.54 (t, 2H), 2.21 (s, 2H), 1.91 (m, 2H), 0.83 (s, 9H);

MS (+ve ESI): 580.2 $(M+H)^+$.

Example 56 - Preparation of compound 56 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(3,3,3-trifluoropropyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 16 but starting with 2-((3,3,3-trifluoropropyl)amino)ethanol (102 mg, 0.65 mmol) yielded compound 56 in table 2 (80 mg, 66 % yield):

^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.16 (s, 1H), 6.92 (m, 1H), 5.07 (s, 2H), 4.41 (m, 1H), 4.17 (t, 2H), 3.96 (s, 3H), 3.45 (t, 2H), 2.72 (t, 2H), 2.63 (t, 2H), 2.53 (m, 2H), 2.40 (m, 2H), 1.92 (m, 2H);

MS (+ve ESI): 606.3 $(M+H)^+$.

Example 57 - Preparation of compound 57 in table 2 - 2-(4-{[7-(3-azetidin-1-ylpropoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 16 but starting with azetidine (37 mg, 0.65 mmol) yielded compound 57 in table 2 (13 mg, 13 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.34 (s, 1H), 7.78 (s, 1H), 7.75 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.14 (s, 1H), 6.91 (m, 1H), 5.06 (s, 2H), 4.13 (m, 2H), 3.95 (s, 3H), 3.09 (t, 4H), 2.51 (m, 2H), 1.95 (m, 2H), 1.76 (m, 2H);

MS (+ve ESI): 506.1 $(M+H)^+$.

Example 58 – Preparation of compound 58 in table 2 - 2-{4-[(6,7-dimethoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

A solution of 2-(4-amino-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide (0.246 g, 1.05 mmol) and 4-chloro-6,7-dimethoxyquinazoline (0.224 g, 1.0 mmol) in dimethylacetamide (5 ml) was heated at 90 °C for 2 hours. The mixture was allowed to cool to room temperature and then diluted with diethyl ether and filtered. The solid was washed with diethyl ether and then dried *in vacuo*. The solid was partitioned between dichloromethane and sodium hydroxide solution (1 M), the organic layer was separated, dried over magnesium sulphate and evaporated to leave compound 58 in table 2 (0.115 g, 27% yield):

^{1}H-NMR (DMSO d_6): 10.54 (br s, 1H), 9.74 (br s, 1H), 8.51 (s, 1H), 8.34 (s, 1H), 7.81 (s, 1H), 7.78 (s, 1H), 7.59 (m, 1H), 7.35 (m, 2H), 7.18 (s, 1H), 6.92 (m, 1H), 5.07 (s, 2H), 3.97 (s, 3H), 3.93 (s, 3H);

MS (+ve ESI): 423 $(M+H)^+$.

Example 59 – Preparation of compound 59 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-hydroxy-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

A mixture of 4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl acetate (0.358 g, ~0.8 mmol) and potassium carbonate (0.14g, 1.0 mmol) in methanol (10 ml) was stirred at room temperature for 2 hours. The solvent was evaporated and the residue was partitioned between water (10 ml) and dichloromethane (10 ml). The aqueous layer was separated and made acidic by the addition of concentrated hydrochloric acid and the resultant precipitate filtered. The solid was washed with methanol and finally with diethyl ether and then dried under nitrogen to yield compound 59 in table 2 (0.225 g, 69% yield) as the hydrochloride salt:

^{1}H-NMR (DMSO d_6): 14.65 (br s, 1H), 11.61 (s, 1H), 11.53 (br s, 1H), 10.74 (s, 1H), 8.84 (s, 1H), 8.40 (s, 1H), 8.33 (s, 1H), 8.03 (s, 1H), 7.60 (m, 1H), 7.37 (m, 3H), 6.91 (m, 1H), 5.13 (s, 2H), 4.03 (s, 3H);

MS (+ve ESI): 409 $(M+H)^+$.

4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl acetate used as starting material, was obtained as follows:

a) A solution of 2-(4-amino-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide (0.246 g, 1.05 mmol) and 4-chloro-6-methoxyquinazolin-7-yl acetate (see WO96/15118, 0.252 g, 1.0 mmol) in dimethylacetamide (5 ml) was heated at 90 °C for 2 hours. The mixture was allowed to cool to room temperature and then diluted with diethyl ether and filtered. The solid was washed with diethyl ether and then dried *in vacuo* to leave 4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl acetate as a mixture with 15% *N*-(3-fluorophenyl)-2-{4-[(7-hydroxy-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (0.358 g, 78% yield):

^{1}H-NMR (DMSO d_6): 12.04 (br s, 1H), 10.72 (br s, 1H), 8.94 (s, 1H), 8.63 (s, 1H), 8.48 (s, 1H), 8.10 (s, 1H), 7.73 (s, 1H), 7.60 (m, 1H), 7.36 (m, 2H), 6.91 (m, 1H), 5.15 (s, 2H), 4.05 (s, 3H), 2.38 (s, 3H);

MS (+ve ESI): 451 $(M+H)^+$.

Example 60 - Preparation of compound 60 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(isobutyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 16 but starting with 2-(4-{[7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide (129 mg, 0.23 mmol) and 2-(isobutylamino)ethanol (146 mg, 0.93 mmol) yielded compound 60 in table 3 (95 mg, 70 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.74 (m, 3H), 7.21 (m, 2H), 7.14 (s, 1H), 5.17 (s, 2H), 4.30 (t, 1H), 4.17 (t, 2H), 3.96 (s, 3H), 3.43 (m, 2H), 2.58 (m, 2H), 2.47 (m, 2H), 2.15 (m, 2H), 1.89 (m, 2H), 1.67 (m, 1H), 0.81 (d, 6H);

MS (+ve ESI): 584.2 $(M+H)^+$.

Example 61 - Preparation of compound 61 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 60 but starting with (2S)-pyrrolidin-2-ylmethanol (98 µl, 1 mmol) yielded compound 61 in table 3 (105 mg, 74 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.74 (m, 3H), 7.21 (m, 2H), 7.16 (s, 1H), 5.16 (s, 2H), 4.33 (t, 1H), 4.17 (t, 2H), 3.95 (s, 3H), 3.39 (m, 1H), 3.18 (m, 1H), 3.08 (m, 1H), 2.97 (m, 1H), 2.42 (m, 2H), 2.15 (m, 1H), 1.95 (m, 2H), 1.79 (m, 1H), 1.65 (m, 2H), 1.55 (m, 1H);

MS (+ve ESI): 568.1 $(M+H)^+$.

Example 62 - Preparation of compound 62 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 60 but starting with 2-(propylamino)ethanol (82 mg, 0.8 mmol) yielded compound 62 in table 3 (88 mg, 77 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.97 (s, 1H), 8.39 (s, 1H), 8.08 (s, 1H), 7.95 (s, 1H), 7.74 (m, 1H), 7.33 (s, 1H), 7.21 (m, 2H), 5.25 (s, 2H), 4.29 (t, 2H), 4.02 (s, 3H), 3.77 (t, 2H), 3.33 (m, 2H), 3.28 (m, 2H), 3.15 (m, 2H), 2.28 (m, 2H), 1.71 (m, 2H), 0.95 (t, 3H);

MS (+ve ESI): 570.3 $(M+H)^+$.

Example 63 - Preparation of compound 63 in table 3 - *N*-(2,3-difluorophenyl)-2-[4-({7-[3-(dimethylamino)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide

An analogous reaction to that described in example 60 but starting with dimethylamine (29 mg, 0.65 mmol) yielded compound 63 in table 3 (51 mg, 56 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.21 (m, 2H), 7.14 (s, 1H), 5.16 (s, 2H), 4.15 (t, 2H), 3.96 (s, 3H), 2.38 (t, 2H), 2.16 (s, 6H), 1.93 (m, 2H);

MS (+ve ESI): 512.1 $(M+H)^+$.

Example 64 - Preparation of compound 64 in table 3 - *N*-(2,3-difluorophenyl)-2-(4-{[6-methoxy-7-(3-piperidin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide

An analogous reaction to that described in example 60 but starting with piperidine (55 mg, 0.65 mmol) yielded compound 64 in table 3 (68 mg, 69 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.45 (s, 1H), 8.34 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.73 (m, 1H), 7.19 (m, 2H), 7.15 (s, 1H), 5.16 (s, 2H), 4.15 (t, 2H), 3.95 (s, 3H), 2.41 (t, 2H), 2.35 (m, 4H), 1.93 (m, 2H), 1.51 (m, 4H), 1.39 (m, 2H);

MS (+ve ESI): 552.2 $(M+H)^+$.

Example 65 - Preparation of compound 65 in table 3 - *N*-(2,3-difluorophenyl)-2-(4-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide

An analogous reaction to that described in example 60 but starting with pyrrolidine (46 mg, 0.65 mmol) yielded compound 65 in table 3 (65 mg, 67 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.49 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.73 (m, 1H), 7.21 (m, 2H), 7.15 (s, 1H), 5.16 (s, 2H), 4.17 (t, 2H), 3.96 (s, 3H), 2.52 (t, 2H), 2.45 (m, 4H), 1.96 (m, 2H), 1.69 (m, 4H);

MS (+ve ESI): 538.1 $(M+H)^+$.

Example 66 - Preparation of compound 66 in table 3 - *N*-(2,3-difluorophenyl)-2-(4-{[6-methoxy-7-(3-piperazin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide

An analogous reaction to that described in example 60 but starting with piperazine (56 mg, 0.65 mmol) yielded compound 66 in table 3 (67 mg, 68 % yield):

^{1}H-NMR (DMSO d_6): 9.67 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.21 (m, 2H), 7.15 (s, 1H), 5.16 (s, 2H), 4.16 (t, 2H), 3.95 (s, 3H), 2.69 (m, 4H), 2.41 (t, 2H), 2.31 (m, 4H), 1.94 (m, 2H);

MS (+ve ESI): 553.1 $(M+H)^+$.

Example 67 - Preparation of compound 67 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 60 but starting with 2-(methylamino)ethanol (49 mg, 0.65 mmol) yielded compound 67 in table 3 (66 mg, 67 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.22 (m, 2H), 7.16 (s, 1H), 5.16 (s, 2H), 4.36 (t, 1H), 4.16 (t, 2H), 3.96 (s, 3H), 3.46 (m, 2H), 2.51 (m, 2H), 2.42 (m, 2H), 2.20 (s, 3H), 1.91 (m, 2H);

MS (+ve ESI): 542.1 $(M+H)^+$.

Example 68 - Preparation of compound 68 in table 3 - 2-[4-({7-[3-(cyclopropylamino)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(2,3-difluorophenyl)acetamide

An analogous reaction to that described in example 60 but starting with cyclopropylamine (37 mg, 0.65 mmol) yielded compound 68 in table 3 (67 mg, 71 % yield):
^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.21 (m, 2H), 7.16 (s, 1H), 5.16 (s, 2H), 4.18 (t, 2H), 3.96 (s, 3H), 2.74 (m, 2H), 2.07 (m, 1H), 1.92 (m, 2H), 0.35 (m, 2H), 0.21 (m, 2H);
MS (+ve ESI): 524.1 $(M+H)^+$.

Example 69 - Preparation of compound 69 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[[2-(dimethylamino)ethyl](methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 60 but starting with N,N,N'-trimethylethane-1,2-diamine (66 mg, 0.65 mmol) yielded compound 69 in table 3 (43 mg, 42 % yield):
^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.21 (m, 2H), 7.14 (s, 1H), 5.16 (s, 2H), 4.16 (t, 2H), 3.96 (s, 3H), 2.49 (m, 2H), 2.40 (m, 2H), 2.29 (m, 2H), 2.19 (s, 3H), 2.11 (s, 6H), 1.91 (m, 2H);
MS (+ve ESI): 569.2 $(M+H)^+$.

Example 70 - Preparation of compound 70 in table 3 - *N*-(2,3-difluorophenyl)-2-[4-({6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide

An analogous reaction to that described in example 60 but starting with 1-methylpiperazine (65 mg, 0.65 mmol) yielded compound 70 in table 3 (85 mg, 84 % yield):
^{1}H-NMR (DMSO d_6): 9.67 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.21 (m, 2H), 7.14 (s, 1H), 5.16 (s, 2H), 4.15 (t, 2H), 3.95 (s, 3H), 2.44 (t, 2H), 2.32 (m, 8H), 2.14 (s, 3H), 1.94 (m, 2H);
MS (+ve ESI): 567.2 $(M+H)^+$.

Example 71 - Preparation of compound 71 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 60 but starting with (2R)pyrrolidin-2-ylmethanol (66 mg, 0.65 mmol) yielded compound 71 in table 3 (80 mg, 78 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.22 (m, 2H), 7.16 (s, 1H), 5.16 (s, 2H), 4.33 (t, 1H), 4.17 (t, 2H), 3.96 (s, 3H), 3.38 (m, 1H), 3.17 (m, 1H), 3.07 (m, 1H), 2.96 (m, 1H), 2.41 (m, 2H), 2.14 (m, 1H), 1.94 (m, 2H), 1.79 (m, 1H), 1.65 (m, 2H), 1.55 (m, 1H);

MS (+ve ESI): 568.1 $(M+H)^+$.

Example 72 - Preparation of compound 72 in table 3 - *N*-(2,3-difluorophenyl)-2-[4-({7-[3-(4-hydroxypiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide

An analogous reaction to that described in example 60 but starting with piperidin-4-ol (66 mg, 0.65 mmol) yielded compound 72 in table 3 (102 mg, 100 % yield):

^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.21 (m, 2H), 7.15 (s, 1H), 5.16 (s, 2H), 4.54 (m, 1H), 4.15 (t, 2H), 3.96 (s, 3H), 3.44 (m, 1H), 2.73 (m, 2H), 2.43 (m, 2H), 2.02 (m, 2H), 1.92 (m, 2H), 1.71 (m, 2H), 1.39 (m, 2H);

MS (+ve ESI): 568.2 $(M+H)^+$.

Example 73 - Preparation of compound 73 in table 3 - 2-{4-[(7-{3-[bis(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

An analogous reaction to that described in example 60 but starting with 2,2'-iminodiethanol (68 mg, 0.65 mmol) yielded compound 73 in table 3 (95 mg, 93 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.72 (m, 1H), 7.21 (m, 2H), 7.17 (s, 1H), 5.16 (s, 2H), 4.34 (t, 2H), 4.18 (t, 2H), 3.96 (s, 3H), 3.41 (m, 4H), 2.52 (m, 4H), 2.63 (m, 2H), 1.91 (m, 2H);

MS (+ve ESI): 572.1 $(M+H)^+$.

Example 74 - Preparation of compound 74 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[ethyl(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 60 but starting with ethyl(methyl)amine (38 mg, 0.65 mmol) yielded compound 74 in table 3 (58 mg, 61 % yield):
^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.72 (m, 1H), 7.21 (m, 2H), 7.15 (s, 1H), 5.16 (s, 2H), 4.16 (t, 2H), 3.96 (s, 3H), 2.46 (m, 2H), 2.36 (q, 2H), 2.16 (s, 3H), 1.92 (m, 2H), 0.98 (t, 3H);
MS (+ve ESI): 526.1 $(M+H)^+$.

Example 75 - Preparation of compound 75 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 60 but starting with 2-(ethylamino)ethanol (58 mg, 0.65 mmol) yielded compound 75 in table 3 (91 mg, 91 % yield):
^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.72 (m, 1H), 7.21 (m, 2H), 7.15 (s, 1H), 5.16 (s, 2H), 4.32 (t, 1H), 4.17 (t, 2H), 3.96 (s, 3H), 3.43 (m, 2H), 2.59 (t, 2H), 2.50 (m, 2H), 1.89 (m, 2H), 0.95 (t, 3H);
MS (+ve ESI): 556.1 $(M+H)^+$.

Example 76 - Preparation of compound 76 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[[2-(dimethylamino)ethyl](ethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 60 but starting with N'-ethyl-N,N-dimethylethane-1,2-diamine (76 mg, 0.65 mmol) yielded compound 76 in table 3 (29 mg, 27 % yield):
^{1}H-NMR (DMSO d_6, TFA): 8.96 (s, 1H), 8.42 (s, 1H), 8.12 (s, 1H), 7.98 (s, 1H), 7.77 (m, 1H), 7.40 (s, 1H), 7.21 (m, 2H), 5.27 (s, 2H), 4.31 (m, 2H), 4.04 (s, 3H), 3.66 (m, 2H), 3.60 (m, 2H), 3.51 (m, 2H), 3.23 (s, 6H), 3.08 (m, 2H), 2.42 (m, 2H), 1.26 (t, 3H);
MS (+ve ESI): 583.2 $(M+H)^+$.

Example 77 - Preparation of compound 77 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[2-(2-hydroxyethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 60 but starting with 2-piperidin-2-ylethanol (84 mg, 0.65 mmol) yielded compound 77 in table 3 (86 mg, 80 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.49 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.21 (m, 2H), 7.15 (s, 1H), 5.16 (s, 2H), 4.38 (t, 1H), 4.15 (t, 2H), 3.96 (s, 3H), 3.44 (m, 2H), 2.76 (m, 2H), 2.44 (m, 2H), 2.23 (m, 1H), 1.91 (m, 2H), 1.73 (m, 1H), 1.58 (m, 2H), 1.46 (m, 3H), 1.28 (m, 2H);

MS (+ve ESI): 596.2 $(M+H)^+$.

Example 78 - Preparation of compound 78 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 60 but starting with 2-piperazine-1-ylethanol (85 mg, 0.65 mmol) yielded compound 78 in table 3 (75 mg, 70 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.77 (s, 1H), 7.76 (s, 1H), 7.73 (m, 1H), 7.22 (m, 2H), 7.14 (s, 1H), 5.16 (s, 2H), 4.37 (t, 1H), 4.15 (t, 2H), 3.95 (s, 3H), 3.47 (m, 2H), 2.43 (m, 2H), 2.41 (m, 8H), 2.36 (m, 2H), 1.94 (m, 2H);

MS (+ve ESI): 597.2 $(M+H)^+$.

Example 79 - Preparation of compound 79 in table 3 - 2-{4-[(7-{3-[(cyclopropylmethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

An analogous reaction to that described in example 60 but starting with (cyclopropylmethyl)amine (46 mg, 0.65 mmol) yielded compound 79 in table 3 (66 mg, 68 % yield):

^{1}H-NMR (DMSO d_6): 10.31 (s, 1H), 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.22 (m, 2H), 7.16 (s, 1H), 5.16 (s, 2H), 4.19 (t, 2H), 3.96 (s, 3H), 2.71 (t, 2H), 2.39 (d, 2H), 1.92 (m, 2H), 0.88 (m, 1H), 0.39 (m, 2H), 0.09 (m, 2H);

MS (+ve ESI): 538.1 $(M+H)^+$.

Example 80 - Preparation of compound 80 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 60 but starting with 2-piperidin-4-ylethanol (84 mg, 0.65 mmol) yielded compound 80 in table 3 (102 mg, 95 % yield):

^{1}H-NMR (DMSO d_6): 9.41 (s, 1H), 8.20 (s, 1H), 8.07 (s, 1H), 7.51 (s, 1H), 7.49 (s, 1H), 7.45 (m, 1H), 6.91 (m, 2H), 6.86 (s, 1H), 4.88 (s, 2H), 4.03 (t, 1H), 3.87 (t, 2H), 3.67 (s, 3H), 3.14 (m, 2H), 2.57 (m, 2H), 2.14 (t, 2H), 1.65 (m, 2H), 1.56 (t, 2H), 1.33 (d, 2H), 1.06 (m, 3H), 0.86 (m, 2H);

MS (+ve ESI): 596.2 $(M+H)^+$.

Example 81 - Preparation of compound 81 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(6-methoxy-7-{3-[methyl(prop-2-yn-1-yl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 60 but starting with N-methylprop-2-yn-1-amine (45 mg, 0.65 mmol) yielded compound 81 in table 3 (55 mg, 57 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.21 (m, 2H), 7.14 (s, 1H), 5.16 (s, 2H), 4.15 (t, 2H), 3.96 (s, 3H), 3.13 (m, 1H), 2.51 (m, 4H), 2.23 (s, 3H), 1.93 (m, 2H);

MS (+ve ESI): 536.1 $(M+H)^+$.

Example 82 - Preparation of compound 82 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[isobutyl(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 60 but starting with N,2-dimethylpropan-1-amine (57 mg, 0.65 mmol) yielded compound 82 in table 3 (29 mg, 29 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.21 (m, 2H), 7.13 (s, 1H), 5.16 (s, 2H), 4.15 (t, 2H), 3.95 (s, 3H), 2.45 (m, 2H), 2.15 (s, 3H), 2.04 (d, 2H), 1.92 (m, 2H), 1.71 (m, 1H), 0.82 (d, 6H);

MS (+ve ESI): 554.2 $(M+H)^+$.

Example 83 - Preparation of compound 83 in table 3 - *N*-(2,3-difluorophenyl)-2-[4-({7-[3-(3-hydroxypiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide

An analogous reaction to that described in example 60 but starting with piperidin-3-ol (66 mg, 0.65 mmol) yielded compound 83 in table 3 (102 mg, 100 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.22 (m, 2H), 7.15 (s, 1H), 5.16 (s, 2H), 4.61 (d, 1H), 4.16 (t, 2H), 3.96 (s, 3H), 3.47 (m, 1H), 2.83 (m, 1H), 2.66 (m, 1H), 2.44 (m, 2H), 1.93 (m, 2H), 1.85 (m, 1H), 1.75 (m, 2H), 1.61 (m, 1H), 1.41 (m, 1H), 1.07 (m, 1H);

MS (+ve ESI): 568.2 $(M+H)^+$.

Example 84 - Preparation of compound 84 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(hydroxymethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 60 but starting with piperidin-4-ylmethanol (75 mg, 0.65 mmol) yielded compound 84 in table 3 (85 mg, 81 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.21 (m, 2H), 7.14 (s, 1H), 5.16 (s, 2H), 4.41 (t, 1H), 4.15 (t, 2H), 3.96 (s, 3H), 3.24 (t, 2H), 2.87 (m, 2H), 2.43 (t, 2H), 1.95 (m, 2H), 1.85 (t, 2H), 1.63 (d, 2H), 1.33 (m, 1H), 1.13 (m, 2H);

MS (+ve ESI): 582.2 $(M+H)^+$.

Example 85 - Preparation of compound 85 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(6-methoxy-7-{3-[methyl(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 60 but starting methyl(propyl)amine (48 mg, 0.65 mmol) yielded compound 85 in table 3 (71 mg, 74 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.22 (m, 2H), 7.14 (s, 1H), 5.16 (s, 2H), 4.16 (t, 2H), 3.96 (s, 3H), 2.46 (t, 2H), 2.26 (t, 2H), 2.16 (s, 3H), 1.92 (m, 2H), 1.41 (m, 2H), 0.83 (t, 3H);

MS (+ve ESI): 540.2 $(M+H)^+$.

Example 86 - Preparation of compound 86 in table 3 - 2-{4-[(7-{3-[(cyclopropylmethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

An analogous reaction to that described in example 60 but starting with (cyclopropylmethyl)propylamine (74 mg, 0.65 mmol) yielded compound 86 in table 3 (85 mg, 82 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.22 (m, 2H), 7.13 (s, 1H), 5.16 (s, 2H), 4.18 (t, 2H), 3.95 (s, 3H), 2.64 (m, 2H), 2.43 (t, 2H), 2.29 (d, 2H), 1.90 (m, 2H), 1.41 (m, 2H), 0.83 (t, 3H), 0.81 (m, 1H), 0.41 (m, 2H), 0.06 (m, 2H);

MS (+ve ESI): 580.2 $(M+H)^+$.

Example 87 - Preparation of compound 87 in table 3 - 2-{4-[(7-{3-[[2-(diethylamino)ethyl](methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

An analogous reaction to that described in example 60 but starting with N,N-diethyl-N'-methylethane-1,2-diamine (85 mg, 0.65 mmol) yielded compound 87 in table 3 (55 mg, 51 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.21 (m, 2H), 7.14 (s, 1H), 5.16 (s, 2H), 4.16 (t, 2H), 3.95 (s, 3H), 2.41 (m, 10H), 2.19 (s, 3H), 1.91 (m, 2H), 0.90 (t, 6H);

MS (+ve ESI): 597.3 $(M+H)^+$.

Example 88 - Preparation of compound 88 in table 3 - 2-{4-[(7-{3-[[2-(diethylamino)ethyl](ethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

An analogous reaction to that described in example 60 but starting with N,N,N'-triethylethane-1,2-diamine (94 mg, 0.65 mmol) yielded compound 88 in table 3 (9 mg, 8 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.34 (s, 1H), 7.77 (s, 1H), 7.76 (s, 1H), 7.72 (m, 1H), 7.20 (m, 2H), 7.14 (s, 1H), 5.15 (s, 2H), 4.17 (t, 2H), 3.95 (s, 3H), 2.57 (t, 2H), 2.43 (m, 10H), 1.89 (m, 2H), 0.95 (t, 3H), 0.91 (t, 6H);

MS (+ve ESI): 611.2 $(M+H)^+$.

Example 89 - Preparation of compound 89 in table 3 - *N*-(2,3-difluorophenyl)-2-[4-({6-methoxy-7-[3-(4-methyl-1,4-diazepan-1-yl)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide

An analogous reaction to that described in example 60 but starting with 1-methyl-1,4-diazepane (74 mg, 0.65 mmol) yielded compound 89 in table 3 (52 mg, 50 % yield):
^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.21 (m, 2H), 7.15 (s, 1H), 5.16 (s, 2H), 4.16 (t, 2H), 3.95 (s, 3H), 2.63 (m, 10H), 2.23 (s, 3H), 1.91 (m, 2H), 1.71 (m, 2H);
MS (+ve ESI): 581.2 $(M+H)^+$.

Example 90 - Preparation of compound 90 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(isopropyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 60 but starting with 2-(isopropylamino)ethanol (67 mg, 0.65 mmol) yielded compound 90 in table 3 (59 mg, 58 % yield):
^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.22 (m, 2H), 7.15 (s, 1H), 5.16 (s, 2H), 4.27 (t, 1H), 4.17 (t, 2H), 3.96 (s, 3H), 3.36 (m, 2H), 2.87 (m, 1H), 2.26 (t, 2H), 2.44 (t, 2H), 1.86 (m, 2H), 0.92 (d, 6H);
MS (+ve ESI): 570.3 $(M+H)^+$.

Example 91 - Preparation of compound 91 in table 3 - 2-{4-[(7-{3-[cyclopropyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

An analogous reaction to that described in example 60 but starting with 2-(cyclopropylamino)ethanol (66 mg, 0.65 mmol) yielded compound 91 in table 3 (58 mg, 56 % yield):
^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.22 (m, 2H), 7.15 (s, 1H), 5.16 (s, 2H), 4.31 (m, 1H), 4.13 (t, 2H), 3.96 (s, 3H), 3.51 (m, 2H), 2.77 (m, 2H), 2.64 (m, 2H), 1.97 (m, 2H), 1.83 (m, 1H), 0.43 (m, 2H), 0.31 (m, 2H);
MS (+ve ESI): 568.2 $(M+H)^+$.

Example 92 - Preparation of compound 92 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 60 but starting with 2-((2-methoxyethyl)amino)ethanol (77 mg, 0.65 mmol) yielded compound 92 in table 3 (75 mg, 71 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.22 (m, 2H), 7.15 (s, 1H), 5.16 (s, 2H), 4.31 (t, 1H), 4.17 (t, 2H), 3.96 (s, 3H), 3.43 (m, 2H), 3.37 (m, 2H), 3.21 (s, 3H), 2.64 (m, 4H), 2.53 (m, 2H), 1.89 (m, 2H);

MS (+ve ESI): 586.2 $(M+H)^+$.

Example 93 - Preparation of compound 93 in table 3 - 2-{4-[(7-{3-[cyclobutyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

An analogous reaction to that described in example 60 but starting with 2-(cyclobutylamino)ethanol (75 mg, 0.65 mmol) yielded compound 93 in table 3 (49 mg, 47 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.49 (s, 1H), 8.48 (s, 1H), 7.81 (s, 1H), 7.78 (s, 1H), 7.73 (m, 1H), 7.22 (m, 2H), 7.15 (s, 1H), 5.16 (s, 2H), 4.35 (m, 1H), 4.15 (t, 2H), 3.95 (s, 3H), 3.40 (m, 2H), 3.12 (m, 1H), 2.56 (m, 2H), 2.46 (m, 2H), 1.95 (m, 2H), 1.89 (m, 2H), 1.76 (m, 2H), 1.54 (m, 2H);

MS (+ve ESI): 582.2 $(M+H)^+$.

Example 94 - Preparation of compound 94 in table 3 - 2-{4-[(7-{3-[(cyclopropylmethyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

An analogous reaction to that described in example 60 but starting with 2-((cyclopropylmethyl)amino)ethanol (75 mg, 0.65 mmol) yielded compound 94 in table 3 (66 mg, 63 % yield):

^{1}H-NMR (DMSO d_6, TFA): 9.05 (s, 1H), 8.41 (s, 1H), 8.09 (s, 1H), 7.97 (s, 1H), 7.75 (m, 1H), 7.34 (s, 1H), 7.21 (m, 2H), 5.27 (s, 2H), 4.32 (m, 2H), 4.03 (s, 3H), 3.82 (m, 2H), 3.45 (m, 2H), 3.40 (m, 1H), 3.34 (m, 1H), 3.18 (m, 2H), 2.31 (m, 2H), 1.17 (m, 1H), 0.69 (m, 2H), 0.45 (m, 2H);

MS (+ve ESI): 582.2 $(M+H)^+$.

Example 95 - Preparation of compound 95 in table 3 - 2-{4-[(7-{3-[(cyclobutylmethyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

An analogous reaction to that described in example 60 but starting with 2-((cyclobutylmethyl)amino)ethanol (84 mg, 0.65 mmol) yielded compound 95 in table 3 (70 mg, 66 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.22 (m, 2H), 7.14 (s, 1H), 5.16 (s, 2H), 4.28 (m, 1H), 4.16 (t, 2H), 3.96 (s, 3H), 3.43 (m, 2H), 2.57 (m, 2H), 2.45 (m, 4H), 1.91 (m, 5H), 1.76 (m, 2H), 1.59 (m, 2H);

MS (+ve ESI): 596.2 $(M+H)^+$.

Example 96 - Preparation of compound 96 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(prop-2-yn-1-yl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 60 but starting with 2-(prop-2-yn-1-ylamino)ethanol (64 mg, 0.65 mmol) yielded compound 96 in table 3 (68 mg, 67 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.22 (m, 2H), 7.16 (s, 1H), 5.16 (s, 2H), 4.43 (t, 1H), 4.15 (t, 2H), 3.96 (s, 3H), 3.44 (m, 2H), 3.38 (m, 2H), 3.09 (m, 1H), 2.63 (t, 2H), 2.54 (m, 2H), 1.92 (m, 2H);

MS (+ve ESI): 566.2 $(M+H)^+$.

Example 97 - Preparation of compound 97 in table 3 - 2-{4-[(7-{3-[allyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

An analogous reaction to that described in example 60 but starting with 2-(allylamino)ethanol (66 mg, 0.65 mmol) yielded compound 97 in table 3 (73 mg, 71 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.49 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.72 (m, 1H), 7.22 (m, 2H), 7.15 (s, 1H), 5.82 (m, 1H), 5.17 (m, 1H), 5.16 (s, 2H), 5.09 (m, 1H), 4.35 (t, 1H), 4.16 (t, 2H), 3.95 (s, 3H), 3.44 (m, 2H), 3.32 (m, 2H), 3.1 (d, 2H), 2.62 (t, 2H), 1.91 (m, 2H);

MS (+ve ESI): 568.2 $(M+H)^+$.

Example 98 - Preparation of compound 98 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2,2-dimethylpropyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 60 but starting with 2-((2,2-dimethylpropyl)amino)ethanol (85 mg, 0.65 mmol) yielded compound 98 in table 3 (67 mg, 62 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.77 (s, 1H), 7.76 (s, 1H), 7.74 (m, 1H), 7.21 (m, 2H), 7.14 (s, 1H), 5.17 (s, 2H), 4.33 (t, 1H), 4.17 (t, 2H), 3.95 (s, 3H), 3.44 (m, 2H), 2.65 (m, 2H), 2.54 (m, 2H), 2.21 (s, 2H), 1.91 (m, 2H), 0.83 (s, 9H);

MS (+ve ESI): 598.2 $(M+H)^+$.

Example 99 - Preparation of compound 99 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(3,3,3-trifluoropropyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 60 but starting with 2-((3,3,3-trifluoropropyl)amino)ethanol (102 mg, 0.65 mmol) yielded compound 99 in table 3 (80 mg, 72 % yield):

^{1}H-NMR (DMSO d_6): 9.73 (s, 1H), 8.49 (s, 1H), 8.35 (s, 1H), 7.79 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.23 (m, 2H), 7.16 (s, 1H), 5.17 (s, 2H), 4.18 (t, 2H), 3.96 (s, 3H), 3.49 (m, 2H), 2.67 (m, 6H), 1.94 (m, 2H);

MS (+ve ESI): 624.2 $(M+H)^+$.

Example 100 – Preparation of compound 100 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide

A 2 : 1 mixture of 2-(4-{[7-(2-chloroethoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide : 2-(4-{[7-(2-bromoethoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide as the di-hydrochloride salt (0.15 g, ~0.3 mmol), triethylamine (0.11 ml, 0.8 mmol), (2*R*)-pyrrolidin-2-ylmethanol (0.081 g, 0.8 mmol) and sodium iodide (0.08 g, 0.53 mmol) in dimethylacetamide (2 ml) was heated at 90°C for 6 hours. The reaction mixture was diluted with dichloromethane and a few drops of methanol and then filtered. The filtrate was purified

directly by silica gel chromatography, eluting with a 1 to 12% mixture of methanol (containing 10% 7N ammonia in methanol) in dichloromethane. The obtained product was triturated with acetonitrile and then diethyl ether to give compound 100 in table 3 (0.08 g, 54% yield) as a fawn coloured solid:

^{1}H-NMR (DMSO d_6 at 373K): 10.18 (br s, 1H), 9.97 (s, 1H), 8.70 (s, 1H), 8.31 (s, 1H), 7.99 (s, 1H), 7.91 (s, 1H), 7.71 (m, 1H), 7.32 (s, 1H), 7.18 (m, 2H), 7.03 (br s, 1H), 5.20 (s, 2H), 4.62 (t, 2H), 4.07 (s, 3H), 3.60 (m, 7H), 1.95 (m, 4H);

MS (+ve ESI): 554 $(M+H)^+$.

Example 101 – Preparation of compound 101 in table 3 - *N*-(2,3-difluorophenyl)-2-(4-{[7-(2-{4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl}ethoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide

An analogous reaction to that described in example 100 but starting with 2-(2-piperazin-1-ylethoxy)ethanol (0.09 ml, 0.53 mmol) yielded compound 101 in table 3 (0.035 g, 31% yield):

^{1}H-NMR (DMSO d_6 at 373K): 9.85 (s, 1H), 9.38 (br s, 1H), 8.47 (s, 1H), 8.27 (s, 1H), 7.84 (s, 1H), 7.80 (s, 1H), 7.75 (m, 1H), 7.19 (m, 3H), 5.21 (s, 2H), 4.28 (t, 2H), 3.98 (s, 3H), 3.52 (m, 6H), 2.80 (m, 12H);

MS (+ve ESI): 627 $(M+H)^+$

MS (-ve ESI): 625 $(M-H)^-$.

Example 102 – Preparation of compound 102 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{2-[2-(hydroxymethyl)piperidin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 100 but starting with piperidin-2-ylmethanol (0.08 g, 0.07 mmol) yielded compound 102 in table 3 (0.04 g, 31% yield):

^{1}H-NMR (DMSO d_6 at 373K): 9.85 (s, 1H), 9.36 (s, 1H), 8.45 (s, 1H), 8.28 (s, 1H), 7.83 (s, 1H), 7.78 (s, 1H), 7.69 (m, 1H), 7.18 (m, 3H), 5.12 (s, 2H), 4.22 (t, 2H), 3.96 (s, 3H), 3.59 (m, 2H), 3.25 (br s, 1H), 2.50 (m, 5H, under DMSO), 1.42 (m, 6H);

MS (+ve ESI): 568 $(M+H)^+$

MS (-ve ESI): 566 $(M-H)^-$.

Example 103 – Preparation of compound 103 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2-hydroxy-1,1-dimethylethyl)amino]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 100 but starting with 2-amino-2-methylpropan-1-ol (0.062 g, 0.7 mmol) yielded compound 103 in table 3 (0.075 g, 60% yield):

MS (+ve ESI): 542 $(M+H)^+$

MS (-ve ESI): 540 $(M-H)^-$.

Example 104 – Preparation of compound 104 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{2-[4-(2-hydroxyethyl)piperazin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 100 but starting with 2-piperazin-1-ylethanol (0.091 g, 0.7 mmol) yielded compound 104 in table 3 (0.112 g, 83% yield):

MS (+ve ESI): 583 $(M+H)^+$.

Example 105 – Preparation of compound 105 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{2-[(*trans*-4-hydroxycyclohexyl)amino]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 100 but starting with *trans*-4-hydroxycyclohexyl amine (0.08 g, 0.7 mmol) yielded compound 105 in table 3 (0.06 g, 46% yield):

MS (+ve ESI): 568 $(M+H)^+$

MS (-ve ESI): 566 $(M-H)^-$.

Example 106 – Preparation of compound 106 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{2-[3-(hydroxymethyl)piperidin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 100 but starting with piperidin-3-ylmethanol (0.08 g, 0.7 mmol) yielded compound 106 in table 3 (0.073 g, 56% yield):

MS (+ve ESI): 568 $(M+H)^+$

MS (-ve ESI): 566 $(M-H)^-$.

Example 107 – Preparation of compound 107 in table 3 - *N*-(2,3-difluorophenyl)-2-(4-{[7-(2-{[1-(hydroxymethyl)cyclopentyl]amino}ethoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide

An analogous reaction to that described in example 100 but starting with (1-aminocyclopentyl)methanol (0.08 g, 0.7 mmol) yielded compound 107 in table 3 (0.069 g, 53% yield):

MS (+ve ESI): 568 $(M+H)^+$

MS (-ve ESI): 566 $(M-H)^-$.

Example 108 – Preparation of compound 108 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{2-[4-(3-hydroxypropyl)piperazin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 100 but starting with 3-piperazin-1-ylpropan-1-ol (0.101 g, 0.7 mmol) yielded compound 108 in table 3 (0.101 g, 74% yield):

MS (+ve ESI): 597 $(M+H)^+$

MS (-ve ESI): 595 $(M-H)^-$.

Example 109 – Preparation of compound 109 in table 3 - 2-{4-[(7-{2-[cyclohexyl(2-hydroxyethyl)amino]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

An analogous reaction to that described in example 100 but starting with 2-(cyclohexylamino)ethanol (0.1g, 0.7 mmol) yielded compound 109 in table 3 (0.02 g, 15% yield):

MS (+ve ESI): 596 $(M+H)^+$.

Example 110 – Preparation of compound 110 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2-hydroxyethyl)(propyl)amino]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 100 but starting with 2-(propylamino)ethanol (0.072 g, 0.7 mmol) yielded compound 110 in table 3 (0.032 g, 25% yield):

MS (+ve ESI): 556 $(M+H)^+$

MS (-ve ESI): 554 $(M-H)^-$.

Example 111 – Preparation of compound 111 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{2-[(3-hydroxy-2,2-dimethylpropyl)amino]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 100 but starting with 3-amino-2,2-dimethylpropan-1-ol (0.072 g, 0.7 mmol) yielded compound 111 in table 3 (0.11 g, 86% yield):

MS (+ve ESI): 556 $(M+H)^+$

MS (-ve ESI): 554 $(M-H)^-$.

Example 112 – Preparation of compound 112 in table 3 - *N*-(2,3-difluorophenyl)-2-[4-({6-methoxy-7-[2-(tetrahydro-2*H*-pyran-4-ylamino)ethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide

An analogous reaction to that described in example 100 but starting with tetrahydro-2*H*-pyran-4-amine (0.069 g, 0.7 mmol) yielded compound 112 in table 3 (0.107 g, 84% yield):

MS (+ve ESI): 554 $(M+H)^+$

MS (-ve ESI): 552 $(M-H)^-$.

Example 113 – Preparation of compound 113 in table 3 -2-{4-[(7-{2-[cyclobutyl(2-hydroxyethyl)amino]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

An analogous reaction to that described in example 100 but starting with 2-(cyclobutylamino)ethanol (0.15 g, 1.3 mmol) yielded compound 113 in table 3 (0.086 g, 37% yield):

^{1}H-NMR (DMSO d_6): 10.26 (br s, 1H), 9.66 (s, 1H), 8.47 (s, 1H), 8.33 (s, 1H), 7.74 (m, 3H), 7.18 (m, 3H), 5.15 (s, 2H), 4.34 (br s, 1H), 4.13 (t, 2H), 3.96 (s, 3H), 3.48 (q, 2H), 2.90 (t, 2H), 2.85 (t, 1H), 2.59 (t, 2H), 2.04 (m, 2H), 1.82 (m, 2H), 1.58 (m, 2H).

MS (+ve ESI): 568 $(M+H)^+$

MS (-ve ESI): 566 $(M-H)^-$.

Example 114 – Preparation of compound 114 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2-hydroxyethyl)(tetrahydro-2*H*-pyran-4-yl)amino]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

A mixture of *N*-(2,3-difluorophenyl)-2-[4-({6-methoxy-7-[2-(tetrahydro-2*H*-pyran-4-ylamino)ethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide (0.17 g, 0.31 mmol), glycolaldehyde (0.028 g, 0.46 mmol) and MP-triacetoxyborohydride (2 mmol/g, 0.39 g, 0.78 mmol) in dimethylformamide (1.5 ml) was stirred at ambient temperature for 2 hours. The resin was removed by filtration and the filtrate evaporated under reduced pressure. The residue was purified by silica gel chromatography eluting with a 0 to 10% mixture of methanol (containing 10% 7N ammonia in methanol) in dichloromethane. The obtained product was triturated with diethyl ether to give compound 114 in table 3 (0.045 g, 24% yield) as a white solid:

^{1}H-NMR (DMSO d_6): 10.28 (br s, 1H), 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.72 (m, 3H), 7.18 (m, 3H), 5.16 (s, 2H), 4.30 (t, 1H), 4.15 (t, 2H), 3.97 (s, 3H), 3.88 (q, 2H), 3.39 (m, 4H, under H_20), 2.97 (t, 2H), 2.80 (m, 1H), 2.63 (t, 2H), 1.68 (m, 2H), 1.43 (m, 2H);
MS (+ve ESI): 598 $(M+H)^+$
MS (-ve ESI): 596 $(M-H)^-$.

Example 115 – Preparation of compound 115 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide.

An analogous reaction to that described in example 100 but starting with (2S)-pyrrolidin-2-ylmethanol (616mg, 6.10mmol) and purification by reverse phase chromatography on C-18 silica using a water / acetonitrile / trifluoroacetic acid gradient as eluent gave compound 115 in table 3 (637 mg, 75% yield) as a pale brown solid:
^{1}H-NMR (DMSO d_6): 9.68 (s(br.), 1H), 8.50 (s, 1H), 8.34 (s, 1H), 7.79 (d, 1H), 7.78 (s, 1H), 7.72 (m, 1H), 7.18 (m, 3H), 5.13 (s, 2H), 4.32 (s (br.), 1H), 4.22 (t, 2H), 3.95 (s, 3H), 3.41 (m, 1H), 3.30 (m, (partially obscured by H_2O), 2H), 3.17 (m, 1H), 2.80 (m, 1H), 2.60 (m, 1H), 2.35 (q, 1H), 1.82 (m, 1H), 1.67 (m, 2H), 1.52 (m, 1H);
MS (+ve ESI): 554 $(M+H)^+$.

Example 116 – Preparation of compound 116 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2*R*)-2-(2-hydroxyethyl)piperidin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide.

An analogous reaction to that described in example 115 but starting with 2-[(2*R*)-piperidin-2-yl]ethanol (6.0 mmol) gave compound 116 in table 3 (604 mg, 68% yield) as a pale yellow solid:

^{1}H-NMR (DMSO d_6): 10.28 (s, 1H), 9.67 (s, 1H), 8.50 (s, 1H), 8.34 (s, 1H), 7.80 (d, 1H), 7.79 (s, 1H), 7.73 (m, 1H), 7.20 (m, 3H), 5.17 (s, 2H), 4.39 (s (br.), 1H), 4.21 (t, 2H), 3.96 (s, 3H), 3.52 (m, 1H), 3.45 (m, 1H), 3.05 (m, 1H), 2.90 (m, 1H), 2.83 (m, 1H), 2.58 (m, 1H), 2.45 (m, 1H), 1.80 (m, 1H), 1.61 (m, 2H), 1.50 (m, 3H), 1.32 (m, 2H);

MS (+ve ESI): 582 $(M+H)^+$.

Example 117 – Preparation of compound 117 in table 3 - *N*-(2,3-Difluorophenyl)-2-{4-[(7-{2-[(2*S*)-2-(2-hydroxyethyl)piperidin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide.

An analogous reaction to that described in example 115 but starting with 2-[(2*S*)-piperidin-2-yl]ethanol (6.0 mmol) gave compound 117 in table 3 (564 mg, 64% yield):

^{1}H-NMR (DMSO d_6): 10.28 (s, 1H), 9.67 (s, 1H), 8.50 (s, 1H), 8.34 (s, 1H), 7.80 (d, 1H), 7.79 (s, 1H), 7.73 (m, 1H), 7.20 (m, 3H), 5.17 (s, 2H), 4.39 (s(br.), 1H), 4.21 (t, 2H), 3.96 (s, 3H), 3.52 (m, 1H), 3.45 (m, 1H), 3.05 (m, 1H), 2.90 (m, 1H), 2.83 (m, 1H), 2.58 (m, 1H), 2.45 (m, 1H), 1.80 (m, 1H), 1.61 (m, 2H), 1.50 (m, 3H), 1.32 (m, 2H);

MS (+ve ESI): 582 $(M+H)^+$.

Example 118 - Preparation of compound 118 in table 4 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

2-(Propylamino)ethanol (95 mg, 0.92 mmol) was added to a solution of 2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide (103 mg, 0.23 mmol) and potassium iodide (76 mg, 0.46 mmol) in dimethylacetamide (0.5 ml) and the mixture heated at 90 °C for 2 hours under argon. The reaction mixture was cooled and water (1 ml) was added resulting in precipitation. The solid was recovered by filtration, dissolved in dichloromethane: methanol (1:1) and the solution filtered through a teflon filter.

The solvent was evaporated and the residual oil triturated in dichloromethane: diethyl ether (1:1) to yield compound 118 in table 4 (70 mg, 56 % yield):

^{1}H-NMR (DMSO d_6, TFA): 9.01 (s, 1H), 8.62 (d, 1H), 8.41 (s, 1H), 7.98 (s, 1H), 7.72 (m, 1H), 7.51 (d, 1H), 7.27 (s, 1H), 7.20 (m, 2H), 5.25 (s, 2H), 4.30 (m, 2H), 3.78 (m, 2H), 3.34 (m, 2H), 3.27 (m, 2H), 3.15 (m, 2H), 2.25 (m, 2H), 1.71 (m, 2H), 0.94 (t, 3H);

MS (+ve ESI): 540.1 $(M+H)^+$.

Example 119 - Preparation of compound 119 in table 4 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(isobutyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 118 but starting with 2-(isobutylamino)ethanol (107 mg, 0.92 mmol) yielded compound 119 in table 4 (85 mg, 67 % yield):

^{1}H-NMR (DMSO d_6, TFA): 9.01 (s, 1H), 8.63 (d, 1H), 8.41 (s, 1H), 7.98 (s, 1H), 7.73 (m, 1H), 7.51 (d, 1H), 7.28 (s, 1H), 7.20 (m, 2H), 5.25 (s, 2H), 4.31 (m, 2H), 3.82 (m, 2H), 3.38 (m, 2H), 3.29 (m, 2H), 3.10 (m, 1H), 3.04 (m, 1H), 2.27 (m, 2H), 2.16 (m, 1H), 1.01 (d, 6H);

MS (+ve ESI): 554.2 $(M+H)^+$.

Example 120 - Preparation of compound 120 in table 4 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 118, but starting with (2S)-pyrrolidin-2-ylmethanol (93 mg, 0.92 mmol) yielded compound 120 in table 4 (83 mg, 67 % yield):

^{1}H-NMR (DMSO d_6, TFA): 9.01 (s, 1H), 8.63 (d, 1H), 8.41 (s, 1H), 7.98 (s, 1H), 7.73 (m, 1H), 7.50 (d, 1H), 7.27 (s, 1H), 7.21 (m, 2H), 5.25 (s, 2H), 4.31 (t, 2H), 3.78 (m, 1H), 3.62 (m, 4H), 3.26 (m, 1H), 3.18 (m, 1H), 2.26 (m, 2H), 2.13 (m, 1H), 2.03 (m, 1H), 1.89 (m, 1H), 1.79 (m, 1H);

MS (+ve ESI): 538.2 $(M+H)^+$.

Example 121 - Preparation of compound 121 in table 4 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 118, but starting with (2R)-pyrrolidin-2-ylmethanol (73 mg, 0.72 mmol) yielded compound 121 in table 4 (58 mg, 59 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.99 (s, 1H), 8.61 (d, 1H), 8.40 (s, 1H), 7.96 (s, 1H), 7.72 (m, 1H), 7.51 (d, 1H), 7.26 (s, 1H), 7.17 (m, 2H), 5.23 (s, 2H), 4.29 (t, 2H), 3.76 (m, 1H), 3.61 (m, 4H), 3.26 (m, 1H), 3.15 (m, 1H), 2.24 (m, 2H), 2.12 (m, 1H), 2.02 (m, 1H), 1.89 (m, 1H), 1.77 (m, 1H);

MS (+ve ESI): 538.2 $(M+H)^+$.

Example 122 - Preparation of compound 122 in table 4- 2-{4-[(7-{3-[cyclopentyl(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

The reaction was carried out in an analogous manner to that described in example 118, but starting with 2-(cyclopentylamino)ethanol (136 mg, 1.06 mmol). On completion of reaction, the reaction mixture was diluted with dichloromethane (10 ml) and loaded directly onto a silica gel chromatography column. Elution with dichloromethane followed by increased polarity to dichloromethane : methanol (20:1) then dichloromethane: methanol : ammonia (20:1:0.1) yielded compound 122 in table 4 (75 mg, 63 % yield):

^{1}H-NMR (DMSO d_6): 10.27 (br s, 1H), 9.91 (br s, 1H), 8.54 (s, 1H), 8.34 (m, 2H), 7.79 (s, 1H), 7.72 (m, 1H), 7.20 (m, 3H), 7.13 (s, 1H), 5.16 (s, 2H), 4.29 (s, 1H), 4.17 (t, 2H), 3.43 (m, 2H), 3.06 (m, 1H), 2.67 (t, 2H), 2.56 (s, 2H), 1.88 (m, 2H), 1.71 (m, 2H), 1.56 (m, 2H), 1.45 (m, 2H), 1.31 (m, 2H);

MS (+ve ESI): 566 $(M+H)^+$.

Example 123 - Preparation of compound 123 in table 4- *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 122, but starting with 2-(ethylamino)ethanol (178 mg, 2 mmol) yielded compound 123 in table 4 (141 mg, 67 % yield):

^{1}H-NMR (DMSO d_6): 8.66 (s, 1H), 8.46 (m, 2H), 7.91 (s, 1H), 7.83 (m, 1H), 7.30 (m, 3H), 7.25 (m, 1H), 5.26 (s, 2H), 4.24 (s, 1H), 4.28 (t, 2H), 3.55 (m, 2H), 2.71 (t, 2H), 2.52 (m, 4H), 1.99 (m, 2H), 1.07 (t, 3H);

MS (+ve ESI): 526 $(M+H)^+$.

Example 124 - Preparation of compound 124 in table 4- *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 122, but starting with 2-piperazin-1-ylethanol (138 mg, 1.06 mmol) yielded compound 124 in table 4 (78 mg, 65 % yield):

^{1}H-NMR (DMSO d_6): 10.26 (br s, 1H), 9.90 (br s, 1H), 8.54 (s, 1H), 8.33 (m, 2H), 7.78 (s, 1H), 7.70 (m, 1H), 7.18 (m, 3H), 7.13 (s, 1H), 5.16 (s, 2H), 4.31 (m, 1H), 4.16 (t, 2H), 3.46 (m, 2H), 2.38 (m, 12H), 1.92 (m, 2H);

MS (+ve ESI): 567 $(M+H)^+$.

Example 125 - Preparation of compound 125 in table 4- *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(hydroxymethyl)piperidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 122, but starting with piperidin-4-ylmethanol (230 mg, 2 mmol) yielded compound 125 in table 4 (111 mg, 50 % yield):

^{1}H-NMR (DMSO d_6): 9.95 (br s, 1H), 8.56 (s, 1H), 8.39 (m, 1H), 8.34 (s, 1H), 7.79 (s, 1H), 7.70 (t, 1H), 7.19 (m, 4H), 5.16 (s, 2H), 4.60 (m, 1H), 4.24 (t, 2H), 3.55 (m, 2H), 3.25 (m, 4H), 2.92 (m, 2H), 2.17 (m, 2H), 1.95 (m, 2H), 1.63 (m, 1H), 1.39 (m, 2H);

MS (+ve ESI): 552 $(M+H)^+$.

Example 126 - Preparation of compound 126 in table 4- *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3-hydroxy-1,1-dimethylpropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 122, but starting with 3-amino-3-methylbutan-1-ol (206 mg, 2 mmol) yielded compound 126 in table 4 (89 mg, 41 % yield):

^{1}H-NMR (DMSO d_6): 8.65 (s, 1H), 8.45 (m, 2H), 7.90 (s, 1H), 7.82 (m, 1H), 7.30 (m, 4H), 5.25 (s, 2H), 4.33 (t, 2H), 3.67 (t, 2H), 2.97 (t, 2H), 2.09 (m, 2H), 1.76 (t, 2H), 1.26 (s, 6H);

MS (+ve ESI): 540 $(M+H)^+$.

Example 127 – Preparation of compound 127 in table 4 - 2-{4-[(7-{3-[(2-cyanoethyl)(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

An analogous reaction to that described in example 122, but starting with 3-[(2-hydroxyethyl)amino]propanenitrile (see Bell, J. A.; Kenworthy, C. *Synthesis*, **1971**, *12*, 650-652, 0.258 g, 2.00 mmol) yielded compound 127 in table 4 (0.076 g, 48% yield):

^{1}H-NMR (DMSO d_6): 10.28 (1H, s), 9.89 (1H, s), 8.54 (1H, s), 8.33 (2H, d), 7.77 (1H, s), 7.70 (1H, m), 7.19 (3H, m), 7.14 (1H, s), 5.13 (2H, s), 4.37 (1H, t), 4.19 (2H, t), 3.48 (2H, m), 2.79 (2H, t), 2.69 (2H, t), 2.58 (3H, m), 1.90 (2H, m);

MS (+ve ESI): 551 $(M+H)^+$

MS (-ve ESI): 549 $(M-H)^-$.

Example 128 – Preparation of compound 128 in table 4 - *N*-(2,3-difluorophenyl)-2-(4-{[7-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide

A solution of 2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide (0.060 g, 0.13 mmol) in morpholine (20 ml) was heated at 80°C for 2 hours and then allowed to cool to room temperature. The mixture was evaporated under reduced pressure to leave a brown solid which was purified by silica gel chromatography eluting with a 0 to 10% mixture methanol (containing 10% 7N ammonia in methanol) in dichloromethane to give compound 128 in table 4 (0.055 g, 81% yield) as a white solid:

^{1}H-NMR (DMSO d_6): 10.27 (br s, 1H), 8.55 (s, 1H), 8.38 (d, 1H), 8.32 (s, 1H), 7.79 (s, 1H), 7.68 (m, 2H), 7.18 (m, 3H), 5.15 (s, 2H), 4.20 (t, 2H), 3.65 (m, 4H), 3.30 (m, 4H), 2.75 (m, 4H);

MS (+ve ESI): 524 $(M+H)^+$.

Example 129 – Preparation of compound 129 in table 4 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3-hydroxy-2,2-dimethylpropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 122, but starting with 3-amino-2,2-dimethylpropan-1-ol (438 mg, 4.25 mmol) yielded compound 129 in table 4 (290 mg, 63% yield) as a white solid:

^{1}H-NMR (DMSO d_6): 10.28 (br s, 1H), 9.90 (s, 1H), 8.50 (s, 1H), 8.38 (d, 1H), 8.30 (s, 1H), 7.79 (s, 1H), 7.68 (t, 1H), 7.16 (m, 4H), 5.25 (s, 2H), 4.20 (t, 2H), 3.30 (br s, 2H), 3.20 (s, 2H), 2.80 (t, 2H), 2.42 (s, 6H), 2.00 (m, 2H);

MS (+ve ESI): 540 $(M+H)^+$

MS (-ve ESI): 538 $(M-H)^-$.

Example 130 – Preparation of compound 130 in table 4 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3-hydroxypropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 122, but starting with 3-aminopropan-1-ol (0.33 ml, 4.25 mmol) yielded compound 130 in table 4 (320 mg, 74% yield):

^{1}H-NMR (DMSO d_6): 9.90 (s, 1H), 8.50 (s, 1H), 8.38 (d, 1H), 8.30 (s, 1H), 7.79 (s, 1H), 7.68 (t, 1H), 7.20 (m, 4H), 5.19 (s, 2H), 4.20 (t, 2H), 3.42 (t, 2H), 2.90 (t, 2H), 2.78 (t, 2H), 2.02 (quintet, 2H), 1.65 (quintet, 2H);

MS (+ve ESI): 512 $(M+H)^+$

MS (-ve ESI): 510 $(M-H)^-$.

Example 131 – Preparation of compound 131 in table 4 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3-hydroxypropyl)(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

A mixture of propionaldehyde (0.020 ml, 0.31 mmol), *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3-hydroxypropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (0.160 g, 0.31 mmol), acetic acid (0.020 ml, 0.31 mmol) and MP-cyanoborohydride (2 mmol / g, 0.024 g, 0.47 mmol) in methanol (4 ml) was stirred at room temperature for 2 hours. The reaction mixture was filtered and the filtrate evaporated under reduced pressure and the residue was then purified by silica gel chromatography eluting with a 0 to 10% mixture of methanol (containing 10% 7N ammonia in methanol) in dichloromethane to give compound 131 in table 4 (0.085 g, 49% yield):

^{1}H-NMR (DMSO d_6): 10.32 (br s, 1H), 10.00 (s, 1H), 8.54 (s, 1H), 8.38 (d, 1H), 8.30 (s, 1H), 7.78 (s, 1H), 7.65 (t, 1H), 7.18 (m, 4H), 5.18 (s, 2H), 4.18 (t, 2H), 3.40 (t, 2H), 2.60 (m, 6H), 2.20 (m, 2H), 1.58 (m, 4H), 0.84 (t, 3H);

MS (+ve ESI): 554 $(M+H)^+$.

Example 132 – Preparation of compound 132 in table 4 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[ethyl(3-hydroxypropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

A mixture of acetaldehyde (0.034 g, 0.78 mmol), *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3-hydroxypropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (0.400 g, 0.78 mmol), acetic acid (0.040 ml, 0.78 mmol) and MP-cyanoborohydride (2mmol/g, 0.586 g, 1.17 mmol) in methanol (8 ml) was stirred at room temperature for 2 hours. The reaction mixture was filtered and then evaporated to leave a brown oil which was purified by silica gel chromatography eluting with a 0 to 10% mixture of methanol (containing 10% 7N ammonia in methanol) in dichloromethane to give compound 132 in table 4 (0.250 g, 60% yield):
^{1}H-NMR (DMSO d_6): 10.29 (br s, 1H), 9.98 (s, 1H), 8.50 (s, 1H), 8.35 (d, 1H), 8.30 (s, 1H), 7.78 (s, 1H), 7.70 (m, 1H), 7.18 (m, 4H), 5.18 (s, 2H), 4.18 (t, 2H), 3.42 (t, 2H), 2.62 (m, 6H), 1.95 (t, 2H), 1.60 (quintet, 2H), 1.02 (t, 3H);
MS (+ve ESI): 540 $(M+H)^+$
MS (-ve ESI): 538 $(M-H)^-$.

Example 133 – Preparation of compound 133 in table 4 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)-3-oxopiperazin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide.

An analogous reaction to that described in example 122 but starting with 1-(2-hydroxyethyl)piperazin-2-one (0.226 g, 1.5 7mmol) yielded compound 133 in table 4 (0.186 g, 82% yield) as a pale orange solid:
^{1}H-NMR (DMSO d_6): 10.29 (s, 1H), 10.18 (s, 1H), 8.61 (s, 1H), 8.40 (d, 1H), 8.34 (s, 1H), 7.81 (s, 1H), 7.72 (m, 1H), 7.27 (m, 1H), 7.20 (m, 3H), 5.17 (s, 2H), 4.70 (m, 1H), 4.21 (t, 2H), 3.52 (t, 2H), 3.42 (m, 2H), 3.30 (m, 2H, partially obscured by H_2O), 3.17 (m, 2H), 2.80 (m, 2H), 2.65 (m, 2H), 2.00 (quintet, 2H);
MS (+ve ESI): 581 $(M+H)^+$.

1-(2-Hydroxyethyl)piperazin-2-one used as starting material, was prepared as follows:

a) A solution of (2-bromoethoxy)-*tert*-butyldimethylsilane (4.71 g, 19.7 mmol) in tetrahydrofuran (20 ml) was added dropwise at room temperature to a stirred solution of *tert*-butyl 3-oxopiperazine-1-carboxylate (3.94 g, 19.7 mmol), powdered potassium hydroxide

(1.32 g, 23.6 mmol) and tetrabutylammonium bromide (1.27 g, 3.94 mmol) in tetrahydrofuran (30 ml) and the resulting mixture was stirred for 4 hours. The mixture was filtered and then evaporated to leave a colourless viscous oil which was purified by silica gel chromatography eluting with methyl *tert*-butyl ether as eluent to give *tert*-butyl 4-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)-3-oxopiperazine-1-carboxylate (3.42 g, 45% yield) as a colourless oil:

^{1}H-NMR ($CDCl_3$): 4.08 (s, 2H), 3.80 (t, 2H), 3.61 (m, 2H), 3.50 (m, 4H), 1.46 (s, 9H), 0.87 (s, 9H), 0.05 (s, 6H).

b) A mixture of *tert*-butyl 4-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)-3-oxopiperazine-1-carboxylate (3.4 g, 9.50 mmol) and hydrogen chloride (15 ml of a 4M solution in 1,4-dioxane) in 1,4-dioxane (10 ml) was stirred at room temperature for 4 hour and then the mixture was evaporated. The residue was dissolved in a mixture of 5% methanol in dichloromethane (30 ml), basified with a 7N solution of ammonia in methanol and then filtered. The filtrate was evaporated and the residue was purified by silica gel chromatography eluting with 10% methanol in dichloromethane containing 0 – 5% 7M ammonia in methanol to give 1-(2-hydroxyethyl)piperazin-2-one (0.708 g, 57% yield) as a pale yellow oil.

^{1}H-NMR ($CDCl_3$): 3.80 (t, 2H), 3.53 (t, 2H), 3.52 (s, 2H), 3.42 (t, 2H), 3.10 (t, 2H), 2.52 (br s, 2H).

Example 134 – Preparation of compound 134 in table 4 - *N*-(2,3-difluorophenyl)-2-[4-({7-[3-(propylamino)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide

An analogous reaction to that described in example 122 but starting with propylamine (0.73 ml, 8.85 mmol) yielded compound 134 in table 4 (0.54 g, 62% yield):

^{1}H-NMR (DMSO d_6): 10.28 (br s, 1H), 9.98 (s, 1H), 8.57 (s, 1H), 8.38 (d, 1H), 8.36 (s, 1H), 7.78 (s, 1H), 7.71 (m, 1H), 7.18 (m, 4H), 5.15 (s, 2H), 4.20 (t, 2H), 3.82 (t, 2H), 2.70 (t, 2H), 1.98 (m, 2H), 1.52 (m, 2H), 0.89 (t, 3H);

MS (+ve ESI): 496 $(M+H)^+$

MS (-ve ESI): 494 $(M-H)^-$.

Example 135 – Preparation of compound 135 in table 4 - *N*-(2,3-difluorophenyl)-2-(4-{[7-(3-piperazin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide

An analogous reaction to that described in example 122 but starting piperazine (0.761 g, 8.85 mmol) yielded compound 135 in table 4 (0.68 g, 74% yield) as a white solid:

^{1}H-NMR (DMSO d_6): 9.94 (s, 1H), 8.55 (s, 1H), 8.36 (d, 1H), 8.34 (s, 1H), 7.78 (s, 1H), 7.71 (m, 1H), 7.18 (m, 4H), 5.15 (s, 2H), 4.18 (t, 2H), 2.80 (s, 8H), 2.42 (m, 2H), 1.95 (m, 2H);
MS (+ve ESI): 523 $(M+H)^+$
MS (-ve ESI): 521 $(M-H)^-$.

Example 136 – Preparation of compound 136 in table 4 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[glycoloyl(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

A mixture of *N*-(2,3-difluorophenyl)-2-[4-({7-[3-(propylamino)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide (0.52 g, 1.05 mmol), glycolic acid (0.08 g, 1.05 mmol), *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.6 g, 1.58 mmol) and diisopropylethylamine (0.55 ml, 3.15 mmol) in dimethyl acetamide (8 ml) was stirred at ambient temperature for 16 hours. The mixture was partitioned between water and dichloromethane, the organic layer was separated, dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by silica gel chromatography eluting with a 3 to 10% mixture of methanol (containing 10% 7N ammonia in methanol) in dichloromethane. The obtained product was triturated with diethyl ether to give compound 136 in table 4 (0.29 g, 50% yield) as a white solid:
^{1}H-NMR (DMSO d_6): 10.22 (br s, 1H), 10.00 (s, 1H), 8.57 (s, 1H), 8.36 (d, 1H), 8.34 (s, 1H), 7.78 (s, 1H), 7.71 (m, 1H), 7.18 (m, 4H), 5.15 (s, 2H), 4.39 (br s, 1H), 4.15 (m, 4H), 3.30 (m, 4H), 2.02 (m, 2H), 1.52 (m, 2H), 0.82 (t, 3H);
MS (+ve ESI): 554 $(M+H)^+$
MS (-ve ESI): 552 $(M-H)^-$.

Example 137 – Preparation of compound 137 in table 4 - *N*-(2,3-difluorophenyl)-2-[4-({7-[3-(4-glycoloylpiperazin-1-yl)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide

An analogous reaction to that described in example 136 but starting with *N*-(2,3-difluorophenyl)-2-(4-{[7-(3-piperazin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide (0.68 g, 1.3 mmol) yielded compound 137 in table 4 (0.232 g, 31% yield) as a white solid:

^{1}H-NMR (DMSO d_6): 10.28 (s, 1H), 9.95 (s, 1H), 8.57 (s, 1H), 8.36 (d, 1H), 8.34 (s, 1H), 7.78 (s, 1H), 7.71 (m, 1H), 7.21 (m, 4H), 5.15 (s, 2H), 4.50 (t, 1H), 4.22 (t, 2H), 4.09 (d, 2H), 3.45 (br s, 2H), 3.34 (br s, 2H), 2.50 (t, 2H under DMSO), 2.38 (br s, 4H), 1.95 (m, 2H);
MS (-ve ESI): 579 $(M-H)^-$.

Example 138 – Preparation of compound 138 in table 4 - *N*-(2,3-difluorophenyl)-2-(4-{[7-(3-{[*trans*-2-(hydroxymethyl)cyclohexyl]amino}propoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide

A mixture of 2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide hydrochloride (0.25 g, 0.49 mmol), *trans*-2-(hydroxymethyl)cyclohexylamine hydrochloride (0.242 g, 1.5 mmol) diisopropylethylamine (0.44 ml, 2.5 mmol) and potassium iodide (0.249 g, 1.5 mmol) in dimethylacetamide (5 ml) was heated at 80°C for 1 hour and then at 125°C overnight. The solvent was evaporated and the residue was purified directly by reverse phase chromatography eluting with a mixture of 5 to 95% acetonitrile (containing 0.2% trifluoroacetic acid) in water (containing 0.2% trifluoroacetic acid). The fractions containing product were combined and then evaporated to approximately quarter volume and the aqueous solution was made basic by the dropwise addition of concentrated sodium hydroxide. The resultant precipitate was filtered, washed with water and allowed to dry in air to give compound 138 in table 4 (0.142 g, 51% yield):
^{1}H-NMR (DMSO d_6): 10.26 (s, 1H), 9.90 (s, 1H), 8.53 (s, 1H), 8.34 (d, 1H), 8.33 (s, 1H), 7.77 (s, 1H), 7.68-7.75 (m, 1H), 7.15-7.24 (m, 3H), 7.12 (d, 1H), 5.14 (s, 2H), 4.18 (t, 2H), 3.47 (dd, 1H), 3.36 (dd, 1H), 2.82-2.92 (m, 1H), 2.53-2.63 (m, 1H), 2.15-2.28 (m, 1H), 1.97-2.06 (m, 1H), 1.82-1.93 (m, 2H), 1.54-1.70 (m, 3H), 0.80-1.35 (m, 5H);
MS (+ve ESI): 566 $(M+H)^+$.

Example 139 – Preparation of compound 139 in table 4 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(1α,5α,6α)-6-(hydroxymethyl)-3-azabicyclo[3.1.0]hex-3-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

A mixture of 2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide hydrochloride (0.738 g, 1.45 mmol), (1α,5α,6α)-3-azabicyclo[3.1.0]hexane-6-methanol (see *Synlett*, **1996**, *11*, 1097-1099, 0.149 g, 1.32 mmol), diisopropylethylamine (0.51 ml, 2.9 mmol) and potassium iodide (0.241 g, 1.45 mmol) in

dimethylacetamide (5 ml) was heated at 80°C for 4 hours. A further portion of diisopropylethylamine (0.25 ml) was added and the mixture heated at 80°C for a further 2 hours. The mixture was allowed to cool to room temperature and then diluted with dichloromethane and purified directly by silica gel chromatography eluting with a 0 to 10% mixture of methanol (containing 10% 7M ammonia in methanol) in dichloromethane to give compound 139 in table 4 (0.320 g, 44% yield):

^{1}H-NMR (DMSO d_6): 10.27 (s, 1H), 9.91 (s, 1H), 8.55 (s, 1H), 8.36 (d, 1H), 8.35 (s, 1H), 7.79 (s, 1H), 7.70-7.75 (m, 1H), 7.17-7.24 (m, 3H), 7.12 (d, 1H), 5.16 (s, 2H), 4.34 (t, 1H), 4.15 (t, 2H), 3.22 (t, 2H), 2.98 (d, 2H), 2.55 (t, 2H), 2.26 (d, 2H), 1.85-1.93 (m, 2H), 1.22-1.27 (m, 3H);

MS (+ve ESI): 550 $(M+H)^+$.

Example 140 – Preparation of compound 140 in table 4 – *N*-(2,3-difluorophenyl)-2-(4-{[7-(3-{[(2*R*)-2-hydroxypropyl]amino}propoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide

An analogous reaction to that described in example 122 but starting with (2*R*)-1-aminopropan-2-ol (0.150 g, 2.0 mmol). After chromatography the obtained solids were triturated with hot acetonitrile and then with diethyl ether to yield compound 140 in table 4 (0.035 g, 14% yield):

^{1}H-NMR (DMSO d_6 + acetic acid d_4): 8.54 (s, 1H), 8.30-8.40 (m, 2H), 7.78 (s, 1H), 7.65-7.77 (m, 1H), 7.10-7.25 (m, 4H), 5.14 (s, 2H), 4.17-4.27 (m, 2H), 3.85-3.98 (m, 1H), 3.03-3.14 (t, 2H), 2.92-3.01 (m, 1H), 2.71-2.81 (m, 1H), 2.08-2.21 (m, 2H), 1.11 (d, 3H);

MS (+ve ESI): 512 $(M+H)^+$.

Example 141 – Preparation of compound 141 in table 4 – *N*-(2,3-difluorophenyl)-2-(4-{[7-(3-{[(1*S*)-2-hydroxy-1-methylethyl]amino}propoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide

An analogous reaction to that described in example 140 but starting with (2*S*)-2-aminopropan-1-ol (0.150 g, 2.0 mmol) yielded compound 141 in table 4 (0.090 g, 35% yield):

^{1}H-NMR (DMSO d_6 + acetic acid d_4): 8.55 (s, 1H), 8.37 (d, 1H), 8.33 (s, 1H), 7.79 (s, 1H), 7.67-7.75 (m, 1H), 7.11-7.25 (m, 4H), 5.14 (s, 2H), 4.24 (t, 2H), 3.66 (dd, 1H), 3.46 (dd, 1H), 3.23-3.35 (m, 1H), 3.14 (t, 2H), 2.09-2.21 (m, 2H), 1.20 (d, 3H);

MS (+ve ESI): 512 $(M+H)^+$.

Example 142 – Preparation of compound 142 in table 4 - N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxy-1,1-dimethylethyl)amino]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide

A mixture of 2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide hydrochloride (0.25 g, 0.49 mmol), diisopropylethylamine (0.171 ml, 0.98 mmol), 2-amino-2-methylpropanol (0.13 g, 1.47 mmol) and potassium iodide (0.16 g, 0.98 mmol) in dimethylacetamide (3 ml) was heated at 75°C for 16 hours. The reaction mixture was diluted with a mixture of dimethylsulphoxide : acetonitrile : water (7 : 2 : 1, 3 ml) and purified by reverse phase chromatography eluting with 0.2% aqueous trifluoroacetic acid in acetonitrile using a 5 to 50% gradient over 25 minutes. The appropriate fractions were concentrated under reduced pressure and then basified with aqueous sodium carbonate. The product was extracted into ethyl acetate, dried over magnesium sulphate, filtered and evaporated under reduced pressure to give compound 142 in table 4 (0.23 g, 90% yield) as a cream coloured solid.

^{1}H-NMR (DMSO d_6): 10.35 (br s, 1H), 9.98 (s, 1H), 8.55 (s, 1H), 8.35 (m, 2H), 7.85 (s, 1H), 7.65 (m, 1H), 7.15 (m, 4H), 5.15 (s, 2H), 4.20 (t, 2H), 2.70 (m, 2H), 2.50 (m, 4H) under DMSO, 1.95 (m, 2H), 1.0 (m, 6H);

MS (+ve ESI): 526 $(M+H)^+$

MS (-ve ESI): 524 $(M-H)^-$.

Example 143 – Preparation of compound 143 in table 4 - N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2,3-dihydroxypropyl)amino]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 142 but starting with (+/-)-3-amino-1,2-propanediol (0.16 g, 1.47 mmol) yielded compound 143 in table 4 (0.05 g, 19% yield):

^{1}H-NMR (DMSO d_6): 10.35 (br s, 1H), 9.90 (s, 1H), 8.50 (s, 1H), 8.40 (m, 2H), 7.80 (s, 1H), 7.70 (m, 1H), 7.20 (m, 4H), 5.20 (s, 2H), 4.25 (t, 2H), 3.50 (m, 4H), 2.75 (t, 2H), 2.6 (m, 1H), 1.90 (m, 2H);

MS (+ve ESI): 528 $(M+H)^+$

MS (-ve ESI): 526 $(M-H)^-$.

Example 144 – Preparation of compound 144 in table 4 - N-(2,3-difluorophenyl)-2-(4-{[7-(3-{[2-(2-hydroxyethoxy)ethyl]amino}propoxy)quinazolin-4-yl]amino}-1H-pyrazol-1-yl)acetamide

A mixture of 2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide hydrochloride (0.25 g, 0.49 mmol), diisopropylethylamine (0.171 ml, 0.98 mmol), 2-(2-aminoethoxy)-ethanol (0.155 g, 1.47 mmol) and potassium iodide (0.16 g, 0.98 mmol) in dimethylacetamide (3 ml) was heated at 75°C for 16 hours. The reaction mixture was diluted with dimethylsulphoxide : acetonitrile : water (7 : 2 : 1, 3 ml) and purified by reverse phase chromatography eluting with 0.2% aqueous trifluoroacetic acid in acetonitrile using a 5 to 50% gradient over 25 minutes. The appropriate fractions were concentrated under reduced pressure and then basified with aqueous sodium carbonate. The resultant precipitate was filtered, washed with water and then dried under vacuum at 60°C to give compound 144 in table 4 (0.195 g, 73% yield) as a white solid:

^{1}H-NMR (DMSO d_6): 10.35 (br s, 1H), 9.90 (br s, 1H), 8.50 (s, 1H), 8.40 (m, 2H), 7.80 (s, 1H), 7.70 (m, 1H), 7.20 (m, 4H), 5.20 (s, 2H), 4.60 (br s, 1H), 4.25 (t, 2H), 3.50 (m, 4H), 3.30 (m, 2H), 2.65 (m, 4H), 1.90 (m, 2H);

MS (+ve ESI): 542 $(M+H)^+$

MS (-ve ESI): 540 $(M-H)^-$.

Example 145 – Preparation of compound 145 in table 4 - 2-[4-({7-[3-(4-acetylpiperazin-1-yl)propoxy]quinazolin-4-yl}amino)-1H-pyrazol-1-yl]-N-(2,3-difluorophenyl)acetamide

An analogous reaction to that described in example 144 but starting with 1-acetylpiperazine (0.188 g, 1.47 mmol) yielded compound 145 in table 4 (0.25 g, 91% yield):

^{1}H-NMR (DMSO d_6): 10.35 (br s, 1H), 9.90 (s, 1H), 8.50 (s, 1H), 8.40 (m, 2H), 7.80 (s, 1H), 7.70 (m, 1H), 7.20 (m, 4H), 5.20 (s, 2H), 4.25 (t, 2H), 3.50 (m, 4H), 3.30 (m, 2H), 2.40 (m, 2H), 2.30 (m, 2H), 1.98 (s, 3H), 1.90 (m, 2H);

MS (+ve ESI): 565 $(M+H)^+$

MS (-ve ESI): 563 $(M-H)^-$.

Example 146 – Preparation of compound 146 in table 4 - N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(tetrahydrofuran-2-ylmethyl)amino]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 144 but starting with (tetrahydrofuran-2-ylmethyl)amine (0.152 g, 1.47 mmol) yielded compound 146 in table 4 (0.19g, 73% yield):

^{1}H-NMR (DMSO d_6): 10.0 (br s, 1H), 8.50 (s, 1H), 8.40 (m, 2H), 7.80 (s, 1H), 7.70 (m, 1H), 7.20 (m, 4H), 5.20 (s, 2H), 4.25 (t, 2H), 3.90 (m, 1H), 3.70 (m, 1H), 3.60 (m, 1H), 2.80 (t, 2H), 2.55 (m, 2H), 1.80 (m, 3H), 1.70 (m, 2H), 1.65 (m, 1H), 1.50 (m, 1H);

MS (+ve ESI): 538 $(M+H)^+$

MS (-ve ESI): 536 $(M-H)^-$.

Example 147 – Preparation of compound 147 in table 4 - 2-[4-({7-[3-(allylamino)propoxy]quinazolin-4-yl}amino)-1H-pyrazol-1-yl]-N-(2,3-difluorophenyl)acetamide

An analogous reaction to that described in example 142 but starting with allylamine (0.084 g, 1.47 mmol) yielded compound 147 in table 4 (0.117 g, 48% yield):

^{1}H-NMR (DMSO d_6): 11.0 (br s, 1H), 10.40 (br s, 1H), 8.90 (s, 1H), 8.60 (m, 1H), 8.40 (s, 1H), 7.90 (s, 1H), 7.70 (m, 1H), 7.40 (m, 1H), 7.20 (m, 3H), 5.95 (m, 1H), 5.50 (m, 2H), 5.20 (s, 2H), 4.25 (t, 2H), 3.80 (m, 2H), 3.15 (m, 2H), 2.15 (m, 2H).;

MS (+ve ESI): 494 $(M+H)^+$

MS (-ve ESI): 492 $(M-H)^-$.

Example 148 – Preparation of compound 148 in table 4 - N-(2,3-difluorophenyl)-2-(4-{[7-(3-{[1-(hydroxymethyl)-2-methylpropyl]amino}propoxy)quinazolin-4-yl]amino}-1H-pyrazol-1-yl)acetamide

An analogous reaction to that described in example 144 but starting with (+/-) valinol (0.152 g, 1.47 mmol) yielded compound 148 in table 4 (0.137g, 52% yield):

^{1}H-NMR (DMSO d_6): 10.35 (br s, 1H), 9.90 (s, 1H), 8.55 (s, 1H), 8.30 (m, 2H), 7.80 (s, 1H), 7.70 (m, 1H), 7.20 (m, 4H), 5.20 (s, 2H), 4.35 (br s, 1H), 4.25 (t, 2H), 3.40 (m, 1H), 3.30 (m, 1H), 2.70 (m, 2H), 2.30 (m, 1H), 1.90 (m, 2H), 1.85 (m, 1H), 1.50 (br s, 1H), 0.85 (m, 6H);

MS (+ve ESI): 540$(M+H)^+$.

Example 149 – Preparation of compound 149 in table 4 N-(2,3-difluorophenyl)-2-(4-{[7-(3-{[(5-methylisoxazol-3-yl)methyl]amino}propoxy)quinazolin-4-yl]amino}-1H-pyrazol-1-yl)acetamide

An analogous reaction to that described in example 144 but starting with [(5-methylisoxazol-3-yl)methyl]amine (0.166 g, 1.47 mmol) yielded compound 149 in table 4 (0.124 g, 46% yield):

^{1}H-NMR (DMSO d_6): 10.35 (br s, 1H), 9.90 (br s, 1H), 8.55 (s, 1H), 8.30 (m, 2H), 7.80 (s, 1H), 7.70 (m, 1H), 7.20 (m, 4H), 6.20 (s, 1H), 5.20 (s, 2H), 4.25 (t, 2H), 3.60 (s, 2H), 2.70 (m, 2H), 2.30 (s, 3H), 2.20 (br s, 1H), 1.90 (m, 2H);
MS (+ve ESI): 549 $(M+H)^+$
MS (-ve ESI): 547 $(M-H)^-$.

Example 150 – Preparation of compound 150 in table 4 N-(2,3-difluorophenyl)-2-[4-({7-[3-(tetrahydro-2H-pyran-4-ylamino)propoxy]quinazolin-4-yl}amino)-1H-pyrazol-1-yl]acetamide

An analogous reaction to that described in example 144 but starting with tetrahydro-2H-pyran-4-amine (0.150 g, 1.47 mmol) yielded compound 150 in table 4 (0.149 g, 56% yield):

^{1}H-NMR (DMSO d_6): 10.35 (br s, 1H), 9.90 (br s, 1H), 8.55 (s, 1H), 8.30 (m, 2H), 7.80 (s, 1H), 7.70 (m, 1H), 7.20 (m, 4H), 5.20 (s, 2H), 4.25 (t, 2H), 3.80 (m, 2H), 2.70 (m, 2H), 2.60 (m, 1H), 1.90 (m, 2H), 1.70 (m, 2H), 1.60 (br s, 1H), 1.20 (m, 2H);
MS (+ve ESI): 538 $(M+H)^+$
MS (-ve ESI): 536 $(M-H)^-$.

Example 151 and 152– Preparation of compound 151 in table 4 - N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3S)-3-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide and compound 152 in table 4 - N-(2,3-difluorophenyl)-2-(4-{[7-(3-hydroxypropoxy)quinazolin-4-yl]amino}-1H-pyrazol-1-yl)acetamide

An analogous reaction to that described in example 144 but starting with (3S)-pyrrolidin-3-ylmethanol (0.150 g, 1.47 mmol) yielded compound 151 in table 4 eluted first (0.075g, 28% yield):

^{1}H-NMR (DMSO d_6): 10.30 (br s, 1H), 9.90 (br s, 1H), 8.55 (s, 1H), 8.30 (m, 2H), 7.80 (s, 1H), 7.70 (m, 1H), 7.20 (m, 4H), 5.20 (s, 2H), 4.25 (t, 2H), 3.80 (m, 2H), 2.50 (m, 5H), 2.30 (m, 1H), 2.20 (m, 1H), 1.90 (m, 2H), 1.80 (m, 1H), 1.40 (m, 1H);

MS (+ve ESI): 538 $(M+H)^+$

MS (-ve ESI): 536 $(M-H)^-$.

and compound 152 in table 4 eluted second (0.027g, 12% yield):

^{1}H-NMR (DMSO d_6): 8.55 (s, 1H), 8.35 (m, 2H), 7.80 (s, 1H), 7.70 (m, 1H), 7.20 (m, 4H), 5.20 (s, 2H), 4.25 (t, 2H), 3.60 (t, 2H), 1.95 (m, 2H);

MS (+ve ESI): 455 $(M+H)^+$

MS (-ve ESI): 453 $(M-H)^-$.

(3S)-pyrrolidin-3-ylmethanol used as starting material, was prepared as follows:

a) *tert*-Butyl (3*S*)-3-(hydroxymethyl)pyrrolidine-1-carboxylate (0.9 g, 4.48 mmol), was dissolved in dichloromethane (10 ml)and trifluoroacetic acid (2 ml) was added. The reaction mixture was stirred for 16 hours at ambient temperature. The reaction mixture was concentrated under reduced pressure and then co-evaporated with toluene. The residue was dissolved in methanol (20 ml) and then macroporous carbonate (3 g) was added and the heterogeneous mixture was stirred for 16 hours at ambient temperature to give a pH 9 mixture. The mixture was filtered and the filtrate was concentrated under reduced pressure to give (3*S*)-pyrrolidin-3-ylmethanol as an oil which was used without further purification:

^{1}H-NMR (DMSO d_6): 3.25 (m, 2H), 3.10 (m, 3H), 2.85 (m, 1H), 2.30 (m, 1H), 1.90 (m, 1H), 1.60 (m, 1H);

MS (+ve ESI): 101 $(M+H)^+$.

Example 153 – Preparation of compound 153 in table 4 - 2-(4-{[7-(3-aminopropoxy)quinazolin-4-yl]amino}-1H-pyrazol-1-yl)-N-(2,3-difluorophenyl)acetamide

N-(2,3-difluorophenyl)-2-[4-({7-[3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propoxy]quinazolin-4-yl}amino)-1H-pyrazol-1-yl]acetamide (0.214g, 0.37mmol) was dissolved in ethanol (10ml). Hydrazine hydrate (2.2 mmol) was added and the mixture was heated at 80°C for 16 hours. The reaction mixture was concentrated, diluted with a mixture of dimethylsulphoxide : acetonitrile : water (7 : 2 : 1, 3 ml) and then purified by reverse phase

chromatography eluting with 0.2% aqueous trifluoroacetic acid in acetonitrile using a 5 to 50% gradient over 25 minutes. The fractions containing product were concentrated under reduced pressure and then basified with aqueous sodium carbonate. The resultant precipitate was filtered, washed with water and dried under vacuum at 60°C to give compound 153 in table 4 (0.086 g, 52% yield) as a white solid:

^{1}H-NMR (DMSO d_6): 10.0 (br s, 1H), 8.55 (s, 1H), 8.30 (m, 2H), 7.80 (s, 1H), 7.70 (m, 1H), 7.20 (m, 4H), 5.20 (s, 2H), 4.20 (t, 2H), 2.70 (t, 2H), 1.80 (m, 2H);

MS (+ve ESI): 454 $(M+H)^+$

MS (-ve ESI): 452$(M-H)^-$.

N-(2,3-difluorophenyl)-2-[4-({7-[3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propoxy]quinazolin-4-yl}amino)-1H-pyrazol-1-yl]acetamide used as starting material, was prepared as follows:

a) A mixture of 2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide hydrochloride (0.25 g, 0.49 mmol), potassium phthalimide (0.109g, 0.59mmol), potassium carbonate (0.081g, 0.59mmol) and potassium iodide (0.098 g, 0.59 mmol) in dimethylacetamide (2 ml) was heated at 75°C for 16 hours. The reaction mixture was allowed to cool to room temperature. Aqueous sodium hydrogen carbonate was added to the mixture and the resultant precipitate was filtered and washed with water, acetonitrile then diethyl ether to give N-(2,3-difluorophenyl)-2-[4-({7-[3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propoxy]quinazolin-4-yl}amino)-1H-pyrazol-1-yl]acetamide (0.214 g, 75% yield):

^{1}H-NMR (DMSO d_6): 10.0 (br s, 1H), 8.55 (s, 1H), 8.30 (m, 2H), 7.85 (m, 3H), 7.80 (s, 1H), 7.70 (m, 1H), 7.20 (m, 2H), 7.05 (m, 1H), 6.95 (m, 1H), 5.20 (s, 2H), 4.20 (t, 2H), 3.80 (t, 2H), 2.15 (m, 2H);

MS (+ve ESI): 584 $(M+H)^+$

MS (-ve ESI): 582$(M-H)^-$.

Example 154 – Preparation of compound 154 in table 4 - N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2S,4R)-4-hydroxy-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 144 but starting with (3R, 5S)-5-(hydroxymethyl)pyrrolidin-3-ol (0.150 g, 1.0 mmol) yielded compound 154 in table 4 (0.138 g, 50% yield):

^{1}H-NMR (DMSO d_6): 10.0 (br s, 1H), 8.55 (s, 1H), 8.30 (m, 2H), 7.80 (s, 1H), 7.70 (m, 1H), 7.20 (m, 4H), 5.20 (s, 2H), 4.70 (br s, 1H), 4.30 (br s, 1H), 4.20 (m, 4H), 3.10 (m, 2H), 2.95 (m, 1H), 2.60 (m, 1H), 2.40 (m, 1H), 2.10 (m, 1H), 1.90 (m, 2H), 1.70 (m, 2H);

MS (+ve ESI): 554 $(M+H)^+$

MS (-ve ESI): 552$(M-H)^-$.

Example 155 – Preparation of compound 155 in table 4 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{2-[(3-hydroxy-2,2-dimethylpropyl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

A mixture of 2-(4-{[7-(2-chloroethoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide hydrochloride (0.20 g, 0.38mmmol), triethylamine (0.15 ml, 1.13 mmol), 3-amino-2,2-dimethylpropan-1-ol (0.117 g, 1.13 mmol) and potassium iodide (0.126 g, 0.76 mmol) in dimethylacetamide (3 ml) was heated at 90°C for 1 hour. The mixture was diluted with dichloromethane and then filtered. The filtrate was purified directly by silica gel chromatography eluting with a 0 to 10% mixture of methanol (containing 10% 7N ammonia in methanol) in dichloromethane. The obtained product was triturated with acetonitrile and then with diethyl ether to give compound 155 in table 4 (0.089g, 65% yield) as a cream coloured solid:

^{1}H-NMR (DMSO d_6): 10.28 (br s, 1H), 9.98 (s, 1H), 8.57 (s, 1H), 8.39 (d, 1H), 8.35 (s, 1H), 7.79 (s, 1H), 7.70 (t, 1H), 7.22 (m, 4H), 5.15 (s, 2H), 4.43 (t, 2H), 3.43 (t, 2H), 3.33 (s, 1H), 3.00 (s, 2H), 2.50 (s, 2H under DMSO), 0.97 (s, 6H);

MS (+ve ESI): 526 $(M+H)^+$

MS (-ve ESI): 524 $(M-H)^-$.

Example 156 – Preparation of compound 156 in table 4 - 2-{4-[(7-{2-[cyclohexyl(2-hydroxyethyl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

An analogous reaction to that described in example 155 but starting with 2-(cyclohexylamino)ethanol (0.162g, 1.13 mmol) yielded compound 156 in table 4 (0.045 g, 21% yield):

^{1}H-NMR (DMSO d_6 at 373K): 9.89 (s, 1H), 9.68 (s, 1H), 8.57 (s, 1H), 8.35 (d, 1H), 8.31 (s, 1H), 7.79 (s, 1H), 7.72 (m, 1H), 7.22 (m, 4H), 5.15 (s, 2H), 4.23 (t, 2H), 3.53 (t, 2H), 3.08 (t, 2H under water), 2.82 (s, 2H), 1.87 (m, 4H), 1.65 (d, 1H), 1.32 (m, 6H);

MS (+ve ESI): 566 $(M+H)^+$

MS (-ve ESI): 564 $(M-H)^-$.

Example 157 – Preparation of compound 157 in table 4 - 2-[4-({7-[2-(cyclopropylamino)ethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(2,3-difluorophenyl)acetamide

An analogous reaction to that described in example 155 but starting with cyclopropyl amine (0.4g, 6.8mmol) yielded compound 157 in table 4 (0.18 g, 44% yield):

^{1}H-NMR (DMSO d_6): 10.27 (br s, 1H), 9.95 (s, 1H), 8.57 (s, 1H), 8.39 (d, 1H), 8.31 (s, 1H), 7.79 (s, 1H), 7.72 (m, 1H), 7.22 (m, 3H), 5.15 (s, 2H), 4.36 (t, 2H), 3.42 (t, 2H), 2.70 (m, 1H), 0.70 (d, 4H);

MS (+ve ESI) 480 $(M+H)^+$

MS (-ve ESI): 478 $(M-H)^-$.

Example 158 – Preparation of compound 158 in table 4 - 2-[4-({7-[2-(cyclobutylamino)ethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(2,3-difluorophenyl)acetamide

An analogous reaction to that described in example 155 but starting with cyclobutyl amine (0.5g, 6.8mmol) yielded compound 158 in table 4 (0.225 g, 54% yield):

^{1}H-NMR (DMSO d_6): 10.27 (br s, 1H), 9.95 (s, 1H), 8.57 (s, 1H), 8.39(d, 1H), 8.31 (s, 1H), 7.79 (s, 1H), 7.72 (m, 1H), 7.22 (m, 3H), 5.15 (s, 2H), 4.33 (t, 2H), 3.66 (m, 1H), 3.17 (t, 2H), 2.20 (m, 2H), 2.02 (m, 2H), 1.77 (m, 2H);

MS (+ve ESI) 494 $(M+H)^+$

MS (-ve ESI): 492 $(M-H)^-$.

Example 159 – Preparation of compound 159 in table 4 - *N*-(2,3-difluorophenyl)-2-[4-({7-[2-(tetrahydro-2*H*-pyran-4-ylamino)ethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide

An analogous reaction to that described in example 155 but starting with 4-aminoterahydro-2*H*-pyran (0.68g, 6.8mmol) yielded compound 159 in table 4 (0.078 g, 18% yield):

^{1}H-NMR (DMSO d_6): 10.27 (br s, 1H), 9.95 (s, 1H), 8.57 (s, 1H), 8.39(d, 1H), 8.33 (s, 1H), 7.79 (s, 1H), 7.72 (m, 1H), 7.22 (m, 4H), 5.15 (s, 2H), 4.39 (t, 2H), 3.88 (m, 2H), 3.34 (2H under water), 3.00 (t, 2H), 2.71 (m, 1H), 1.80 (m, 2H), 1.28 (m, 2H);

MS (+ve ESI) 524 $(M+H)^+$

MS (-ve ESI): 522 $(M-H)^-$.

Example 160 – Preparation of compound 160 in table 4 - 2-[4-({7-[2-(cyclopentylamino)ethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(2,3-difluorophenyl)acetamide

An analogous reaction to that described in example 155 but starting with cyclopentyl amine (1.9g, 22.4mmol) yielded compound 160 in table 4 (0.640 g, 45% yield):

^{1}H-NMR (DMSO d_6): 10.27 (br s, 1H), 9.95 (s, 1H), 8.57 (s, 1H), 8.38(d, 1H), 8.33 (s, 1H), 7.79 (s, 1H), 7.72 (m, 1H), 7.22 (m, 4H), 5.15 (s, 2H), 4.29 (t, 2H), 3.34 (1H under water), 3.13 (s, 2H), 1.87 (m, 2H), 1.69 (m, 2H), 1.50 (m, 4H);

MS (+ve ESI) 508 $(M+H)^+$

MS (-ve ESI): 506 $(M-H)^-$.

Example 161 – Preparation of compound 161 in table 4 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2-hydroxyethyl)(tetrahydro-2*H*-pyran-4-yl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 155 but starting with 2-(tetrahydro-2*H*-pyran-4-ylamino)ethanol (0.569 g, 3.93mmol) yielded compound 161 in table 4 (0.391 g, 53% yield):

^{1}H-NMR (DMSO d_6): 10.28 (s, 1H), 9.91 (s, 1H), 8.54 (s, 1H), 8.36 (d, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.72 (m, 1H), 7.20 (m, 4H), 5.16 (s, 2H), 4.29 (t, 1H), 4.14 (t, 2H), 3.89 (m, 2H), 3.42 (m, 2H), 3.25 (m, 2H), 2.94 (t, 2H), 2.76 (m, 1H), 2.65 (t, 2H), 1.65 (m, 2H), 1.45 (m, 2H);

MS (+ve ESI): 568 $(M+H)^+$.

2-(tetrahydro-2*H*-pyran-4-ylamino)ethanol used as a starting material, was prepared as follows:

a) A mixture of ethanolamine (1.76 ml, 0.029 mmol) and tetrahydro-4*H*-pyran-4-one (3.5 g, 0.035 mmol) in ethanol (30 ml) was stirred at ambient temperature for 30 minutes. The reaction mixture was cooled in ice and then sodium borohydride (1.33 g, 0.035 mmol) was added slowly over 20 minutes. The mixture was stirred for a further 15 minutes and then water (10 ml) was added. The mixture was evaporated under reduced pressure and the residue dissolved in dichloromethane and dried over magnesium sulphate and then evaporated under reduced pressure. The residue was purified by silica gel chromatography eluting with a 0 to 15% mixture of methanol (containing 10% 7N ammonia in methanol) in dichloromethane to give 2-(tetrahydro-2*H*-pyran-4-ylamino)ethanol (1.25 g, 30% yield) as a clear oil:
^{1}H-NMR ($CDCl_3$): 4.00 (m, 2H), 3.66 (t, 2H), 3.42 (m, 2H), 2.83 (t, 2H), 2.70 (m, 1H), 1.88 (m, 2H), 1.43 (m, 2H);
MS (+ve ESI) 146 $(M+H)^+$.

Example 162 – Preparation of compound 162 in table 4 - 2-{4-[(7-{2-[cyclopentyl(2-hydroxyethyl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

A mixture of 2-(4-{[7-(2-chloroethoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide hydrochloride (0.25 g, 0.47 mmol), triethylamine (0.2 ml, 1.41 mmol), 2-(cyclopentylamino)ethanol (0.121 g, 0.094 mmol) and potassium iodide (0.156 g, 0.94 mmol) in dimethylacetamide (3 ml) was heated at 90°C for 1hour. The mixture was diluted with dimethylacetamide and then filtered. The filtrate was purified directly by reverse phase chromatography eluting with a 5 to 95% mixture of acetonitrile (containing 0.2% trifluoroacetic acid) in water (containing 0.2% trifluoroacetic acid). The fractions containing product were concentrated to half volume and then sodium carbonate (1.5 g) was added. The resultant precipitate was filtered and dried to give compound 162 in table 4 (0.027 g, 10% yield) as a off white solid:
^{1}H-NMR (DMSO d_6): 8.54 (s, 1H), 8.36 (d, 1H), 8.33 (s, 1H), 7.77 (s, 1H), 7.70 (m, 1H), 7.17 (m, 4H), 5.13 (s, 2H), 4.16 (t, 2H), 3.45 (t, 2H), 3.14 (m, 1H under water), 2.91 (t, 2H), 2.64 (t, 2H), 1.78 (m, 2H), 1.61 (m, 2H), 1.50 (m, 2H), 1.34 (m, 2H);

MS (+ve ESI): 552$(M+H)^+$

MS (-ve ESI): 550 $(M-H)^-$.

2-(cyclopentylamino)ethanol used as a starting material, was prepared as follows:

a) A mixture of ethanolamine (4 ml, 0.066 mmol) and cyclopentanone (6.85 ml, 0.08 mmol) in ethanol (60 ml) was stirred at ambient temperature for 30 minutes. The mixture was cooled in ice and then sodium borohydide (3.04 g, 0.08 mmol) was added slowly over 20 minutes. The mixture was stirred for 15 minutes before water (10ml) was added. The mixture was evaporated under reduced pressure and the residue dissolved in dichloromethane and dried over magnesium sulphate and then evaporated under reduced pressure. The crude product was purified by vacuum distillation to give 2-(cyclopentylamino)ethanol (3 g, 35% yield) as a clear oil:

^{1}H-NMR ($CDCl_3$): 3.63 (t, 2H), 3.07 (quintet, 1H), 2.77 (t, 2H), 1.83 (m, 2H), 1.68 (m, 2H), 1.56 (m, 2H), 1.34 (m, 2H).

Example 163 – Preparation of compound 163 in table 4 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 162 but starting with (2R)-pyrrolidin-2ylmethanol (0.16g, 1.6 mmol) to give compound 163 in table 4 (0.105 g, 37% yield):

^{1}H-NMR (DMSO d_6 + CD_3COOH): 8.90 (s, 1H), 8.57 (d, 1H), 8.37 (s, 1H), 7.93 (s, 1H), 7.70 (m, 1H), 7.48 (d, 1H), 7.28 (s, 1H), 7.18 (m, 2H), 5.20 (s, 2H), 4.58 (s, 2H), 3.66 (m, 7H), 1.92 (m, 4H);

MS (+ve ESI) 524 $(M+H)^+$

MS (-ve ESI): 522 $(M-H)^-$.

Example 164 – Preparation of compound 164 in table 4 - 2-{4-[(7-{2-[cyclopropyl(2-hydroxyethyl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

A mixture of 2-[4-({7-[2-(cyclopropylamino)ethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(2,3-difluorophenyl)acetamide (0.15 g, 0.31 mmol), glycolaldehyde (0.028 g, 0.46 mmol) and MP-triacetoxyborohydride (2 mmol/g, 0.39 g, 0.78 mmol) in

dimethylformamide (1.5 ml) was stirred at ambient temperature for 1 hour. The mixture was filtered and the filtrate evaporated under reduced pressure. The residue was purified by silica gel chromatography eluting with a mixture of 0 to 10% methanol (containing 10% 7N ammonia in methanol) in dichloromethane. The obtained product was triturated with diethyl ether to give compound 164 in table 4 (0.065 g, 40% yield) as a yellow solid:
^{1}H-NMR (DMSO d_6): 10.27 (s, 1H), 9.95 (s, 1H), 8.57 (s, 1H), 8.39 (d, 1H), 8.38 (s, 1H), 7.79 (s, 1H), 7.72 (m, 1H), 7.22 (m, 4H), 5.15 (s, 2H), 4.39 (t, 1H), 4.29 (t, 2H), 3.57 (q, 2H), 3.02 (t, 2H), 2.82 (t, 2H), 2.00 (m, 1H), 0.49 (m, 2H), 0.37 (m, 2H);
MS (+ve ESI) 524 $(M+H)^+$.

Example 165 – Preparation of compound 165 in table 4 - 2-{4-[(7-{2-[cyclobutyl(2-hydroxyethyl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

An analogous reaction to that described in example 164 but starting with 2-[4-({7-[2-(cyclobutylamino)ethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(2,3-difluorophenyl)acetamide (0.13 g, 0.26mmol) yielded compound 165 in table 4 (0.072 g, 52% yield):
^{1}H-NMR (DMSO d_6): 10.27 (br s, 1H), 9.95 (s, 1H), 8.57 (s, 1H), 8.35(d, 1H), 8.33 (s, 1H), 7.79 (s, 1H), 7.72 (m, 1H), 7.22 (m, 4H), 5.15 (s, 2H), 4.35 (t, 1H), 4.16 (t, 2H), 3.46 (m, 2H), 3.23 (1H under water), 2.88 (t, 2H), 2.55 (t, 2H), 2.01 (m, 2H), 1.82 (m, 2H), 1.58 (m, 2H);
MS (+ve ESI) 538 $(M+H)^+$.

Example 166 – Preparation of compound 166 in table 4 - 2-{4-[(7-{2-[cyclopentyl(3-hydroxypropyl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

A mixture of 2-[4-({7-[2-(cyclopentylamino)ethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(2,3-difluorophenyl)acetamide (0.15 g, 0.296 mmol), potassium carbonate (0.121 g, 0.88 mmol), 3-chloropropanol (0.075 ml, 0.088 mmol) and potassium iodide (0.098 g, 0.59 mmol) in dimethylacetamide (2 ml) was heated at 90°C for 1 hour. The mixture was diluted with dichloromethane and a few drops of methanol and then filtered. The filtrate was purified directly by silica gel chromatography eluting with a mixture of 0 to 10% methanol (containing 10% 7N ammonia) in dichloromethane. The obtained product was triturated with diethyl ether to give compound 166 in table 4 (0.022 g, 13% yield) as a yellow coloured solid:

^{1}H-NMR (DMSO d_6): 10.26 (br s, 1H), 9.93 (s, 1H), 8.54 (s, 1H), 8.44 (d, 1H), 8.42 (s, 1H), 7.80 (s, 1H), 7.68 (m, 1H), 7.18 (m, 4H), 5.15 (s, 2H), 4.37 (br s, 1H), 4.13 (t, 2H), 3.45 (t, 2H), 3.14 (m, 1H), 2.91 (t, 2H), 2.64 (t, 2H), 1.80 (m, 2H), 1.61 (m, 4H), 1.50 (m, 2H), 1.34 (m, 2H);

MS (+ve ESI): 566$(M+H)^+$

MS (-ve ESI): 564 $(M-H)^-$.

Example 167 – Preparation of compound 167 in table 4 - 2-{4-[(7-{2-[cyclopentyl(glycoloyl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

A mixture of 2-[4-({7-[2-(cyclopentylamino)ethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(2,3-difluorophenyl)acetamide (0.15 g, 0.3 mmol), glycolic acid (0.023 g, 0.3 mmol), *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.171 g, 0.45 mmol) and diisopropylethylamine (0.156 ml, 0.9 mmol) in dimethylacetamide (2 ml) was stirred at ambient temperature for 16 hour. The mixture was diluted with dichloromethane and then purified first by silica gel chromatography eluting with a 0 to 10% mixture of methanol (containing 10% 7N ammona) in dichloromethane and then by reverse phase chromatography eluting with a 5 to 95% mixture of acetonitrile (containing 0.2% trifluoroacetic acid) water (containing 0.2% trifluoroacetic acid) to give compound 167 in table 4 (0.038 g, 22% yield) as a white solid:

^{1}H-NMR (DMSO d_6 at 373K): 9.86 (br s, 1H), 9.72 (s, 1H), 8.57 (s, 1H), 8.38 (d, 1H), 8.33 (s, 1H), 7.98 (s, 1H), 7.81 (s, 1H), 7.70 (m, 1H), 7.18 (m, 4H), 5.15 (s, 2H), 4.32 (t, 2H), 4.20 (m, 3H), 3.70 (t, 2H), 3.20 (1H under water), 1.87 (m, 2H), 1.74(m, 4H), 1.56 (m, 2H);

MS (+ve ESI) 566 $(M+H)^+$

MS (-ve ESI): 564 $(M-H)^-$.

Example 168 – Preparation of example 168 in table 4 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{2-[(3*S*)-3-(hydroxymethyl)-4-methylpiperazin-1-yl]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

MP-sodium cyanoborohydride (2.0 mmol/g, 0.363 g, 0.726 mmol) was added to a mixture of *N*-(2,3-difluorophenyl)-2-(4-{[7-(2-oxoethoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide (0.202 g, 0.46 mmol), acetic acid (0.039 ml, 0.68 mmol), [(2*S*)-1-methylpiperazin-2-yl]methanol (0.089 g, 0.68 mmol) in methanol (5 ml) and the mixture was

stirred at room temperature for 5 hours. Sodium bicarbonate (0.049 g, 0.58 mmol) was added and the mixture stirred at room temperature overnight. The mixture was filtered and the residue polymer washed exhaustively with methanol. The filtrate was evaporated and the residue was purified by silica gel chromatography eluting with a 3 to 10% mixture of 7N ammonia in methanol in dichloromethane to give compound 168 in table 4 (0.086 g, 34 % yield):

^{1}H-NMR (DMSO d_6): 10.28 (s, 1H), 9.93 (s, 1H), 8.54 (s, 1H), 8.36 (d, 1H), 8.34 (s, 1H), 7.79 (s, 1H), 7.69-7.75 (m, 1H), 7.12-7.24 (m, 4H), 5.15 (s, 2H), 4.45 (br s, 1H), 4.22 (t, 2H), 3.51-3.60 (m, 1H), 3.25-3.43 (m, 1H), 2.95 (d, 1H), 2.65-2.80 (m, 4H), 2.20 (s, 3H), 2.15-2.22 (m, 2H), 2.06-2.09 (m, 1H), 1.96 (t, 1H);

MS (+ve ESI): 553 $(M+H)^+$.

[(2*S*)-1-methylpiperazin-2-yl]methanol used as starting material, was prepared as follows:

a) A solution of lithium aluminium hydride in tetrahydrofuran (1M, 22.0 ml, 22.0 mmol) was added dropwise to a solution of (2*S*)-1-(*tert*-butoxycarbonyl)piperazine-2-carboxylic acid (see US5348955, 1.007 g, 4.38 mmol) in tetrahydrofuran (20 ml) cooled to -15°C. The mixture was allowed to warm to 15°C over 1.5 hours and then heated at reflux for 3 hours. The mixture was cooled in an ice bath and then water (0.4 ml) was added dropwise followed by a dilute solution of sodium hydroxide (1M, 0.4 ml) and a further portion of water (1.2 ml). The mixture was stirred at room temperature for 0.5 hours and then allowed to stand overnight. The resultant precipitate was filtered and the residue was washed with diethyl ether. The filtrate was evaporated and the residue purified by silica gel chromatography eluting with a 10% mixture of methanol (containing 10% 7M ammonia in methanol) in dichloromethane to give [(2*S*)-1-methylpiperazin-2-yl]methanol (0.3802 g, 67% yield):

^{1}H-NMR ($CDCl_3$): 3.88 (dd, 1H), 3.46 (dd, 1H), 2.79-2.96 (m, 4H), 2.25-2.35 (m, 1H), 2.33 (s, 3H), 2.00-2.15 (m, 4H);

^{13}C-NMR ($CDCl_3$): 43.1, 46.3, 49.0, 56.2, 61.6, 63.6.

N-(2,3-difluorophenyl)-2-(4-{[7-(2-oxoethoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide used as starting material, was prepared as follows:

a) A solution of *N*-(2,3-difluorophenyl)-2-(4-{[7-(2,2-dimethoxyethoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide (0.104 g, 0.21 mmol) in a dilute solution of hydrochloric acid (1M, 1 ml) and tetrahydrofuran (5 ml) was heated at reflux for 10 hours.

The mixture was allowed to cool to room temperature and was then filtered. The filtered solid was triturated with tetrahydrofuran and then dried under vaccum to give *N*-(2,3-difluorophenyl)-2-(4-{[7-(2-oxoethoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide as an approximate 1 : 1 mixture of aldehyde : hemiacetal (0.080 g, 87% yield) which was used in the next step without further purification:

MS (+ve ESI): 457 $(M+H_2O+H)^+$.

Example 169 – Preparation of example 169 in table 4 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 168 but starting with (2*S*)-2-(hydroxymethyl)pyrrolidine (0.016 g, 0.158 mmol) yielded compound 169 in table 4 (0.0395 g, 48% yield):

^{1}H-NMR (DMSO d_6): 10.27 (s, 1H), 9.91 (s, 1H), 8.53 (s, 1H), 8.34 (d, 1H), 8.33 (s, 1H), 7.77 (s, 1H), 7.68-7.74 (m, 1H), 7.14-7.23 (m, 4H), 5.14 (s, 2H), 4.37 (br s, 1H), 4.21 (t, 2H), 3.36-3.44 (m, 1H), 3.19-3.33 (m, 2H), 3.10-3.17 (m, 1H), 2.70-2.79 (m, 1H), 2.55-2.59 (m, 1H), 2.26-2.38 (m, 1H), 1.75-1.84 (m, 1H), 1.61-1.70 (m, 2H), 1.48-1.55 (m, 1H);

MS (+ve ESI): 524 $(M+H)^+$.

Example 170 – Preparation of example 170 in table 4 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2*R*)-2-(hydroxymethyl)-4-methylpiperazin-1-yl]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 168 but starting with [(2*R*)-4-methylpiperazin-2-yl]methanol (*Synlett.*, **1996**, 143-144, 0.089 g, 0.68 mmol) yielded compound 170 in table 4 (0.050 g, 20 % yield):

^{1}H-NMR (DMSO d_6): 10.27 (s, 1H), 9.92 (s, 1H), 8.53 (s, 1H), 8.35 (d, 1H), 8.33 (s, 1H), 7.78 (s, 1H), 7.68-7.73 (m, 1H), 7.15-7.21 (m, 4H), 5.14 (s, 2H), 4.20 (m, 2H), 3.61 (dd, 1H), 3.20-3.45 (under H_2O), 3.12-3.16 (m, 2H), 2.72-2.87 (m, 2H), 2.60 (d, 1H), 2.20-2.49 (under DMSO), 2.13 (s, 3H), 2.05-2.18 (m, 1H), 1.92-1.99 (m, 1H);

MS (+ve ESI): 553 $(M+H)^+$.

Example 171 – Preparation of example 171 in table 4 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{2-[4-(hydroxymethyl)piperidin-1-yl]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 168 but starting with piperidin-4-ylmethanol (0.079 g, 0.69 mmol) yielded compound 171 in table 4 (0.040 g, 16 % yield):
^{1}H-NMR (DMSO d_6): 10.27 (s, 1H), 9.91 (s, 1H), 8.53 (s, 1H), 8.35 (d, 1H), 8.33 (s, 1H), 7.77 (s, 1H), 7.68-7.74 (m, 1H), 7.14-7.24 (m, 4H), 5.14 (s, 2H), 4.37 (t, 1H), 4.22 (t, 2H), 3.23 (t, 2H), 2.95 (d, 2H), 2.73 (t, 2H), 2.00 (t, 2H), 1.63 (d, 2H), 1.26-1.38 (m, 1H), 1.06-1.19 (m, 2H);
MS (+ve ESI): 538 $(M+H)^+$.

Example 172 – Preparation of example 172 in table 4 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{2-[4-(2-hydroxyethyl)piperidin-1-yl]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 168 but starting with 2-piperidin-4-ylethanol (0.088 g, 0.68 mmol) yielded compound 172 in table 4 (0.098 g, 39 % yield):
^{1}H-NMR (DMSO d_6): 10.27 (s, 1H), 9.91 (s, 1H), 8.53 (s, 1H), 8.35 (d, 1H), 8.33 (s, 1H), 7.77 (s, 1H), 7.68-7.75 (m, 1H), 7.13-7.27 (m, 4H), 5.15 (s, 2H), 4.29 (t, 1H), 4.22 (t, 2H), 3.39-3.45 (m, 2H), 2.88-2.96 (m, 2H), 2.72 (t, 2H), 2.01 (t, 2H), 1.56-1.65 (m, 2H), 1.30-1.39 (m, 3H), 1.07-1.21 (m, 2H);
MS (+ve ESI): 552 $(M+H)^+$.

Example 173 – Preparation of example 173 in table 4 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2-hydroxyethyl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 168 but starting with 2-aminoethanol (0.042 g, 0.69 mmol) yielded compound 173 in table 4 (0.011 g, 5% yield):
^{1}H-NMR (DMSO d_6): 10.27 (br s, 1H), 9.92 (s, 1H), 8.53 (s, 1H), 8.35 (d, 1H), 8.33 (s, 1H), 7.78 (s, 1H), 7.66-7.75 (m, 1H), 7.12-7.25 (m, 4H), 5.14 (s, 2H), 4.52 (m, 1H), 4.19 (t, 2H), 3.48 (m, 2H), 2.98 (t, 2H), 2.68 (t, 2H);
MS (+ve ESI): 484 $(M+H)^+$.

Example 174 – Preparation of example 174 in table 4 - *N*-(2,3-difluorophenyl)-2-(4-{[7-(2-{[*trans*-2-(hydroxymethyl)cyclohexyl]amino}ethoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide

An analogous reaction to that described in example 168 but starting with *trans*-2-(hydroxymethyl)cyclohexylamine hydrochloride (0.113 g, 0.68 mmol) yielded compound 174 in table 4 (0.041 g, 16% yield):

^{1}H-NMR (DMSO d_6): 10.27 (br s, 1H), 9.91 (s, 1H), 8.54 (s, 1H), 8.34 (d, 1H), 8.34 (s, 1H), 7.78 (s, 1H), 7.68-7.75 (m, 1H), 7.10-7.24 (m, 4H), 5.15 (s, 2H), 4.14 (t, 2H), 3.48 (dd, 1H), 3.37 (dd, 1H), 3.04-3.13 (m, 1H), 2.79-2.89 (m, 1H), 2.28 (td, 1H), 1.96-2.05 (m, 1H), 1.55-1.75 (m, 3H), 0.80-1.38 (m, 5H);

MS (+ve ESI): 552 $(M+H)^+$.

Example 175 – Preparation of compound 175 in table 4 -*N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 122, but starting with ethanolamine (0.15 ml, 1.90 mmol) yielded compound 175 in table 4 (0.125 g, 66% yield):

^{1}H-NMR (DMSO d_6): 9.62 (br s, 1H), 8.52 (s, 1H), 8.32 (d, 1H), 8.28 (s, 1H), 7.82 (s, 1H), 7.70 (m, 1H), 7.15 (m, 4H), 5.09 (s, 2H), 4.25 (t, 2H), 4.00 (br s, 1H), 3.50 (t, 2H), 2.70 (t, 2H), 2.60 (t, 2H), 1.98 (quintet, 2H);

MS (+ve ESI): 498 $(M+H)^+$.

Example 176 – Preparation of compound 176 in table 4 - *N*-(2,3-difluorophenyl)-2-(4-{[7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide

An analogous reaction to that described in example 122, but starting with pyrrolidine (0.059 g, 0.39 mmol) yielded compound 176 in table 4 (0.110 g, 56% yield):

^{1}H-NMR (DMSO d_6): 10.30 (br s, 1H), 9.89 (br s, 1H), 8.59 (s, 1H), 8.38 (d, 1H), 8.32 (s, 1H), 7.80 (s, 1H), 7.65 (m, 1H), 7.20 (m, 3H), 7.15 (s, 1H), 5.18 (s, 2H), 4.20 (t, 2H), 3.15 (m, 10H), 2.08 (m, 2H);

MS (+ve ESI): 507 $(M+H)^+$.

Example 177 – Preparation of compound 177 in table 4 - *N*-(2,3-difluorophenyl)-2-{4-[(7-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

A mixture of caesium carbonate (0.122 g, 0.38 mmol), *N*-(2,3-difluorophenyl)-2-{4-[(7-hydroxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (0.150 g, 0.38 mmol) and methyl iodide (0.054 g, 0.38 mmol) in dimethylacetamide (5 ml) was stirred at room temperature for 1 hour. The reaction mixture was evaporated under reduced pressure and the residue was then triturated with acetonitrile to give a yellow solid which was purified by reverse phase chromatography eluting with 0.2% aqueous trifluoroacetic acid in acetonitrile using a 5 to 50% gradient over 25 minutes. The fractions containing product were concentrated under reduced pressure and then basified with aqueous sodium carbonate. The resultant solid was filtered and washed with water to give compound 177 in table 4 (0.026 g, 17% yield):

^{1}H-NMR (DMSO d_6): 10.27 (br s, 1H), 8.40 (s, 1H), 8.25 (d, 1H), 8.18 (s, 1H), 7.75 (s, 1H), 7.65 (m, 1H), 7.20 (m, 4H), 6.75 (s, 1H), 5.15 (s, 2H), 3.64 (s, 3H);

MS (+ve ESI): 412 $(M+H)^+$.

Example 178 – Preparation of compound 178 in table 4 - N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(tetrahydro-2H-pyran-4-yl)amino]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide

A mixture of 2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide hydrochloride salt (0.5g 0.98 mmol), *N*-*N*-diispropylethylamine (0.342 ml, 1.97 mmol), 2-(tetrahydro-2*H*-pyran-4-ylamino)ethanol (0.285g, 1.97 mmol) and potassium iodide (0.326 g, 1.97 mmol) in dimethylacetamide (4 ml) was heated at 70°C for 16 hours. The reaction mixture was diluted with dimethylsulphoxide:acetonitrile:water (7:2:1, 3ml) and purified by reverse phase chromatography eluting with 0.2% aqueous trifluoroacetic acid in acetonitrile using a 5 to 50% gradient over 25 minutes. The eluent was concentrated under reduced pressure and basified with aqueous sodium carbonate. The product was filtered, washed with water then triturated with diethylether to give compound 178 in table 4 (0.308 g, 54% yield) as a cream coloured solid.

^{1}H-NMR (DMSO d_6): 10.35 (br s, 1H), 9.90 (s, 1H), 8.55 (s, 1H), 8.35 (m, 2H), 7.80 (s, 1H), 7.65 (m, 1H), 7.25 (m, 3H), 7.10 (s, 1H), 5.20 (s, 2H), 4.30 (t, 1H), 4.20 (t, 2H), 3.90-3.80

(m, 2H), 3.45-3.35 (m, 4H), 3.30 (t, 2H), 2.75-2.60 (m, 3H), 1.90-1.80 (m, 2H), 1.65-1.55 (m, 2H), 1.50-1.40 (m, 2H);

MS (+VE ESI): 582 $(M+H)^+$

MS (-VE ESI): 580 $(M-H)^-$.

Example 179 – Preparation of compound 179 in table 4 - N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2R)-2-(2-hydroxyethyl)piperidin-1-yl]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide

A mixture of 2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide hydrochloride salt (0.5g 0.98 mmol), *N*-*N*-diispropylethylamine (1.37 ml, 7.86 mmol), 2-[(2*R*)-piperidin-2-yl]ethanol hydrochloride (0.57g, 3.94 mmol) and potassium iodide (0.652 g, 3.94 mmol) in dimethylacetamide (4 ml) was heated at 80°C for 32 hours. The reaction mixture was diluted with dimethylsulphoxide:acetonitrile:water (7:2:1, 6ml) and purified by reverse phase chromatography eluting with 0.2% aqueous trifluoroacetic acid in acetonitrile using a 5 to 50% gradient over 25 minutes. The eluent was concentrated under reduced pressure and basified with aqueous sodium carbonate. The product was filtered, washed with water and dried in vacuum oven at 40°C for 16 hours to give compound 179 in table 4 (0.228 g, 41% yield) as a cream coloured solid.

^{1}H-NMR (DMSO d_6): 10.30 (br s, 1H), 9.90 (s, 1H), 8.52 (s, 1H), 8.30 (m, 2H), 7.80 (s, 1H), 7.70 (m, 1H), 7.30 (m, 3H), 7.20 (s, 1H), 5.20 (s, 2H), 4.50 (m, 1H), 4.20 (t, 2H), 3.50 (m, 2H), 2.70 (m, 2H), 2.40 (m, 2H), 2.20 (m, 1H), 1.90 (m, 2H), 1.80 (m, 1H), 1.70 (m, 2H), 1.50 (m, 3H), 1.30 (m, 2H);

MS (+VE ESI): 566 $(M+H)^+$.

Example 180 – Preparation of compound 180 in table 4 - N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2S)-2-(2-hydroxyethyl)piperidin-1-yl]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 179 but starting with 2-[(2*S*)-piperidin-2-yl]ethanol hydrochloride (0.0.57g, 3.94 mmol) gave compound 180 in table 4 (0.280 g, 50% yield) as a cream coloured solid.

^{1}H-NMR (DMSO d_6): 10.30 (br s, 1H), 9.90 (s, 1H), 8.52 (s, 1H), 8.30 (m, 2H), 7.80 (s, 1H), 7.70 (m, 1H), 7.30 (m, 3H), 7.20 (s, 1H), 5.20 (s, 2H), 4.50 (m, 1H), 4.20 (t, 2H), 3.50 (m, 2H), 2.70 (m, 2H), 2.40 (m, 2H), 2.20 (m, 1H), 1.90 (m, 2H), 1.80 (m, 1H), 1.70 (m, 2H), 1.50 (m, 3H), 1.30 (m, 2H);

MS (+VE ESI): 566 $(M+H)^+$.

Example 181 – Preparation of compound 181 in table 4 - N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2R)-2-(hydroxymethyl)-4-methylpiperazin-1-yl]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 179 but starting with [(2*R*)-4-methylpiperazin-2-yl]methanol (0.216g, 1.66 mmol) gave compound 181 in table 4 (0.161g, 34% yield) as a cream coloured solid.

^{1}H-NMR (DMSO d_6): 10.35 (bs, 1H), 9.90 (s, 1H), 8.55 (s, 1H), 8.35 (m, 2H), 7.80 (s, 1H), 7.70 (m, 1H), 7.20 (m, 3H), 7.10 (s, 1H), 5.15 (s, 2H), 4.50 (bs, 1H), 4.20 (t, 2H), 3.60 (m, 1H), 2.95 (m, 1H), 2.80 (m, 1H), 2.60 (m, 1H), 2.50 (m, 2H), 2.30 (m, 4H), 2.15 (m, 3H), 1.80 (m, 3H);

MS (+VE ESI): 567 $(M+H)^+$

MS (-VE ESI): 565 $(M-H)^-$.

Example 182 – Preparation of compound 182 in table 4 - N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3S)-3-(hydroxymethyl)-4-methylpiperazin-1-yl]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide

A mixture of 2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide hydrochloride salt (0.550g, 1.08 mmol), *N*-*N*-diispropylethylamine (0.376ml, 2.16mmol), [(2*S*)-1-methylpiperazin-2-yl]methanol (0.281g, 2.16 mmol) and potassium iodide (0.356 g, 2.16mmol) in dimethylacetamide (4 ml) was heated at 80°C for 16 hours. The reaction mixture was diluted with dimethylsulphoxide:acetonitrile:water (7:2:1, 6ml) and purified by reverse phase chromatography eluting with 0.2% aqueous trifluoroacetic acid in acetonitrile using a 5 to 50% gradient over 25 minutes. The eluent was concentrated under reduced pressure and basified with aqueous sodium carbonate. The product was extracted into 10% methanol in

dichloromethane, dried over magnesium sulphate and concentrated under reduced pressure to give compound 182 in table 4 (0.466g, 76% yield) as a white solid.

^{1}H-NMR (DMSO d_6): 10.10 (bs, 2H), 8.55 (s, 1H), 8.35 (m, 2H), 7.75 (s, 1H), 7.70 (m, 1H), 7.20 (m, 3H), 7.10 (s, 1H), 5.10 (s, 2H), 4.40 (bs, 1H), 4.20 (t, 2H), 3.60 (m, 1H), 2.90 (m, 1H), 2.70 (m, 2H), 2.40 (t, 2H), 2.20 (s, 3H), 2.0 (m, 2H), 1.90 (m, 2H), 1.80 (m, 1H);

MS (-VE ESI): 565 $(M-H)^-$.

Example 183 – Preparation of compound 183 in table 4 - N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2R)-2-(hydroxymethyl)morpholin-4-yl]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 179 but starting with (2*R*)-morpholin-2-ylmethanol (0.200g, 1.71 mmol) gave compound 183 in table 4 (0.161g, 34% yield) as a cream coloured solid.

^{1}H-NMR (DMSO d_6): 10.30 (bs, 1H), 9.90 (s, 1H), 8.55 (s, 1H), 8.40 (m, 2H), 7.75 (s, 1H), 7.70 (m, 1H), 7.20 (m, 3H), 7.10 (s, 1H), 5.10 (s, 2H), 4.60 (t, 1H), 4.20 (t, 2H), 3.75 (m, 1H), 3.50 (m, 1H), 3.40 (m, 2H), 2.80 (m, 1H), 2.70 (m, 1H), 2.40 (m, 2H), 2.0 (m, 3H), 1.75 (m, 1H);

MS (-VE ESI): 552 $(M-H)^-$.

Example 184 – Preparation of compound 184 in table 4 - N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3S)-3-(hydroxymethyl)morpholin-4-yl]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 179 but starting with (3*S*)-morpholin-3-ylmethanol (0.567g, 4.84 mmol) gave compound 184 in table 4 (0.292g, 27% yield) as a white solid.

^{1}H-NMR (DMSO d_6): 8.55 (s, 1H), 8.35 (m, 2H), 7.80 (s, 1H), 7.65 (m, 1H), 7.25-7.04 (m, 4H), 5.10 (s, 2H), 4.20 (t, 2H), 3.75-3.55 (m, 3H), 3.50-3.40 (m, 1H), 3.0-2.85 (m, 1H), 2.80-2.65 (m, 1H), 2.50 (4H, m under DMSO), 2.40-2.20 (m, 4H), 2.0-1.80 (m, 2H);

MS (+VE ESI): 554 $(M+H)^+$

MS (-VE ESI): 552 $(M-H)^-$.

Example 185 – Preparation of compound 185 in table 4 - N-(2,3-difluorophenyl)-2-[4-({7-[3-(glycoloylamino)propoxy]quinazolin-4-yl}amino)-1H-pyrazol-1-yl]acetamide

A mixture of 2-(4-{[7-(3-aminopropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide (0.15g 0.33 mmol), hydroxyacetic acid (0.033g, 0.43mmol), *N*-*N*-diispropylethylamine (0.115 ml, 0.66 mmol) and *O*-(7-Azabenzotriazole-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophospahte (0.164g, 1.97 mmol) in dimethylacetamide (4 ml) was stirred at ambient temperature for 16 hours. The reaction mixture was diluted with dimethylsulphoxide:acetonitrile:water (7:2:1, 3ml) and purified by reverse phase chromatography eluting with 0.2% aqueous trifluoroacetic acid in acetonitrile using a 5 to 70% gradient over 25 minutes. The eluent was concentrated under reduced pressure and basified with aqueous sodium carbonate. The product was filtered, washed with water and then triturated with diethylether to give compound 185 in table 4 (0.055 g, 32% yield) as a cream coloured solid.

^{1}H-NMR (DMSO d_6): 10.35 (br s, 1H), 8.55 (s, 1H), 8.35 (m, 1H), 8.30 (m, 2H), 7.90 (m, 1H), 7.75 (m, 1H), 7.70(m, 1H), 7.30-7.05 (m, 4H), 5.50 (br s, 1H), 5.10 (s, 2H), 4.15 (t, 2H), 3.70 (s, 2H), 2.70 (s, 2H), 2.0 (m, 2H);

MS (+VE ESI): 512 $(M+H)^+$

MS (-VE ESI): 510 $(M-H)^-$.

Example 186 - Preparation of compound 186 in table 5- *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 122, but starting with 2-(propylamino)ethanol (129 mg, 1.25 mmol) and 2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide (113 mg, 0.25 mmol) yielded compound 186 in table 5 (60 mg, 46 % yield):

^{1}H-NMR (DMSO d_6): 10.50 (s, 1H), 9.90 (s, 1H), 8.45 (s, 1H), 8.32 (m, 2H), 7.78 (s, 1H), 7.56 (m, 1H), 7.34 (m, 1H), 7.31 (m, 1H), 7.20 (m, 1H), 7.11 (s, 1H), 6.90 (m, 1H), 5.04 (s, 2H), 4.26 (t, 1H), 4.16 (t, 2H), 2.60 (t, 2H), 2.48 (m, 2H), 2.38 (m, 2H), 1.87 (m, 2H), 1.38 (m, 2H), 0.81 (t, 3H);

MS (+ve ESI): 522 $(M+H)^+$.

Example 187 - Preparation of compound 187 in table 5- 2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 186, but starting with 2-(ethylamino)ethanol (111 mg, 1.25 mmol) yielded compound 187 in table 5 (40 mg, 32 % yield):

^{1}H-NMR (DMSO d_6): 10.58 (s, 1H), 9.96 (s, 1H), 8.56 (s, 1H), 8.36 (m, 2H), 7.79 (s, 1H), 7.60 (m, 1H), 7.33 (m, 2H), 7.23 (m, 1H), 7.14 (s, 1H), 6.91 (m, 1H), 5.08 (s, 2H), 4.36 (br s, 1H), 4.19 (m, 2H), 3.46 (m, 2H), 2.61 (m, 2H), 2.51 (m, 4H), 1.90 (m, 2H), 0.98 (t, 3H);

MS (+ve ESI): 508 $(M+H)^+$.

Example 188 - Preparation of compound 188 in table 5- *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 186, but starting with (2R)-pyrrolidin-2-ylmethanol (126 mg, 1.25 mmol) yielded compound 188 in table 5 (101 mg, 78 % yield):

^{1}H-NMR (DMSO d_6): 9.92 (br s, 1H), 8.55 (s, 1H), 8.35 (m, 2H), 7.77 (s, 1H), 7.59 (m, 1H), 7.33 (m, 2H), 7.22 (m, 1H), 7.15 (s, 1H), 6.90 (m, 1H), 5.05 (s, 2H), 4.40 (br s, 1H), 4.20 (t, 2H), 3.40 (m, 1H), 3.30 (m, 1H), 2.50 (m, 2H), 2.28 (m, 1H), 1.96 (m, 2H), 1.82 (m, 1H), 1.67 (m, 2H), 1.58 (m, 1H);

MS (+ve ESI): 520 $(M+H)^+$.

Example 189 - Preparation of compound 189 in table 5- *N*-(3-fluorophenyl)-2-{4-[(7-{3-[4-(hydroxymethyl)piperidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 186, but starting with piperidin-4-ylmethanol (144 mg, 1.25 mmol) yielded compound 189 in table 5 (122 mg, 92 % yield):

^{1}H-NMR (DMSO d_6): 10.50 (br s, 1H), 9.92 (br s, 1H), 8.57 (s, 1H), 8.34 (m, 2H), 7.79 (s, 1H), 7.57 (m, 1H), 7.30 (m, 2H), 7.21 (m, 1H), 7.17 (s, 1H), 6.90 (m, 1H), 5.06 (s, 2H), 4.54 (br s, 1H), 4.21 (t, 2H), 3.31 (m, 2H), 2.98 (m, 2H), 2.50 (m, 4H), 2.10 (m, 2H), 1.79 (m, 2H), 1.53 (m, 1H), 1.30 (m, 2H);

MS (+ve ESI): 534 $(M+H)^+$.

Example 190 - Preparation of compound 190 in table 5- *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(3-hydroxy-1,1-dimethylpropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 186, but starting with 3-amino-3methylbutan-1-ol (129 mg, 1.25 mmol) yielded compound 190 in table 5 (105 mg, 81 % yield):

^{1}H-NMR (DMSO d_6): 10.51 (s, 1H), 9.91 (s, 1H), 8.56 (s, 1H), 8.36 (m, 1H), 8.33 (s, 1H), 7.77 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.23 (m, 1H), 7.16 (s, 1H), 6.91 (m, 1H), 5.05 (s, 2H), 4.24 (t, 2H), 3.58 (t, 2H), 2.97 (t, 2H), 2.03 (m, 2H), 1.70 (t, 2H), 1.22 (s, 6H);

MS (+ve ESI): 522 $(M+H)^+$.

Example 191 – Preparation of compound 191 in table 5 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[2-(2-hydroxyethyl)piperidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 186, but starting with 2-(2-hydroxyethyl)piperidine (0.258 g, 2.00 mmol) yielded compound 191 in table 5 (0.150 g, 77% yield):

^{1}H-NMR (DMSO d_6, 373K): 10.19 (1H, s), 9.63 (1H, s), 8.53 (1H, s), 8.33 (1H, d), 8.27 (1H, s), 7.79 (1H, s), 7.52 (1H, d), 7.33 (2H, m), 7.18 (2H, m), 6.86 (1H, m), 5.02 (2H, s), 4.21 (2H, t), 3.50 (2H, m), 2.74 (2H, m), 2.54 (1H, m), 2.01 (3H, m), 1.84 (1H, m), 1.72 (1H, m), 1.59 (5H, m), 1.39 (2H, m);

MS (+ve ESI): 548 $(M+H)^+$

MS (-ve ESI): 546 $(M-H)^-$.

Example 192 – Preparation of compound 192 in table 5 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 186, but starting with 2-piperazin-1-ylethanol (0.26 ml, 2.15 mmol) yielded compound 192 in table 5 (0.214 g, 91% yield):

^{1}H-NMR (DMSO d_6): 10.27 (br s, 1H), 9.20 (br s, 1H), 8.62 (s, 1H), 8.43 (d, 1H), 8.38 (s, 1H), 7.82 (s, 1H), 7.62 (d, 1H), 7.30 (m, 3H), 7.15 (s, 1H), 6.92 (t, 1H), 5.28 (br s, 1H), 5.15 (s, 2H), 4.20 (s, 2H), 3.35 (m, 16H);

MS (+ve ESI): 549 $(M+H)^+$.

Example 193 – Preparation of compound 193 in table 5 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(tetrahydrofuran-3-yl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

2-{4-[(7-{3-[(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)(tetrahydrofuran-3-yl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide (0.110 g, 0.16 mmol) was dissolved in anhydrous tetrahydrofuran (10 ml) under a nitrogen atmosphere and then a solution of tetra-*N*-butylammonium fluoride in tetrahydrofuran (1M solution, 0.8 ml, 0.8 mmol) was added. After stirring for 1 hour a further portion of tetra-*N*-butylammonium fluoride in tetrahydrofuran (1M solution, 0.64 ml, 0.64 mmol) was added and the reaction mixture was left to stir overnight at room temperature. The solvent was evaporated under reduced pressure and the residue purified by silica gel chromatography eluting with a gradient of 0 to 10% methanol in dichloromethane containing 2% 7N ammonia in methanol. The obtained product was triturated with acetonitrile to give compound 193 in table 5 (0.028 g, 32% yield):

^{1}H-NMR (DMSO d_6): 10.51 (1H, s), 9.90 (1H, s), 8.53 (1H, s), 8.33 (2H, d), 7.78 (1H, s), 7.58 (1H, d), 7.34 (2H, m), 7.21 (1H, d), 7.16 (1H, s), 6.90 (1H, t), 5.05 (2H, s), 4.37 (1H, t), 4.18 (2H, t), 3.81 (1H, m), 3.69 (1H, m), 3.57 (1H, m), 3.45 (4H, m), 2.62 (3H, m), 1.92 (3H, m), 1.72 (1H, m);

MS (+ve ESI): 550 $(M+H)^+$

MS (-ve ESI): 548 $(M-H)^-$.

2-{4-[(7-{3-[(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)(tetrahydrofuran-3-yl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide used as starting material, was prepared as follows:

a) A solution of tetrahydrofuran-3-amine (see WO98/08855, 0.500 g, 4.04 mmol) and sodium acetate (0.331 g, 4.04 mmol) in a 1 : 3 mixture of methanol and tetrahydrofuran (60 ml) was stirred at room temperature. To this was added (*tert*-butyl-dimethylsilanyloxy)acetaldehyde (2.112 g, 12.12 mmol) followed by glacial acetic acid (1.456

g, 24.24 mmol) and then sodium triacetoxyborohydride (2.568 g, 12.12 mmol) was then added in 5 portions over 3 minutes (CAUTION: vigorous effervescence) and the resulting suspension was left to stir at room temperature for 4 hours. The mixture was evaporated under reduced pressure to leave a thick brown paste which was dissolved in dichloromethane (20 ml) and to this was added a solution of ammonia in methanol (7M solution, 25 ml). The mixture was stirred for 10 minutes and then evaporated under reduced pressure to leave an orange paste which was triturated with dichloromethane (50 ml) and filtered through Celite. The mixture was evaporated under reduced pressure to leave a brown gum which was dissolved in methyl *tert*-butyl ether (3 ml) and then purified by silica gel chromatography using methyl *tert*-butyl ether as eluent to give *N*-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)tetrahydrofuran-3-amine (0.446 g, 48% yield) as a brown oil:
^{1}H-NMR ($CDCl_3$): 3.68 (8H, m), 2.68 (2H, m), 2.04 (1H, m), 1.73 (1H, m), 0.82 (9H, s), 0.00 (6H, s).

b) An analogous reaction to that described in example 186, but starting with *N*-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)tetrahydrofuran-3-amine (0.446 g, 1.81 mmol) yielded 2-{4-[(7-{3-[(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)(tetrahydrofuran-3-yl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide (0.112 g, 39% yield):
^{1}H-NMR ($CDCl_3$): 11.01 (1H, br s), 9.79 (1H, br s), 8.70 (1H, d), 8.63 (1H, s), 8.48 (1H, s), 8.09 (1H, s), 7.58 (1H, d), 7.51 (1H, s), 7.30 (2H, d), 7.24 (1H, m), 6.78 (1H, m), 5.09 (2H, s), 4.33 (1H, m), 4.14 (2H, m), 3.96 (2H, t), 3.88 (2H, m), 3.72 (2H, m), 3.34 (1H, br s), 3.13 (2H, m), 2.32 (5H, m), 0.92 (9H, s), 0.11 (6H, s);
MS (+ve ESI): 664 $(M+H)^+$
MS (-ve ESI): 662 $(M-H)^-$.

Example 194 – Preparation of compound 194 in table 5 - *N*-(3-fluorophenyl)-2-(4-{[7-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide

A solution of 2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide (0.060 g, 0.13 mmol) in morpholine (20 ml) was heated at 80°C for 2 hours and then allowed to cool to room temperature. The mixture was evaporated under reduced pressure to leave a brown solid, which was washed with water, dried and triturated with diethyl ether to give compound 194 in table 5 (0.052 g, 76% yield) as a white solid:

^{1}H-NMR (DMSO d_6): 10.72 (br s, 1H), 8.55 (s, 1H), 8.40 (d, 1H), 8.35 (s, 1H), 7.79 (s, 1H), 7.58 (d, 1H), 7.35 (m, 2H), 7.20 (dd, 1H), 7.15 (d, 1H), 6.85 (m, 1H), 5.05 (s, 2H), 4.16 (t, 2H), 3.65 (m, 6H), 3.35 (quintet, 2H), 2.35 (m, 2H), 1.98 (quintet, 2H);

MS (+ve ESI): 506 $(M+H)^+$

MS (-ve ESI): 504 $(M-H)^-$.

Example 195 – Preparation of compound 195 in table 5 - *N*-(3-fluorophenyl)-2-[4-({7-[(2*S*)-pyrrolidin-2-ylmethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide

A solution of *tert*-butyl (2*S*)-2-[({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)methyl]pyrrolidine-1-carboxylate (0.332 g, 0.59 mmol) in trifluoroacetic acid (5 ml) was stirred at room temperature for 1 hour. The solvent was evaporated and the residue triturated with diethyl ether to yield compound 195 in table 5 (0.355 g, 87% yield) as the di-trifluoroacetate salt:

^{1}H-NMR (DMSO d_6): 11.17 (br s, 1H), 10.60 (s, 1H), 9.37 (br s, 1H), 8.91 (m, 2H), 8.59 (d, 1H), 8.38 (s, 1H), 7.92 (s, 1H), 7.59 (m, 1H), 7.47 (dd, 1H), 7.39 (m, 1H), 7.31 (m, 2H), 6.92 (m, 1H), 5.12 (s, 2H), 4.50 (m, 1H), 4.33 (m, 1H), 4.03 (br m, 1H), 3.28 (br m, 2H), 2.19 (m, 1H), 2.01 (m, 2H), 1.83 (m, 1H);

MS (+ve ESI): 462 $(M+H)^+$.

tert-butyl (2*S*)-2-[({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)methyl]pyrrolidine-1-carboxylate used as starting material, was obtained as follows:

a) Methane sulphonyl chloride (0.11 ml, 1.4 mmol) was added to a solution of *tert*-butyl (2*S*)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (0.25 g, 1.24 mmol) and 4-(dimethylamino)pyridine (0.167 g, 1.4 mmol) in dichloromethane (5 ml). The mixture was stirred at room temperature for 1 hour and then 4-(dimethylamino)pyridine (0.051 g, 0.42 mmol) and methane sulphonyl chloride (0.033 ml, 0.42 mmol) were added and the mixture stirred at room temperature for a further 1 hour. The mixture was purified directly by silica gel chromatography, eluting with a 3 : 1 to 1 : 1 mixture of *iso*-hexane : ethyl acetate to yield *tert*-butyl (2*S*)-2-{[(methylsulphonyl)oxy]methyl}pyrrolidine-1-carboxylate (0.325 g, 94% yield):

^{1}H-NMR ($CDCl_3$): 4.28 (m, 2H), 4.03 (m, 1H), 3.36 (m, 2H), 3.00 (s, 3H), 1.92 (m, 4H).

b) A solution of *N*-(3-fluorophenyl)-2-{4-[(7-hydroxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (0.590 g, 0.97 mmol), cesium carbonate (1.95 g, 5.98 mmol) and *tert*-butyl (2*S*)-2-{[(methylsulphonyl)oxy]methyl}pyrrolidine-1-carboxylate (0.325 g, 1.16 mmol) in dimethylacetamide (10 ml) was heated at 80°C for 18 hours. The mixture was poured into water and extracted with ethyl acetate. The organic layer was separated, dried over magnesium sulphate and evaporated *in vacuo* to leave a brown oil which was purified by silica gel chromatography. Elution with 5 to 7% methanol in dichloromethane gave *tert*-butyl (2*S*)-2-[({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)methyl]pyrrolidine-1-carboxylate (0.332 g, 61% yield) as a light brown solid.
^{1}H-NMR (DMSO d_6): 10.51 (s, 1H), 9.94 (s, 1H), 8.55 (s, 1H), 8.38 (d, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.58 (m, 1H), 7.35 (m, 2H), 7.26 (m, 1H), 7.20 (m, 1H), 6.91 (m, 1H), 5.06 (s, 2H), 4.23 (m, 1H), 4.10 (m, 2H), 3.30 (m, 2H under water), 1.97 (m, 3H), 1.82 (m, 1H), 1.42 (s, 9H);
MS (+ve ESI): 562 $(M+H)^+$.

Example 196 – Preparation of compound 196 in table 5 - *N*-(3-fluorophenyl)-2-{4-[(7-{[(2*S*)-1-(2-hydroxyethyl)pyrrolidin-2-yl]methoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

A solution of tetra-butylammonium fluoride (1 M in tetrahydrofuran, 0.5 ml, 0.5 mmol) was added to a solution of 2-{4-[(7-{[(2*S*)-1-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)pyrrolidin-2-yl]methoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide (0.055 g, 0.09 mmol) in tetrahydrofuran (5 ml) and the mixture was stirred at room temperature for 15 minutes. The mixture was poured into water and extracted with dichloromethane. The organic layer was separated, dried over magnesium sulphate and then evaporated to leave a yellow film which was purified by silica gel chromatography. Elution with 5 to 10% methanol and then 10% methanol containing 7M ammonia, gave the title compound as a colourless film which was dissolved in methanol (5 ml) and a solution of hydrogen chloride in diethyl ether (1M, 0.5 ml, 0.5 mmol) was added. The solvent was evaporated and the residue triturated with diethyl ether to yield compound 196 in table 5 as the dihydrochloride salt (0.027 g, 52% yield):
^{1}H-NMR (DMSO d_6): 12.06 (s, 1H), 10.82 (s, 1H), 10.53 (br s, 1H), 8.96 (m, 2H), 8.45 (s, 1H), 8.07 (s, 1H), 7.58 (m, 2H), 7.39 (m, 3H), 6.92 (m, 1H), 5.15 (s, 2H), 4.64 (m, 1H), 4.56

(m, 1H), 4.09 (m, 1H), 3.81 (m, 2H), 3.71 (m, 1H), 3.59 (m, 1H), 3.29 (m, 2H), 2.30 (m, 1H), 2.05 (m, 2H), 1.89 (m, 1H);
MS (+ve ESI): 506 $(M+H)^+$.

2-{4-[(7-{[(2*S*)-1-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)pyrrolidin-2-yl]methoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide used as starting material, was obtained as follows:

a) Sodium triacetoxyborohydride (0.11 g, 0.52 mmol) was added to a mixture of *N*-(3-fluorophenyl)-2-[4-({7-[(2*S*)-pyrrolidin-2-ylmethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide bis(trifluoroacetate) (0.20 g, 0.29 mmol) and (*tert*-butyldimethylsilyloxy)acetaldehyde (0.10 ml, 0.52 mmol) in tetrahydrofuran (9 ml) and methanol (3 ml) containing a catalytic amount of acetic acid. The mixture was stirred at room temperature for 1 hour. A further portion of sodium triacetoxyborohydride (0.22g, 1.04 mmol) was added and the mixture stirred at room temperature for 1 hour. A further portion of sodium triacetoxyborohydride (0.22g, 1.04 mmol) was added and the mixture stirred at room temperature overnight. The mixture was poured into sodium hydroxide solution (1M, 50 ml) and extracted with dichloromethane. The organic layer was separated, washed with brine, dried over magnesium sulphate and then evaporated to leave a yellow film which was purified by silica gel chromatography. Elution with 5 to 10% methanol in dichloromethane gave 2-{4-[(7-{[(2*S*)-1-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)pyrrolidin-2-yl]methoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide (0.055 g, 31% yield):
MS (+ve ESI): 620 $(M+H)^+$.

Example 197 – Preparation of compound 197 in table 5 - *N*-(3-fluorophenyl)-2-{4-[(7-{[(2*S*)-1-glycoloylpyrrolidin-2-yl]methoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

Acetoxyacetyl chloride (0.017 ml, 0.16 mmol) was added to a solution of *N*-(3-fluorophenyl)-2-[4-({7-[(2*S*)-pyrrolidin-2-ylmethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide bis(trifluoroacetate) (0.112 g, 0.16 mmol) and triethylamine (0.1 ml, 0.7 mmol) in tetrahydrofuran (5 ml) and the mixture was stirred at room temperature for 30 minutes. The mixture was evaporated and the residue was dissolved in methanol (5 ml). A solution of sodium hydroxide (2M, 0.5 ml) was added and the mixture stirred at room temperature for 2.5 hours. The mixture was evaporated and the residue sonicated in water (5 ml) and then

filtered. The solid was purified by reverse phase chromatography to yield compound 197 in table 5 (0.029 g, 35% yield):

^{1}H-NMR (DMSO d_6): 10.55 (br s, 1H), 9.94 (br s, 1H), 8.55 (s, 1H), 8.38 (d, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.58 (m, 1H), 7.36 (m, 2H), 7.24 (m, 2H), 6.91 (m, 1H), 5.06 (s, 2H), 4.56 and 4.37 (m, 2H), 4.29 (m, 1H), 4.11 (m, 1H), 4.04 (m, 1H), 3.40 (m, 2H under water), 1.98 (m, 4H);

MS (+ve ESI): 520 $(M+H)^+$.

Example 198 – Preparation of compound 198 in table 5 - *N*-(3-fluorophenyl)-2-(4-{[7-(pyrrolidin-3-ylmethoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide

A solution of *tert*-butyl 3-[({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)methyl]pyrrolidine-1-carboxylate (0.435 g, 0.78 mmol) in trifluoroacetic acid (10 ml) was stirred at room temperature for 30 minutes. The mixture was evaporated and the residue was stirred in diethyl ether (25 ml) and then filtered and dried under nitrogen to yield compound 198 in table 5 (0.537 g, 100% yield):

^{1}H-NMR (DMSO d_6): 11.43 (s, 1H), 10.63 (s, 1H), 8.97 (br s, 2H), 8.94 (s, 1H), 8.60 (d, 1H), 8.39 (s, 1H), 7.94 (s, 1H), 7.59 (m, 1H), 7.50 (m, 1H), 7.38 (m, 1H), 7.31 (m, 2H), 6.92 (m, 1H), 5.13 (s, 2H), 4.25 (m, 2H), 3.43 (m, 1H), 3.33 (m, 1H), 3.25 (m, 1H), 3.11 (m, 1H), 2.84 (m, 1H), 2.17 (m, 1H), 1.83 (m, 1H);

MS (+ve ESI): 462 $(M+H)^+$.

tert-butyl 3-[({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)methyl]pyrrolidine-1-carboxylate used as starting material, was obtained as follows:

a) Methane sulphonyl chloride (0.39 ml, 5.0 mmol) was added dropwise to a solution of *tert*-butyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate (0.51 g, 2.5 mmol) and 4-(dimethylamino)pyridine (0.61 g, 5.0 mmol) in dichloromethane (15 ml). The mixture was stirred at room temperature for 30 minutes and then concentrated to approximately half volume and purified by silica gel chromatography. Elution with a mixture of 3 : 1 to 1 : 1 *iso*-hexane : ethyl acetate yielded *tert*-butyl 3-{[(methylsulphonyl)oxy]methyl}pyrrolidine-1-carboxylate.

^{1}H-NMR ($CDCl_3$): 4.16 (m, 2H), 3.28-3.61 (m, 3H), 3.15 (m, 1H), 3.03 (s, 3H), 2.63 (m, 1H), 2.05 (m, 1H), 1.74 (m, 1H), 1.47 (s, 9H).

b) A mixture of *N*-(3-fluorophenyl)-2-{4-[(7-hydroxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (0.59 g, 1.2 mmol), cesium carbonate (1.95 g, 6.0 mmol) and *tert*-butyl 3-{[(methylsulphonyl)oxy]methyl}pyrrolidine-1-carboxylate (assumed 1.3 mmol) in dimethyl acetamide (10 ml) was heated at 80°C for 6 hours. The mixture was poured into water and extracted with ethyl acetate. The organic layer was separated, washed with brine, dried over magnesium sulphate and evaporated *in vacuo*. The residue was purified by silica gel chromatography eluting with 4 to 7% methanol in dichloromethane to yield *tert*-butyl 3-[({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)methyl]pyrrolidine-1-carboxylate (0.435 g, 65% yield):

MS (+ve ESI): 562 $(M+H)^+$.

Example 199 – Preparation of compound 199 in table 5 - *N*-(3-fluorophenyl)-2-{4-[(7-{[1-(2-hydroxyethyl)pyrrolidin-3-yl]methoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

Sodium triacetoxyborohydride (0.23 g, 1.1 mmol) was added to a mixture of *N*-(3-fluorophenyl)-2-(4-{[7-(pyrrolidin-3-ylmethoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide bis(trifluoroacetate) (0.30 g, 0.44 mmol) and (*tert*-butyldimethylsilyloxy)acetaldehyde (0.20 ml, 1.0 mmol) in tetrahydrofuran (9 ml) and methanol (3 ml) containing a catalytic amount of acetic acid. The mixture was stirred at room temperature for 1 hour. The mixture was poured into sodium hydroxide solution (1M) and extracted with dichloromethane. The organic layer was separated, washed with brine, dried over magnesium sulphate and then evaporated to leave a brown oil which was purified by silica gel chromatography. Elution with 3 to 6% methanol in dichloromethane gave 2-{4-[(7-{[1-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)pyrrolidin-3-yl]methoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide.

MS (+ve ESI): 620 $(M+H)^+$.

A solution of tetra-butylammonium fluoride (1 M in tetrahydrofuran, 0.6 ml, 0.6 mmol) was added to a solution of the 2-{4-[(7-{[1-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)pyrrolidin-3-yl]methoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide in tetrahydrofuran (5 ml) and the mixture was stirred at room temperature for 4 hours. The solution was made acidic by the addition of acetic acid and then a solution of ammonia in methanol (7M, 1 ml) was added and the mixture was concentrated *in vacuo*. The residue was purified by silica gel chromatography, elution with 5

to 10% methanol and then 10% methanol containing 7M ammonia, gave the title compound as a colourless film which was dissolved in methanol (5 ml) and a solution of hydrogen chloride in diethyl ether (4M, 0.5 ml, 2.0 mmol) was added. The solvent was evaporated and the residue triturated with diethyl ether to leave a bright yellow solid which was purified by reverse phase chromatography to yield compound 199 in table 5 (0.041 g, 19% yield over 2 steps):

^{1}H-NMR (DMSO d_6): 10.52 (s, 1H), 9.92 (s, 1H), 8.55 (s, 1H), 8.36 (d, 1H), 8.34 (s, 1H), 7.78 (s, 1H), 7.58 (m, 1H), 7.35 (m, 2H), 7.23 (dd, 1H), 7.15 (d, 1H), 6.91 (m, 1H), 5.06 (s, 2H), 4.39 (m, 1H), 4.04 (m, 2H), 3.49 (m, 2H), 2.70 (m, 1H), 2.58 (m, 3H), 2.44 (m, 1H), 1.96 (m, 1H), 1.55 (m, 1H);

MS (+ve ESI): 506 $(M+H)^+$.

Example 200 – Preparation of compound 200 in table 5 - *N*-(3-fluorophenyl)-2-[4-({7-[(1-glycoloylpyrrolidin-3-yl)methoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide

Acetoxyacetyl chloride (0.025 ml, 0.23 mmol) was added to a solution of *N*-(3-fluorophenyl)-2-(4-{[7-(pyrrolidin-3-ylmethoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide bis(trifluoroacetate) (0.161 g, 0.23 mmol) and triethylamine (0.11 ml, 0.79 mmol) in tetrahydrofuran (5 ml) and the mixture was stirred at room temperature for 30 minutes. The mixture was evaporated and the residue was dissolved in methanol (5 ml). A solution of sodium hydroxide (2M, 0.5 ml) was added and the mixture stirred at room temperature for 2.5 hours. The mixture was evaporated and the residue sonicated in water (5 ml) and then filtered. The solid was purified by reverse phase chromatography eluting with a mixture of 5 to 95% acetonitrile (containing 0.2% trifluoroacetic acid) in water (containing 0.2% trifluoroacetic acid) to yield compound 200 in table 5 (0.026 g, 22% yield):

MS (+ve ESI): 520 $(M+H)^+$.

Example 201 – Preparation of compound 201 in table 5 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 186, but starting with 2-((2-methoxyethyl)amino)ethanol (0.931 g, 2 mmol) yielded compound 201 in table 5 (0.533 g, 49% yield) as a pale yellow solid:

^{1}H-NMR (DMSOd_6): 10.55 (s, 1H), 9.94 (s, 1H), 8.54 (s, 1H), 8.37 (d, 1H), 8.35 (s, 1H), 7.77 (s, 1H), 7.58 (d, 1H), 7.37 (m, 1H), 7.31 (d, 1H), 7.22 (m, 1H), 7.14 (m, 1H), 6.91 (m, 1H), 5.06 (s, 2H), 4.31 (m, 1H), 4.17 (t, 2H), 3.43 (m, 2H), 3.38 (m, 2H), 3.2 (s, 3H), 2.64 (m, 4H), 2.55 (m, 2H), 1.88 (t, 2H);

MS (+ve ESI): 538.19 $(M+H)^+$.

Example 202 – Preparation of compound 202 in table 5 - *N*-(3-fluorophenyl)-2-{4-[(7-hydroxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

A solution of 2-(4-{[7-(benzyloxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide hydrochloride (0.30 g, 0.59 mmol) in trifluoroacetic acid (4ml) was heated at reflux for 2 hours. The solvent was evaporated *in vacuo* and the residue triturated with diethyl ether to yield compound 202 in table 5 (0.295 g, 100% yield) as the trifluoroacetate salt:

^{1}H-NMR (DMSO d_6): 11.57 (br s, 1H), 11.38 (br s, 1H), 10.59 (br s, 1H), 8.89 (s, 1H), 8.50 (d, 1H), 8.34 (s, 1H), 7.91 (s, 1H), 7.57 (dt, 1H), 7.33 (m, 3H), 7.11 (m, 1H), 6.91 (m, 1H), 5.11 (s, 2H);

MS (+ve ESI): 379 $(M+H)^+$.

2-(4-{[7-(benzyloxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide used as starting material, was obtained as follows:

a) Benzyl alcohol (12.6 ml, 122 mmol) was added dropwise over 15 minutes to a slurry of sodium hydride (60% dispersion in mineral oil, 7.6 g, 190 mmol) in dimethylacetamide (100 ml) cooled in an ice-bath. The mixture was stirred at 0°C for 15 minutes and then 7-fluoroquinazolin-4(3*H*)-one (prepared as described in WO03/055491) (10.0 g, 61 mmol) was added portionwise over 15 minutes. The mixture was warmed to room temperature and then heated at 60°C for 15 hours and then at 80°C for 3 hours. The mixture was poured into water (600 ml) and made acidic (pH ~ 6) by the addition of concentrated hydrochloric acid. The resultant precipitate was filtered and washed with water to yield 7-(benzyloxy)quinazolin-4(3*H*)-one as a colourless solid (11.5 g, 75% yield):

^{1}H-NMR (DMSO d_6): 12.07 (br s, 1H), 8.03 (m, 2H), 7.49 (m, 2H), 7.38 (m, 3H), 7.18 (m, 2H), 5.27 (s, 2H);

MS (+ve ESI): 253 $(M+H)^+$.

b) A solution of 7-(benzyloxy)quinazolin-4(3*H*)-one (5.0 g, 19.8 mmol) in thionyl chloride (40ml) containing a catalytic amount of dimethylformamide was heated at 90°C for 2 hours. The solvent was concentrated *in vacuo* and the oily residue co-evaporated with toluene (2 x 100ml) to leave a yellow solid which was triturated with diethyl ether to yield 7-(benzyloxy)-4-chloroquinazoline (4.79g, 90% yield) as a pale yellow solid:
^{1}H-NMR (DMSO d_6): 8.96 (s, 1H), 8.17 (d, 1H), 7.53 (m, 4H), 7.39 (m, 3H), 5.36 (s, 2H);
MS (+ve ESI): 271 $(M+H)^+$.

c) A mixture of 7-(benzyloxy)-4-chloroquinazoline (1.94 g, 7.17 mmol) and 2-(4-amino-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide (1.66 g, 7.09 mmol) in dimethylacetamide (25 ml) was heated at 90°C for 1 hour. The mixture was cooled to room temperature and then diluted with diethyl ether (75 ml) and filtered. The solid was washed with diethyl ether and dried to yield 2-(4-{[7-(benzyloxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide hydrochloride (2.92 g, 82% yield) as a yellow solid:
^{1}H-NMR (DMSO d_6): 11.76 (br s, 1H), 10.74 (br s, 1H), 8.93 (s, 1H), 8.76 (d, 1H), 8.40 (s, 1H), 7.99 (s, 1H), 7.53 (m, 4H), 7.39 (m, 7H), 6.90 (m, 1H), 5.34 (s, 2H), 5.13 (s, 2H).
MS (+ve ESI): 469 $(M+H)^+$

Example 203 – Preparation of compound 203 in table 6 - *N*-(2-Fluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 186, but starting with 2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2-fluorophenyl)acetamide (0.240 g, 0.53 mmol) and (2R)-pyrrolidin-2-ylmethanol (0.201 g, 1.99 mmol) yielded compound 203 in table 6 (0.193 g, 70% yield):
^{1}H-NMR (DMSO d_6): 10.04 (s, 1H), 9.91 (s, 1H), 8.55 (s, 1H), 8.36 (d, 1H), 8.35 (s, 1H), 7.94 (m, 1H), 7.80 (s, 1H), 7.30 (m, 1H), 7.20 (m, 4H), 5.14 (s, 2H), 4.38 (s(br.), 1H), 4.21 (t, 2H), 3.42 (m, 2H), 3.15 (m, 3H), 2.25 (m, 1H), 2.55 (m partially obscured by DMSO, 1H), 2.00 (m, 2H), 1.86 (m, 1H), 1.72 (m, 2H), 1.62 (m, 1H);
MS (+ve ESI): 520 $(M+H)^+$.

2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2-fluorophenyl)acetamide used as starting material, was prepared as follows:

a) A solution of (4-nitro-1*H*-pyrazol-1-yl)acetic acid (2.0 g, 11.7 mmol) in toluene (40 ml) was heated to 80°C and then N,N-dimethylformamide di-*tert*-butyl acetal (7.0 g, 34.5 mmol) was added dropwise over 1 hour. The reaction mixture was heated at 80°C for a further 20 minutes and then allowed to cool to room temperature. The mixture was concentrated and the residue purified by silica gel chromatography eluting with 50% methyl *tert*-butyl ether in iso-hexane to give *tert*-butyl (4-nitro-1*H*-pyrazol-1-yl)acetate (2.21 g, 83% yield) as a colourless solid:

^{1}H-NMR ($CDCl_3$): 8.25 (s, 1H), 8.10 (s, 1H), 4.83 (s, 2H), 1.52 (s, 9H).

b) *Tert*-butyl (4-nitro-1*H*-pyrazol-1-yl)acetate (1.0 g, 4.40 mmol) and 10% palladium on carbon (0.100 g) in methanol (20 ml) were stirred under an atmosphere of hydrogen for 2 hours and then the mixture was filtered through Celite and the filtrate evaporated to give *tert*-butyl (4-amino-1*H*-pyrazol-1-yl)acetate

(0.860 g, 99% yield) as a dark orange, viscous oil:

^{1}H-NMR ($CDCl_3$): 7.20 (s, 1H), 7.06 (s, 1H), 4.67 (s, 2H), 2.92 (s, 2H), 1.48 (s, 9H).

c) A mixture of *tert*-butyl (4-amino-1*H*-pyrazol-1-yl)acetate (0.305 g, 1.55 mmol) and 4-chloro-7-(3-chloropropoxy)quinazoline (0.398 g, 1.55 mmol) in isopropanol (8 ml) was heated at 90°C for 5 minutes and then allowed to cool to room temperature. The mixture was diluted with diethyl ether and then filtered to give *tert*-butyl (4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetate as the hydrochloride salt (0.674 g, 96% yield):

^{1}H-NMR (DMSO d_6): 11.85 (s, 1H), 8.93 (s, 1H), 8.82 (d, 1H), 8.36 (s, 1H), 8.01 (s, 1H), 7.49 (dd, 1H), 7.37 (d, 1H), 5.03 (s, 2H), 4.33 (t, 2H), 3.86 (t, 2H), 2.28 (quintet, 2H);
MS (+ve ESI): 418 $(M+H)^+$.

d) A solution of *tert*-butyl (4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetate hydrochloride (7.33 g,16.1 mmol) in trifluoroacetic acid (60 ml) was stirred at room temperature for 30 minutes. The mixture was concentrated and the residue was suspended in water (120 ml), basified to pH 12 with 40% aqueous sodium hydroxide solution and then re-acidified to pH 4.8 with 2N aqueous hydrochloric acid to give (4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetic acid (5.74 g, 98% yield) as a cream coloured solid:

^{1}H-NMR (DMSO d_6): 11.10 (s, 1H), 8.70 (s, 1H), 8.50 (d, 1H), 8.31 (s, 1H), 7.83 (s, 1H), 7.34 (dd, 1H), 7.22 (d, 1H), 5.00 (s, 2H), 4.30 (t, 2H), 3.85 (t, 2H), 2.26 (quintet, 2H);
MS (+ve ESI): 362 $(M+H)^+$.

e) Pentafluorophenyl trifluoroacetate (0.325 g, 1.16 mmol) was added dropwise, at room temperature, to a stirred suspension of (4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetic acid (0.300 g, 0.83 mmol) and pyridine (0.092 g, 1.16 mmol) in dimethylformamide (3 ml). After stirring for 5 minutes 2-fluoroaniline (0.184 g, 1.66 mmol) was added and the reaction stirred for 5 hours. The mixture was poured into 0.2N aqueous hydrochloric acid (25 ml) to give 2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2-fluorophenyl)acetamide as a cream coloured solid:
MS (+ve ESI): 455 $(M+H)^+$.

Example 204 – Preparation of compound 204 in table 6 - 2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2-fluorophenyl)acetamide.

An analogous reaction to that described in example 203, but starting with 2-(ethylamino)ethanol (0.177 g, 1.99 mmol) yielded compound 204 in table 6 (0.178 g, 66% yield):
^{1}H-NMR (DMSO d_6): 10.05 (s, 1H), 9.90 (s, 1H), 8.55 (s, 1H), 8.37 (d, 1H), 8.35 (s, 1H), 7.94 (m, 1H), 7.79 (s, 1H), 7.28 (m, 1H), 7.20 (m, 4H), 5.15 (s, 2H), 4.35 (s(br.), 1H), 4.20 (t, 2H), 3.47 (m, 2H), 2.67 (m, 2H), 2.58 (m, 4H), 1.92 (m, 2H), 1.00 9t, 3H);
MS (+ve ESI): 508 $(M+H)^+$.

Example 205 – Preparation of compound 205 in table 6 - 2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-phenylacetamide.

An analogous reaction to that described in example 203, but starting with 2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-phenylacetamide (0.240 g, 0.55 mmol) and (2R)-pyrrolidin-2-ylmethanol (0.166 g, 1.64 mmol) yielded compound 205 in table 6 (0.201 g, 73% yield):
^{1}H-NMR (DMSO-d_6): 10.28 (s, 1H), 9.91 (s, 1H), 8.55 (s, 1H), 8.36 (d, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.61 (d, 2H), 7.34 (t, 2H), 7.23 (dd, 1H), 7.17 (d, 1H), 7.09 (t, 1H), 5.05 (s, 2H), 4.20 (t, 2H), 3.45 (m, 2H), 3.20 (m partially obscured by H_2O, 5H), 2.03 (m, 2H), 1.90 (m, 1H), 1.72 (m, 2H), 1.63 (m, 1H);
MS (+ve ESI): 502 $(M+H)^+$.

2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-phenylacetamide used as starting material, was prepared as follows:

Pentafluorophenyl trifluoroacetate (0.867 g, 3.10 mmol) was added dropwise, at room temperature, to a stirred suspension of (4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetic acid (0.800 g, 2.21 mmol) and pyridine (0.245 g, 3.10 mmol) in dimethylformamide (8 ml). After stirring for 5 minutes, aniline (0.412 g, 4.43 mmol) was added and the reaction mixture was stirred for 2 hours. The mixture was poured into dilute hydrochloric acid (0.2N, 25 ml) and the resultant solid filtered and then washed with water. The residue was stirred in dilute aqueous sodium hydroxide solution and filtered and the residue washed successively with water, methanol and diethylether to give 2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-phenylacetamide (0.520 g, 54% yield):

MS (+ve ESI): 437 $(M+H)^+$.

Example 206 – Preparation of example 206 in table 6 - 2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-phenylacetamide

An analogous reaction to that described in example 205, but starting with 2-(ethylamino)ethanol (0.147 g, 1.65 mmol) yielded compound 206 in table 6 (0.184 g, 68% yield):

^{1}H-NMR (DMSO d_6): 10.28 (s, 1H), 9.91 (s, 1H), 8.54 (s, 1H), 8.36 (d, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.60 (d, 2H), 7.33 (t, 2H), 7.23 (dd, 1H), 7.16 (d, 1H), 7.09 (t, 1H), 5.05 (s, 2H), 4.40 (s(br.), 1H), 4.20 (t, 2H), 3.52 (m, 2H), 2.65 (m, 6H), 1.94 (m, 2H), 1.03 T, 3H);

MS (+ve ESI): 490 $(M+H)^+$.

Example 207 – Preparation of compound 207 in table 6 - *N*-(2,6-difluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide.

An analogous reaction to that described in example 203, but starting with 2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,6-difluorophenyl)acetamide (0.280 g, 0.59 mmol) and (2R)-pyrrolidin-2-ylmethanol (0.180 g, 1.78 mmol) yielded compound 207 in table 6 (0.208 g, 65% yield):

^{1}H-NMR (DMSO d_6): 10.01 (s, 1H), 9.90 (s, 1H), 8.54 (s, 1H), 8.36 (d, 1H), 8.35 (s, 1H), 7.79 (s, 1H), 7.37 (m, 1H), 7.20 (m, 4H), 5.13 (s, 2H), 4.33 (s(br.), 1H), 4.20 (t,2H), 3.42 (m, 1H), 3.24 (m, 1H), 3.11 (m, 1H), 3.02 (m, 1H), 2.50 (m partially obscured by DMSO, 2H), 2.22 (m, 1H), 1.97 (m, 2H), 1.82 (m, 1H), 1.68 (m, 2H), 1.57 (m, 1H);
MS (+ve ESI): 538 $(M+H)^+$.

2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,6-difluorophenyl)acetamide used as starting material,l was prepared as follows:

a) 4-(4,6-dimethoxytriazin-2-yl)-4-methylmorpholinium chloride (0.391 g, 1.32 mmol) was added in one go, at room temperature, to a stirred suspension of (4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetic acid (0.400 g, 1.11 mmol) and 2,6-difluoroaniline (0.171 g, 1.32 mmol) in dimethylformamide (7 ml). The mixture was stirred for 2 hours and then poured into water (30 ml) the resultant solid was filtered to give 2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,6-difluorophenyl)acetamide (0.403 g, 77% yield) as a pale brown solid:
MS (+ve ESI): 473 (M+H).

Example 208 – Preparation of compound 208 in table 7 - 2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}-6-fluoroquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

A mixture of 2-(4-{[7-(3-chloropropoxy)-6-fluoroquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide (0.300 g, 0.63 mmol), 2-(ethylamino)ethanol (0.169 g, 1.90 mmol) and potassium iodide (0.211 g, 1.27 mmol) in dimethylacetamide (2 ml) was heated at 90°C for 90 minutes and then allowed to cool to room temperature. The resulting solution was diluted with dichloromethane and then purified directly by silica gel chromatography eluting with a mixture of 10% methanol in dichloromethane containing 0-4% 7N ammonia in methanol to give compound 208 in table 7 (0.203 g, 61% yield) as a pale yellow solid:
^{1}H-NMR (DMSO d_6): 10.52 (s, 1H), 9.85 (s, 1H), 8.58 (s, 1H), 8.34 (m, 2H), 7.77 (s, 1H), 7.59 (d, 1H), 7.40 (m, 2H), 7.33 (m, 1H), 6.92 (m, 1H), 5.33 (m, 1H), 5.08 (s, 2H), 4.35 (m, 2H), 3.74 (m, 2H), 3.25 (m (partially obscured by H_2O), 6H), 2.22 (m, 2H), 1.23 (m, 3H);
MS (+ve ESI): 526 $(M+H)^+$.

Example 209 – Preparation of compound 209 in table 7 - 2-{4-[(7-{3-[(cyclopropylmethyl)(2-hydroxyethyl)amino]propoxy}-6-fluoroquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

An analogous reaction to example 208, but starting with 2-(4-{[7-(3-chloropropoxy)-6-fluoroquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide (0.300 g, 0.61 mmol) and 2-[(cyclopropylmethyl)amino]ethanol (0.211 g, 1.83 mmol) yielded compound 209 in table 7 (0.210 g, 60% yield):

^{1}H-NMR (DMSO d_6): 10.28 (s, 1H), 9.83 (s, 1H), 8.58 (s, 1H), 8.35 (s, 1H), 8.32 (d, 1H), 7.78 (s, 1H), 7.73 (m, 1H), 7.36 (d, 1H), 7.21 (m, 2H), 5.17 (s, 2H), 4.30 (m, 3H), 3.49 (m, 2H), 2.71 (t,2H), 2.61 (t, 2H), 2.37 (d, 2H), 1.94 (quintet, 2H), 0.85 (m, 1H), 0.42 (m, 2H), 0.09 (m, 2H);

MS (+ve ESI): 570 $(M+H)^+$.

Example 210 – Preparation of compound 210 in table 7 -*N*-(2,3-difluorophenyl)-2-{4-[(6-fluoro-7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide.

An analogous reaction to example 209, but starting with 2-(propylamino)ethanol (0.189 g, 1.83 mmol) yielded compound 210 in table 7 (0.195 g, 57% yield):

^{1}H-NMR (DMSO d_6): 10.27 (s, 1H), 9.81 (s, 1H), 8.56 (s, 1H), 8.33 (s, 1H), 8.31 (d, 1H), 7.78 (s, 1H), 7.72 (m, 1H), 7.34 (d, 1H), 7.20 (m, 2H), 5.15 (s, 2H), 4.28 (m, 3H), 3.43 (m, 2H), 2.61 (t, 2H), 2.50 (m (partially obscured by DMSO), 2H), 2.40 (t, 2H), 1.91 (quintet, 2H), 1.41 (m, 2H), 0.81 (t, 3H);

MS (+ve ESI): 558 $(M+H)^+$.

Example 211 – Preparation of compound 211 in table 7 -*N*-(2,3-difluorophenyl)-2-{4-[(6-fluoro-7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to example 209, but starting with (2R)-pyrrolidin-2ylmethanol (0.310 g, 3.06 mmol) yielded compound 211 in table 7 (0.324 g, 57% yield):

^{1}H-NMR (DMSO d_6): 10.28 (s, 1H), 9.82 (s, 1H), 8.56 (s, 1H), 8.33 (s, 1H), 8.30 (d, 1H), 7.78 (s, 1H), 7.72 (m, 1H), 7.35 (d, 1H), 7.20 (m, 2H), 5.16 (s, 2H), 4.28 (m, 3H), 3.40 (m, 1H), 3.20 (m, 1H), 3.10 (m, 1H), 2.99 (m, 1H), 2.43 (m, 2H), 2.18 (m, 1H), 1.97 (m, 2H), 1.81 (m, 1H), 1.63 (m, 2H), 1.55 (m, 1H);

MS (+ve ESI): 556 $(M+H)^+$.

Example 212 – Preparation of compound 212 in table 7 - 2-{4-[(7-{3-[cyclopentyl(2-hydroxyethyl)amino]propoxy}-6-fluoroquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

An analogous reaction to example 209, but starting with 2-(cyclopentylamino)ethanol (0.237 g, 1.83 mmol) yielded compound 212 in table 7 (0.241 g, 67% yield):

^{1}H-NMR (DMSO d_6): 10.28 (s, 1H), 9.81 (s, 1H), 8.56 (s, 1H), 8.33 (s, 1H), 8.31 (d, 1H), 7.78 (s, 1H), 7.72 (m, 1H), 7.35 (d, 1H), 7.20 (m, 2H), 5.16 (s, 2H), 4.28 (m, 3H), 3.42 (m, 2H), 3.06 (quintet, 1H), 2.67 (t, 2H), 2.55 (m, 2H), 1.92 (quintet, 2H), 1.72 (m, 2H), 1.56 (m, 2H), 1.48 (m, 2H), 1.33 (m, 2H);

MS (+ve ESI): 584 $(M+H)^+$.

Example 213 – Preparation of compound 213 in table 8 - 2-{4-[(7-{3-[bis(2-hydroxyethyl)amino]propoxy}-5-isopropoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

A mixture of sodium iodide (9.9mg, 0.66 mmol), 2,2'-iminodiethanol (60 µl, 0.66 mmol) and 2-(4-{[7-(3-chloropropoxy)-5-isopropoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide (117 mg, 0.22 mmol) in dimethylacetamide (5 ml) was heated at 90°C for 1 hour. The mixture was evaporated under reduced pressure and the residue purified by silica gel chromatography eluting with a 0 to 10% mixture of methanol (containing 10% 7N ammonia in methanol) in dichloromethane to give compound 213 in table 8 (28 mg, 21% yield) as a white solid:

^{1}H-NMR ($CDCl_3$): 9.82 (s, 1H), 8.80 (br s, 1H), 8.54 (s, 1H), 8.42 (s, 1H), 8.04 (t, 1H), 7.70 (s, 1H), 7.08 (m, 1H), 6.98 (d, 1H), 6.85 (m, 1H), 6.44 (s, 1H), 5.01 (s, 2H), 4.86 (septet, 1H), 4.22 (t, 2H), 3.70 (m, 2H), 2.67 (m, 8H), 2.00 (t, 2H), 1.60 (d, 6H);

MS (+ve ESI): 600 $(M+H)^+$

MS (-ve ESI): 598 $(M-H)^-$.

Example 214 – Preparation of compound 214 in table 8 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-5-isopropoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 213, but starting with (2R)-pyrrolin-2-ylmethanol (30 µl, 0.30 mmol) yielded compound 214 in table 8 (135 mg, 76% yield):

^{1}H-NMR (DMSO d_6): 10.01 (s, 1H), 9.85 (s, 1H), 8.62 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.68 (m, 1H), 7.20 (m, 2H), 6.78 (s, 1H), 6.64 (s, 1H), 5.12 (s, 2H), 4.96 (septet, 1H), 4.22 (t, 2H), 3.80 (dd, 1H), 3.62 (m, 4H), 3.25 (m, 2H), 2.10 (m, 6H), 1.50 (d, 6H);

MS (+ve ESI): 596 $(M+H)^+$

MS (-ve ESI): 594 $(M-H)^-$.

Example 215 – Preparation of compound 215 in table 8 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy}-5-isopropoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 213, but starting with N-(2-hydroxyethyl)piperazine (0.17 ml, 1.41 mmol) yielded compound 215 in table 8 (40 mg, 23% yield):

^{1}H-NMR (DMSO d_6): 10.20 (s, 1H), 9.98 (s, 1H), 8.62 (s, 1H), 8.35 (s, 1H), 7.82 (s, 1H), 7.65 (m, 1H), 7.18 (m, 2H), 6.85 (s, 1H), 6.80 (s, 1H), 5.18 (s, 2H), 4.99 (septet, 1H), 4.22 (t, 2H), 3.70 (m, 2H), 3.18 (m,4H), 3.05 (m, 2H), 2.90 (m, 2H), 2.82 (m, 2H), 2.10 (m, 2H), 2.05 (quintet, 2H), 1.50 (d, 6H);

MS (+ve ESI): 625 $(M+H)^+$

MS (-ve ESI): 623 $(M-H)^-$.

Example 216 – Preparation of compound 216 in table 8 - *N*-(2,3-difluorophenyl)-2-(4-{[5-isopropoxy-7-(3-piperazin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide

An analogous reaction to that described in example 213, but starting with piperazine (97 mg, 1.13 mmol) yielded compound 216 in table 8 (60 mg, 27% yield):

^{1}H-NMR (DMSO d_6): 9.98 (br s, 1H), 9.70 (s, 1H), 8.45 (s, 1H), 8.30 (s, 1H), 7.75 (s, 1H), 7.70 (t, 1H), 7.88 (m, 2H), 6.80 (s, 1H), 6.65 (s, 1H), 5.18 (s, 2H), 4.90 (septet, 1H), 4.18 (t, 2H), 3.00 (m, 10H), 2.60 (t, 2H), 1.50 (d, 6H);

MS (+ve ESI): 581 $(M+H)^+$

MS (-ve ESI): 579 $(M-H)^-$.

Example 217 – Preparation of compound 217 in table 8 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-5-isopropoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 213, but starting with (2S)-pyrrolin-2-ylmethanol (0.17 ml, 1.9 mmol) yielded compound 217 in table 8 (150 mg, 66% yield):

^{1}H-NMR (DMSO- $_6$): 10.01 (s, 1H), 9.85 (s, 1H), 8.62 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.68 (m, 1H), 7.20 (m, 2H), 6.78 (s, 1H), 6.64 (s, 1H), 5.12 (s, 2H), 4.96 (septet, 1H), 4.22 (t, 2H), 3.80 (dd, 1H), 3.62 (m, 4H), 3.25 (m, 2H), 2.10 (m, 6H), 1.50 (d, 6H);

MS (+ve ESI): 596 $(M+H)^+$

MS (-ve ESI): 594 $(M-H)^-$.

Example 218 – Preparation of compound 218 in table 8 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)amino]propoxy}-5-isopropoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 213, but starting with ethanolamine (0.11 ml, 1.9 mmol) yielded compound 218 in table 8 (282 mg, 80% yield):

^{1}H-NMR (DMSO d_6): 9.72 (s, 1H), 8.42 (s, 1H), 8.30 (s, 1H), 7.72 (s, 1H), 7.62 (m, 1H), 7.10 (m, 2H), 6.78 (s, 1H), 6.70 (s, 1H), 5.12 (s, 2H), 4.93 (septet, 1H), 4.20 (t, 2H), 3.45 (t, 2H), 2.90 (t, 2H), 2.78 (t, 2H), 2.02 (quintet, 2H), 1.52 (d, 6H);

MS (+ve ESI): 556 $(M+H)^+$

MS (-ve ESI): 554 $(M-H)^-$.

Example 219 – Preparation of compound 219 in table 8 - *N*-(2,3-difluorophenyl)-2-[4-({7-[3-(4-glycoloylpiperazin-1-yl)propoxy]-5-isopropoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide

A mixture of glycolic acid (5 mg, 0.07 mmol), di-*iso*-propylethylamine (0.02 ml, 0.14 mmol) and *N*-(2,3-difluorophenyl)-2-(4-{[5-isopropoxy-7-(3-piperazin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide (40 mg, 0.07 mmol) in dichloromethane (5 ml) was stirred at room temperature for 10 minutes. *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (30 mg, 0.08 mmol) was added and the reaction mixture was stirred at room temperature for 1 hour. The volatiles were removed by evaporation under reduced pressure and the residue purified by silica gel chromatography eluting with a 0 to 10% mixture of methanol (containing 10% 7N ammonia in methanol) in dichloromethane to give compound 219 in table 8 (30 mg, 67% yield):

^{1}H-NMR (DMSO d_6): 9.98 (br s, 1H), 9.70 (s, 1H), 8.42 (s, 1H), 8.22 (s, 1H), 7.75 (s, 1H), 7.70 (m, 1H), 7.20 (m, 2H), 6.75 (s, 1H), 6.62 (s, 1H), 5.05 (s, 2H), 4.98 (septet, 1H), 4.15 (t, 2H), 4.04 (s, 1H), 3.35 (app.s, 2H), 3.02 (m, 8H), 2.40 (m, 2H), 1.98 (m, 2H), 1.50 (d, 6H);
MS (+ve ESI): 639 $(M+H)^+$
MS (-ve ESI): 638 $(M-H)^-$.

Example 220 – Preparation of compound 220 in table 8 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-5-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

A mixture of potassium iodide (0.120 g, 0.8 mmol), (2*R*)-pyrrolidin-2-ylmethanol (0.080 ml, 0.8 mmol) and 2-(4-{[7-(3-chloropropoxy)-5-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide (0.200 g, 0.4 mmol) in dimethylacetamide (5 ml) was heated at 90°C for 1 hour. The mixture was evaporated under reduced pressure and the residue purified by silica gel chromatography eluting with a 0 to 10% mixture methanol (containing 10% 7N ammonia in methanol) in dichloromethane to give compound 220 in table 8 (0.070 g, 31% yield) as a white solid:

^{1}H-NMR (DMSO d_6): 10.20 (s, 1H), 9.98 (s, 1H), 8.65 (s, 1H), 8.25 (s, 1H), 7.88 (s, 1H), 7.68 (m, 1H), 7.18 (m, 2H), 6.78 (s, 1H), 6.72 (s, 1H), 5.05 (s, 2H), 4.25 (t, 2H), 4.15 (s, 3H), 3.80 (m, 1H), 3.52 (m, 2H), 2.15 (m, 10H);
MS (+ve ESI): 568 $(M+H)^+$.

Example 221 – Preparation of compound 221 in table 8 - *N*-(2,3-difluorophenyl)-2-{4-[(5,7-dimethoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

Phosphoryl chloride (1 ml, 10.8 mmol) was added to a solution of 5,7-dimethoxyquinazolin-4-ol (0.653 g, 3.17 mmol) and di-*iso*-propylethylamine (3.75 ml, 21.6 mmol) in 1,2-dichloroethane (40 ml) and the reaction was heated at 80°C for 4 hours. The mixture was evaporated under reduced pressure and the residue suspended in dimethylacetamide (20 ml) and then 2-(4-amino-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide (0.799 g, 3.17 mmol) was added and the mixture was heated at 90°C for 1 hour. The mixture was evaporated under reduced pressure and the residue triturated with diethyl ether to give compound 221 in table 8 (1.1 g, 79% yield):
^{1}H-NMR (DMSO d_6): 8.80 (s, 1H), 8.38 (s, 1H), 7.98 (s, 1H), 7.68 (m, 1H), 7.18 (m, 2H), 6.98 (s, 2H), 5.20 (s, 2H), 4.18 (s, 3H), 3.98 (s, 3H);
MS (+ve ESI): 441 $(M+H)^+$.

Example 222 – Preparation of compound 222 in table 8 - *N*-(2,3-difluorophenyl)-2-{4-[(5-hydroxy-7-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

Pyridine hydrochloride (0.027 g, 0.23 mmol) was added to a solution of *N*-(2,3-difluorophenyl)-2-{4-[(5,7-dimethoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (0.100 g, 0.23 mmol) in pyridine (2 ml) and the reaction was heated at 120°C for 24 hours. The mixture was evaporated under reduced pressure and the residue purified by reverse phase chromatography eluting with 0.2% aqueous trifluoroacetic acid in acetonitrile using a 5 to 50% gradient over 25 minutes. The fractions containing product were concentrated under reduced pressure and then basified with aqueous sodium carbonate. The resultant solid was filtered and washed with water to give compound 222 in table 8 (0.050 g, 32% yield):
^{1}H-NMR (DMSO d_6): 9.95 (s, 1H), 8.50 (s, 1H), 8.20 (s, 1H), 7.80 (s, 1H), 7.68 (m, 1H), 7.18 (m, 2H), 6.65 (s, 1H), 6.62 (s, 1H), 5.10 (s, 2H), 3.92 (s, 3H);
MS (+ve ESI): 427 $(M+H)^+$.

Example 223 – Preparation of compound 223 in table 8 - *N*-(2,3-difluorophenyl)-2-[4-({7-methoxy-5-[(2*R*)-pyrrolidin-2-ylmethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide

A mixture of *tert*-butyl (2*R*)-2-[({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-7-methoxyquinazolin-5-yl}oxy)methyl]pyrrolidine-1-carboxylate (0.430 g, 0.70 mmol) and trifluoroacetic acid (3 ml) in dichloromethane (15 ml) was stirred at room temperature for 1 hour. The reaction mixture was evaporated under reduced pressure and the residue was then triturated with diethyl ether to give compound 223 in table 8 (0.370 g, 100% yield) as the di-trifluoroacetic acid salt:

^{1}H-NMR (DMSO d_6): 9.95 (br s, 1H), 8.59 (s, 1H), 8.32 (s, 1H), 7.80 (s, 1H), 7.65 (m, 1H), 7.20 (m, 2H), 6.88 (s, 1H), 6.82 (s, 1H), 5.15 (s, 2H), 4.60 (m, 2H), 4.20 (m, 1H), 4.00 (s, 3H), 3.35 (t, 2H), 2.05 (m, 4H);

MS (+ve ESI): 510 $(M+H)^+$.

tert-butyl (2*R*)-2-[({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-7-methoxyquinazolin-5-yl}oxy)methyl]pyrrolidine-1-carboxylate used as starting material, was prepared as follows:

a) *tert*-butyl (2*R*)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (1.70 g, 8.6 mmol) was added to a solution of [7-(benzyloxy)-5-hydroxy-4-oxoquinazolin-3(4*H*)-yl]methyl pivalate (see WO01/094341, 3.0 g, 7.8 mmol) and PS-triphenylphosphine (1.5 mmol/g, 7.2 g, 4.2 mmol) in dichloromethane (120 ml). The reaction mixture was cooled to 0°C and then a solution of di-*tert*-butylazodicarboxylate (2.1 g, 9.3 mmol) in dichloromethane (15 ml) was added dropwise over 30 minutes. The mixture was allowed to warm to room temperature and then stirred for 2 hours. The mixture was evaporated under reduced pressure and the residue was purified by silica gel chromatography eluting with a 0 to 10% mixture methanol in dichloromethane to give *tert*-butyl (2*R*)-2-{[(7-(benzyloxy)-3-{[(2,2-dimethylpropanoyl)oxy]methyl}-4-oxo-3,4-dihydroquinazolin-5-yl)oxy]methyl}pyrrolidine-1-carboxylate (1.58 g, 36% yield):

^{1}H-NMR (DMSO d_6): 8.60 (s, 1H), 8.35 (s, 1H), 7.40 (m, 5H), 6.78 (s, 1H), 5.80 (s, 2H), 5.22 (s, 2H), 4.88 (m, 1H), 4.15 (m, 4H), 2.05 (m, 4H), 1.38 (s, 9H);

MS (+ve ESI): 566 $(M+H)^+$.

b) Ammonium formate (1.80 g, 28 mmol) and 10% palladium on carbon (0.180 g) were added to a solution of *tert*-butyl (2*R*)-2-{[(7-(benzyloxy)-3-{[(2,2-

dimethylpropanoyl)oxy]methyl}-4-oxo-3,4-dihydroquinazolin-5-yl)oxy]methyl}pyrrolidine-1-carboxylate (1.58 g, 2.8 mmol) in ethyl acetate (30 ml) and the mixture stirred at 70°C for 24 hours. The mixture was filtered through Celite and then evaporated under reduced pressure. The residue was purified by silica gel chromatography eluting with a 0 to 10% mixture methanol in dichloromethane to give *tert*-butyl (2*R*)-2-{[(3-{[(2,2-dimethylpropanoyl)oxy]methyl}-7-hydroxy-4-oxo-3,4-dihydroquinazolin-5-yl)oxy]methyl}pyrrolidine-1-carboxylate (0.750 g, 52% yield):

^{1}H-NMR (DMSO d_6): 10.35 (s, 1H), 9.92 (s, 1H), 8.59 (s, 1H), 8.25 (s, 1H), 7.90 (s, 1H), 7.75 (m, 1H), 7.15 (m, 2H), 6.85 (m, 2H), 5.12 (s, 2H), 4.48 (m, 2H), 4.20 (m, 1H), 3.97 (s, 3H), 3.35 (m, 2H), 2.05 (m, 4H), 1.40 (s, 9H);

MS (+ve ESI): 476 $(M+H)^+$.

c) Potassium carbonate (1.60 g, 12.6 mmol) was added to a solution of *tert*-butyl (2*R*)-2-{[(3-{[(2,2-dimethylpropanoyl)oxy]methyl}-7-hydroxy-4-oxo-3,4-dihydroquinazolin-5-yl)oxy]methyl}pyrrolidine-1-carboxylate (1.50 g, 3.2 mmol) in dimethylformamide (10 ml) and the mixture stirred at 0°C for 5 minutes. Dimethyl sulphate (0.6 ml, 6.3 mmol) was added and the reaction stirred at 0°C for a further 5 minutes and then warmed to room temperature and stirred for 1 hour. The reaction mixture was evaporated under reduced pressure and the residue dissolved in dichloromethane (20 ml) and washed with water (2 x 20 ml). The organics were dried over magnesium sulphate, filtered and evaporated under reduced pressure to give *tert*-butyl (2*R*)-2-{[(3-{[(2,2-dimethylpropanoyl)oxy]methyl}-7-methoxy-4-oxo-3,4-dihydroquinazolin-5-yl)oxy]methyl}pyrrolidine-1-carboxylate (0.750 g, 48% yield) which was used in the next stage without further purification.

d) *tert*-butyl (2*R*)-2-{[(3-{[(2,2-dimethylpropanoyl)oxy]methyl}-7-methoxy-4-oxo-3,4-dihydroquinazolin-5-yl)oxy]methyl}pyrrolidine-1-carboxylate (0.750 g, 1.5 mmol) was stirred in a 7N solution of ammonia in methanol (250 ml) at room temperature for 24 hours. The mixture was evaporated under reduced pressure to give *tert*-butyl (2*R*)-2-{[(7-methoxy-4-oxo-3,4-dihydroquinazolin-5-yl)oxy]methyl}pyrrolidine-1-carboxylate (0.560 g, 100% yield) which was used in the next stage without further purification.

e) Phosphoryl chloride (0.27 ml, 2.94 mmol) was added to a solution of *tert*-butyl (2*R*)-2-{[(7-methoxy-4-oxo-3,4-dihydroquinazolin-5-yl)oxy]methyl}pyrrolidine-1-carboxylate (0.550 g, 1.47 mmol) and di-*iso*-propylethylamine (1.02 ml, 5.88 mmol) in 1,2-dichloroethane (20 ml) and the reaction was heated at 80°C for 1 hour. The mixture was evaporated under reduced pressure and the residue suspended in dimethylacetamide (10 ml) and then 2-(4-

amino-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide (0.370 g, 1.47 mmol) was added and the mixture was heated at 90°C for 1 hour. The mixture was evaporated under reduced pressure and the residue stirred in a 7N solution of ammonia in methanol (100 ml) at ambient temperature for 2 hours. The mixture was evaporated under reduced pressure to leave a yellow solid which was stirred in water (50 ml) for 1 hour and then filtered and the residue purified by silica gel chromatography eluting with a 0 to 10% mixture methanol in dichloromethane to give *tert*-butyl (2*R*)-2-[({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-7-methoxy-3,4-dihydroquinazolin-5-yl}oxy)methyl]pyrrolidine-1-carboxylate (0.400 g, 44% yield over 3 steps):

^{1}H-NMR (DMSO d_6): 10.35 (s, 1H), 9.92 (s, 1H), 8.59 (s, 1H), 8.25 (s, 1H), 7.90 (s, 1H), 7.75 (m, 1H), 7.15 (m, 2H), 6.85 (m, 2H), 5.12 (s, 2H), 4.48 (m, 2H), 4.20 (m, 1H), 3.97 (s, 3H), 3.35 (m, 2H), 2.05 (m, 4H), 1.40 (s, 9H);

MS (+ve ESI): 610 $(M+H)^+$.

Example 224 – Preparation of compound 224 in table 8 - *N*-(2,3-difluorophenyl)-2-{4-[(5-{[(2*R*)-1-glycoloylpyrrolidin-2-yl]methoxy}-7-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

A mixture of glycolic acid (0.049 g, 0.16 mmol), di-*iso*-propylethylamine (0.08 ml, 0.48 mmol) and *N*-(2,3-difluorophenyl)-2-[4-({7-methoxy-5-[(2R)-pyrrolidin-2-ylmethoxy]quinazolin-4-yl}amino}-1*H*-pyrazol-1-yl]acetamide (example 223 in table 8, 0.100 g, 0.16 mmol) in dichloromethane (5 ml) was stirred at room temperature for 10 minutes. *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.068 g, 0.18 mmol) was added and the reaction mixture was stirred at room temperature for 1 hour. The volatiles were removed by evaporation under reduced pressure and the residue purified by silica gel chromatography eluting with a 0 to 10% mixture methanol (containing 10% 7N ammonia in methanol) in dichloromethane to give compound 224 in table 8 (0.030 g, 33% yield):

^{1}H-NMR (DMSO d_6): 9.65 (br s, 1H), 8.40 (s, 1H), 8.28 (s, 1H), 7.85 (s, 1H), 7.70 (m, 1H), 7.15 (m, 2H), 6.78 (s, 2H), 5.02 (s, 2H), 4.60 (m, 1H), 4.45 (m, 1H), 4.25 (m, 1H), 4.10 (m, 2H), 3.88 (s, 3H), 3.45 (m, 2H), 2.05 (m, 4H);

MS (+ve ESI): 568 $(M+H)^+$.

Example 225 – Preparation of compound 225 in table 8 - *N*-(2,3-difluorophenyl)-2-{4-[(5-{[(2*R*)-1-(*N*,*N*-dimethylglycyl)pyrrolidin-2-yl]methoxy}-7-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

A mixture of *N*,*N*-dimethylglycine (0.019 g, 0.18 mmol), di-*iso*-propylethylamine (0.08 ml, 0.48 mmol) and *N*-(2,3-difluorophenyl)-2-[4-({7-methoxy-5-[(2R)-pyrrolidin-2-ylmethoxy]quinazolin-4-yl}amino}-1*H*-pyrazol-1-yl]acetamide (example 223 in table 8, 0.100 g, 0.16 mmol) in dichloromethane (5 ml) was stirred at room temperature for 10 minutes. *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (0.068 g, 0.18 mmol) was added and the reaction mixture was stirred at room temperature for 1 hour. The volatiles were removed by evaporation under reduced pressure and the residue purified by silica gel chromatography eluting with a 0 to 10% mixture methanol (containing 10% 7N ammonia in methanol) in dichloromethane to give compound 225 in table 8 (0.040 g, 42% yield):

^{1}H-NMR (DMSO d_6): 8.42 (s, 1H), 8.32 (s, 1H), 7.85 (s, 1H), 7.68 (m, 1H), 7.15 (m, 2H), 6.78 (s, 1H), 6.72 (s, 1H), 5.02 (s, 2H), 4.60 (m, 1H), 4.45 (m, 1H), 4.25 (m, 1H), 3.85 (s, 3H), 3.52 (m, 2H), 2.64 (s, 2H), 2.58 (s, 6H), 2.05 (m, 4H);
MS (+ve ESI): 595 $(M+H)^+$.

Example 226 – Preparation of compound 226 in table 8 - *N*-(2,3-difluorophenyl)-2-{4-[(5-{[(2*R*)-1-(2-hydroxyethyl)pyrrolidin-2-yl]methoxy}-7-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

A mixture of hydroxyacetaldehyde (0.009 g, 0.14 mmol), *N*-(2,3-difluorophenyl)-2-[4-({7-methoxy-5-[(2R)-pyrrolidin-2-ylmethoxy]quinazolin-4-yl}amino}-1*H*-pyrazol-1-yl]acetamide (example 223 in table 8, 0.070 g, 0.14 mmol), acetic acid (0.010 ml, 0.14 mmol) and MP-cyanoborohydride (2mmol/g, 0.100 g, 0.21 mmol) in methanol (10 ml) was stirred at room temperature for 2 hour. The reaction mixture was filtered and evaporated under reduced pressure and the residue was then purified by reverse phase chromatography eluting with 0.2% aqueous trifluoroacetic acid in acetonitrile using a 5 to 50% gradient over 25 minutes. The fractions containing product were concentrated under reduced pressure and then basified with aqueous sodium carbonate. The resultant solid was filtered and washed with water to give compound 226 in table 8 (0.024 g, 31% yield):

^{1}H-NMR (DMSO d_6): 10.00 (s, 1H), 9.78 (s, 1H) 8.58 (s, 1H), 8.30 (s, 1H), 7.75 (s, 1H), 7.65 (m, 1H), 7.15 (m, 2H), 6.82 (m, 2H), 5.12 (s, 2H), 4.30 (d, 2H), 3.98 (s, 3H), 3.80 (t, 2H), 3.52 (m, 2H), 3.42 (q, 2H), 3.15 (m, 4H), 1.85 (m, 2H);
MS (+ve ESI): 554 $(M+H)^+$.

Example 227 – Preparation of compound 227 in table 8 - *N*-(2,3-difluorophenyl)-2-{4-[(5-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

Phosphoryl chloride (0.5 ml, 5.3 mmol) was added to a solution of 5-methoxyquinazolin-4-ol (see WO96/09294, 0.300 g, 1.7 mmol) and di-*iso*-propylethylamine (2.20 ml, 12.9 mmol) in 1,2-dichloroethane (20 ml) and the reaction was heated at 80°C for 4 hours. The mixture was evaporated under reduced pressure and the residue suspended in dimethylacetamide (20 ml) and then 2-(4-amino-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide (0.428 g, 1.7 mmol) was added and the mixture was heated at 90°C for 1 hour. The mixture was evaporated under reduced pressure and the residue was purified by silica gel chromatography eluting with a 0 to 10% mixture methanol in dichloromethane to give compound 227 in table 8 (0.080 g, 11% yield):
^{1}H-NMR (DMSO d_6): 10.40 (s, 1H), 9.98 (s, 1H), 8.75 (s, 1H), 8.25 (s, 1H), 7.90 (s, 1H), 7.80 (t, 1H), 7.65 (m, 1H), 7.35 (d, 1H), 7.20 (d, 1H), 7.08 (m, 2H), 5.20 (s, 2H), 4.15 (s, 3H);
MS (+ve ESI): 411 $(M+H)^+$.

Example 228 – Preparation of compound 228 in table 8 *N*-(2,3-difluorophenyl)-2-{4-[(5-fluoroquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

2-(4-Amino-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide (1.5 g, 6 mmol) was added to a solution of 4-chloro-5-fluoroquinazoline (see WO01/094341, 1.0 g, 5.5 mmol) in isopropanol (40 ml) and the mixture was then heated at 80°C for 1 hour. The resultant solid was filtered and then washed with isopropanol to give compound 228 in table 8 (1.95 g, 89% yield):
^{1}H-NMR (DMSO d_6): 10.70 (br s, 1H), 10.48 (br s, 1H) 8.98 (s, 1H), 8.40 (s, 1H), 8.05 (m, 2H), 7.80 (d, 1H), 7.62 (m, 2H), 7.18 (m, 2H), 5.22 (s, 2H);
MS (+ve ESI): 399 $(M+H)^+$.

Example 229 – Preparation of compound 229 in table 9 - *N*-(3-fluorophenyl)-2-(4-{[7-methoxy-6-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide.

A mixture of 4-chloro-7-methoxy-6-(3-morpholin-4-ylpropoxy)quinazoline (120 mg, 0.35 mmol), 2-(4-amino-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide (83 mg, 0.35 mmol) and hydrogen chloride (100ul of a 4M solution in 1,4-dioxane) in dimethylacetamide (2.0 ml) was heated at 90°C for 2 hours and then allowed to cool to room temperature. The mixture was diluted with diethyl ether, filtered and washed with diethyl ether to give compound 229 in table 9 as the hydrochloride salt (222 mg) as a pale yellow solid:

^{1}H-NMR (DMSO d_6): 12.07 (s, 1H), 10.84 (br s), 1H), 10.76 (s, 1H), 8.91 (s, 1H), 8.63 (s, 1H), 8.46 (s, 1H), 8.13 (s, 1H), 7.60 (m, 1H), 7.36 (m, 3H), 6.92 (m, 1H), 5.15 (s, 2H), 4.41 (t, 2H), 4.00 (s, 3H), 3.98 (m, 2H), 3.83 (m, 2H), 3.52 (m, 2H), 3.34 (m, 2H partially obscured by H_2O), 3.16 (m, 2H), 2.33 (quintet, 2H);

MS (+ve ESI): 536 $(M+H)^+$.

4-Chloro-7-methoxy-6-(3-morpholin-4-ylpropoxy)quinazoline used as starting material, was prepared as follows:

a) Di-*tert*-butyl azodicarboxylate (1.44 g, 6.26 mmol) was added portionwise at room temperature to a stirred suspension of 4-chloro-7-methoxyquinazolin-6-ol (1.20 g, 5.70 mmol), 3-morpholin-4-ylpropan-1-ol (0.91 g, 6.27 mmol) and triphenylphosphine (1.8 g, 6.87 mmol) in dichloromethane (25 ml). The reaction mixture was stirred for 2 hours and then the resulting orange solution was purified directly by silica gel chromatography eluting with a mixture of 5% methanol in dichloromethane to give 4-chloro-7-methoxy-6-(3-morpholin-4-ylpropoxy)quinazoline (1.28 g, 67% yield) as a pale yellow solid:

^{1}H-NMR ($CDCl_3$): 8.86 (s, 1H), 7.40 (s, 1H), 7.31 (s, 1H), 4.28 (t, 2H), 4.05 (s, 3H), 3.73 (m, 4H), 2.60 (t, 2H), 2.50 (m, 4H), 2.13 (quintet, 2H);

MS (+ve ESI): 338 $(M+H)^+$.

Example 230 – Preparation of compound 230 in table 9 - *N*-(3-fluorophenyl)-2-[4-({7-methoxy-6-[(1-methylpyrrolidin-3-yl)oxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide.

An analogous reaction to that described in example 229 but starting with 4-chloro-7-methoxy-6-[(1-methylpyrrolidin-3-yl)oxy]quinazoline (120 mg, 0.41 mmol) yielded compound 230 in table 9 as the hydrochloride salt (221 mg) as a pale yellow solid:
^{1}H-NMR (DMSO d_6): 12.52(s) & 12.28(s) (1H), 11.10(s) & 10.55(s) (1H), 10.75 (s, 1H), 8.90 (s, 1H), 8.89(s) & 8.74(s) (1H), 8.51(s) & 8.49(s) (1H), 8.22(s) & 8.16(s) (1H), 7.60 (m, 1H), 7.41 (s, 1H), 7.36 (m, 2H), 6.91 (m, 1H), 6.58(m) & 6.50(m) (1H), 5.14 (s, 2H), 4.24(m) & 3.84(m) (1H), 4.00 (s, 3H), 3.74 (m, 2H), 3.25 (m, 2H), 2.92 (s, 3H), 2.32 (m) and 2.16(m) (1H);
MS (+ve ESI): 492 $(M+H)^+$.

4-Chloro-7-methoxy-6-[(1-methylpyrrolidin-3-yl)oxy]quinazoline used as starting material, was prepared as follows:

a) Diethyl azodicarboxylate (793 mg, 4.56 mmol) was added portionwise at room temperature to a stirred suspension of 4-chloro-7-methoxyquinazolin-6-ol (800 mg, 3.80 mmol), 1-methylpyrrolidin-3-ol (422 mg, 4.18 mmol) and triphenylphosphine (1.3 g, 4.96 mmol) in dichloromethane (16 ml). The reaction mixture was stirred for 1hour and then a further portion of diethyl azodicarboxylate (360 ul) and triphenylphosphine (0.65 mg) were added. The mixture was stirred for 1hour and the resulting orange solution was purified directly by silica gel chromatography eluting with a 0 – 10% mixture of methanol in dichloromethane to 4-chloro-7-methoxy-6-[(1-methylpyrrolidin-3-yl)oxy]quinazoline (330 mg, 28% yield) as a tan coloured solid:
^{1}H-NMR (DMSO d_6): 8.87 (s, 1H), 7.45 (s, 1H), 7.30 (s, 1H), 5.14 (m, 1H), 4.01 (s, 3H), 2.80 (m, 3H), 2.40 (m, 2H), 2.29 (s, 3H), 1.88 (m, 1H);
MS (+ve ESI): 294 $(M+H)^+$.

Example 231 – Preparation of compound 231 in table 9 - *N*-(3-fluorophenyl)-2-(4-{[7-methoxy-6-(2-morpholin-4-ylethoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide.

An analogous reaction to that described in example 229 but starting with 4-chloro-7-methoxy-6-(2-morpholin-4-ylethoxy)quinazoline (120 mg, 0.37 mmol) yielded compound 231 in table 9 as the hydrochloride salt (211 mg) as a pale yellow coloured solid:

^{1}H-NMR (DMSO-d_6): 12.13 (s, 1H), 10.75 (s, 1H), 8.91 (s, 1H), 8.78 (s, 1H), 8.48 (s, 1H), 8.14 (s, 1H), 7.60 (m, 1H), 7.40 (s, 1H), 7.38 (m, 2H), 6.92 (m, 1H), 5.14 (s, 2H), 4.78 (t, 2H), 4.00 (s, 3H), 3.92 (m, 4H), 3.70 (t, 2H), 3.35 (m, 4H, partially obscured by H_2O);
MS (+ve ESI): 522 $(M+H)^+$.

4-Chloro-7-methoxy-6-(2-morpholin-4-ylethoxy)quinazoline used as starting material, was prepared as follows:

a) Di-*tert*-butyl azodicarboxylate (1.44g, 6.26mmol) was added portionwise at room temperature to a stirred suspension of 4-chloro-7-methoxyquinazolin-6-ol (1.20 g, 5.70 mmol), 2-morpholin-4-ylethanol (0.82 g, 6.2 6mmol) and triphenylphosphine (1.8 g, 6.87 mmol) in dichloromethane (25 ml). The reaction mixture was stirred for 2 hour and then the resulting orange solution was purified directly by silica gel chromatography eluting with a mixture of 3% methanol in dichloromethane and then purified further by chromatography on neutral alumina eluting with a 3% mixture of methanol in dichloromethane to give 4-chloro-7-methoxy-6-(2-morpholin-4-ylethoxy)quinazoline (1.40 g, 76% yield) as a pale yellow solid: ^{1}H-NMR ($CDCl_3$): 8.86 (s, 1H), 7.42 (s, 1H), 7.33 (s, 1H), 4.34 (t, 2H), 4.04 (s, 3H), 3.75 (m, 4H), 2.94 (t, 2H), 2.64 (m, 4H).

Example 232 – Preparation of compound 232 in table 9 - 2-(4-{[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide

A mixture of 2-(4-amino-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide (152 mg, 0.6 mmol) and 4-chloro-6,7-bis(2-methoxyethoxy)quinazoline (see WO96/15118, 180 mg, 0.6 mmol) in dimethylacetamide (5 ml) was heated at 80°C for 15 minutes and then allowed to cool to room temperature. The resulting solid was filtered and washed with methanol to give compound 232 in table 9 (248 mg, 78% yield):
^{1}H-NMR (DMSO d_6): 11.54 (br s, 1H), 10.39 (br s, 1H), 8.85 (s, 1H), 8.40 (s, 1H), 8.30 (s, 1H), 8.00 (s, 1H), 7.65 (m, 1H), 7.30 (s, 1H), 7.18 (m, 2H), 5.20 (s, 2H), 4.30 (m, 4H), 3.78 (m, 4H), 3.28 (s, 3H), 3.27 (s, 3H);
MS (+ve ESI): 529 $(M+H)^+$
MS (-ve ESI): 527 $(M-H)^-$.

Example 233 – Preparation of compound 233 in table 9 - *N*-(3-fluorophenyl)-2-{4-[(6-hydroxy-7-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

A solution of 4-chloro-7-methoxyquinazolin-6-ol (see WO03/064413, 0.119 g, 0.57 mmol) and 2-(4-amino-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide (0.132 g, 0.56 mmol) in dimethylacetamide (5 ml) was heated at 90°C for 2 hours and then at 120°C for 3 hours. The mixture was cooled to room temperature and diluted with diethyl ether (25 ml) and then filtered to yield compound 233 in table 9 as the hydrochloride salt (0.119 g, 48% yield) as a yellow solid.

^{1}H-NMR (DMSO d_6): 11.27 (br s, 1H), 10.74 (br s, 1H), 8.86 (s, 1H), 8.36 (s, 1H), 8.00 (s, 1H), 7.95 (s, 1H), 7.58 (m, 1H), 7.34 (m, 3H), 6.93 (m, 1H), 5.12 (s, 2H), 4.01 (s, 3H);
MS (+ve ESI): 409 $(M+H)^+$.

Example 234 – Preparation of compound 234 in table 9 – 4-((1-(2-((2,3-difluorophenyl)amino)-2-oxoethyl)-1*H*-pyrazol-4-yl)amino)-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-6-yl benzoate

A solution of 4-chloro-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-6-yl benzoate (0.250 g, 0.55mmol) and 2-(4-amino-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide (0.140 g, 0.55 mmol) in dimethylacetamide (2 ml) was stirred at 35°C for 3 hours. The precipitate was collected by filtration, washed with dimethylacetamide and then dried *in vacuo* (25 °C, 0.1 mm Hg) to yield compound 234 in table 9 (0.323 g, 67% yield) as the hydrochloride salt:

^{1}H-NMR (DMSO d_6): 11.90 (br s, 1H), 10.50 (br s, 1H), 10.42 (s, 1H), 8.99 (m, 2H), 8.45 (s, 1H), 8.18 (d, 2H), 8.05 (s, 1H), 7.82 (m, 1H), 7.69 (m, 4H), 7.19 (m, 2H), 5.20 (s, 2H), 4.29 (d, 0.2H), and 4.07 (d, 0.8H), 3.31 (d, 2H), 2.81 (m, 1H), 2.65 (s, 3H), 2.55 (m, 1H), 1.95 (m, 1H), 1.79 (m, 2H), 1.55 (m, 2H);
MS (+ve ESI): 628 $(M+H)^+$.

4-chloro-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-6-yl benzoate used as starting material, was prepared as follows:

a) A mixture of 4-chloro-6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazoline (see *Journal of Medicinal Chemistry*, **2002**, *45*, 1300-12, 9.8 g, 30 mmol), D,L-methionine (7.15g, 48 mmol) and methanesulphonic acid (50ml) was heated at 150°C for 32 hours. The

reaction mixture was allowed to cool to room temperature. The pH was adjusted to 8 with aqueous sodium hydroxide then, aqueous sodium hydrogen carbonate and concentrated to half the original volume. The resultant solid was filtered and washed with water and then dried for 16 hours at 60°C to give 7-[(1-methylpiperidin-4-yl)methoxy]quinazoline-4,6-diol (6.16 g, 71% yield).

^{1}H-NMR (DMSO d_6): 7.85 (s, 1H), 7.40 (s, 1H), 7.0 (s, 1H), 4.0 (d, 2H), 2.80-2.75 (m, 2H), 2.20 (s, 3H), 2.0-1.65 (m, 5H), 1.45-1.30 (m, 2H);

MS (+VE ESI): 290 $(M+H)^+$

MS (-VE ESI): 288 $(M-H)^-$.

b) A mixture of 7-[(1-methylpiperidin-4-yl)methoxy]quinazoline-4,6-diol (6.16g, 21.3 mmol), benzoic anhydride (6.24g, 27.7 mmol) and diphenyl ether (60ml) was heated at 100°C for 2 hours. The reaction mixture was allowed to cool to 50°C and then diethyl ether and hexane were added to give a solid which was filtered and washed with diethyl ether and hexane. The product was absorbed on to alumina and purified by flash chromatography on alumina eluting with a gradient of 5-20% methanol in dichloromethane to give 4-hydroxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-6-yl benzoate (7.16 g, 86% yield).

^{1}H-NMR (DMSO d_6): 8.10 (d, 2H), 8.05 (s, 1H), 7.85 (s, 1H), 7.80-7.70 (m, 1H), 7.65-7.55 (m, 2H), 7.30 (s, 1H), 4.0 (d, 2H), 2.65-2.55 (m, 2H), 2.0 (s, 3H), 1.70-1.60 (m, 2H), 1.60-1.50 (m, 3H), 1.30-1.10 (m, 2H);

MS (+VE ESI): 394 $(M+H)^+$.

MS (-VE ESI): 392 $(M-H)^-$.

c) A mixture of 4-hydroxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-6-yl benzoate (0.215 g, 0.55mmol), thionyl chloride (2 ml) and dimethylformamide (0.05 ml) were refluxed for 15minutes. The solvent was evaporated in vacuo to yield 4-chloro-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-6-yl benzoate (0.250 g, 94% yield) as the hydrochloride salt:

MS (+ve ESI): 412 $(M+H)^+$.

Example 235 – Preparation of compound 235 in table 9 – *N*-(2,3-difluorophenyl)-2-(4-((6-hydroxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-yl)amino)-1*H*-pyrazol-1-yl)acetamide

4-((1-(2-((2,3-difluorophenyl)amino)-2-oxoethyl)-1*H*-pyrazol-4-yl)amino)-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-6-yl benzoate (0.220 g, 0.33 mmol) was dissolved in methanol (25 ml) and 7M ammonia in methanol (5 ml) added and the solution heated at

50°C for 1hour. The solvent was evaporated and the residue was dissolved in methanol (5ml) and applied to an SCX column and the product eluted with 0.5M to 2.0M ammonia in methanol. The fractions containing product were combined and evaporated to yield compound 235 in table 9 (0.146 g, 80% yield):

^{1}H-NMR (DMSO d_6): 10.25 (s, 1H), 9.60 (s, 1H), 9.34 (br s, 1H), 8.45 (s, 1H), 8.32 (s, 1H), 7.78 (s, 1H), 7.71 (s, 1H), 7.71 (m, 1H), 7.20 (m, 1H), 7.13 (s, 1H), 5.15 (s, 2H), 4.00 (d, 2H), 3.18 (s, 1H), 2.80 (d, 2H), 2.16 (s, 3H), 1.85 (m, 5H), 1.35 (m, 2H);
MS (+ve ESI): 524 $(M+H)^+$.

Example 236 – Preparation of compound 236 in table 10 – 1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-4-[(7-{3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazole-3-carboxamide

A mixture of 4-{[7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl]amino}-1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazole-3-carboxamide (152 mg, 0.25 mmol), 2-((2-methoxyethyl)amino)ethanol (90 mg, 0.75 mmol) and potassium iodide (83 mg) in 1-methyl-2-pyrrolidinone (1 ml) was heated at 80°C for 6 hours. The mixture was purified directly by silica gel chromatography. Elution first with a 4% solution of methanol in dichloromethane and then a 4 to 7% mixture of methanol (containing 7N ammonia) in dichloromethane yielded compound 236 in table 10 (54 mg, 35% yield) as an off white solid:

^{1}H-NMR (DMSOd_6, TFA): 9.04 (s, 1H), 8.61 (s, 1H), 7.60 (d, 1H), 7.55 (s, 1H), 7.41 (s, 1H), 7.38 (m, 1H), 7.33 (m, 1H), 6.93 (t, 1H), 5.28 (s, 2H), 4.32 (t, 2H), 4.05 (s, 3H), 3.80 (t, 2H), 3.73 (t, 2H), 3.46 (m, 6H), 3.34 (s, 3H), 2.29 (m, 2H);
MS (+ve ESI): 611.26 $(M+H)^+$.

Example 237 – Preparation of compound 237 in table 10 - 1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazole-3-carboxamide

An analogous reaction to that described in example 236 but starting with (2S)-pyrrolidin-2-yl methanol (74 μl, 0.75 mmol) yielded compound 237 in table 10 (75 mg, 50% yield):

^{1}H-NMR (DMSOd_6, TFA): 9.04 (s, 1H), 8.61 (s, 1H), 7.6 (d, 1H), 7.56 (s, 1H), 7.41 (s, 1H), 7.39 (m, 1H), 7.33 (m, 1H), 6.93 (m, 1H), 5.28 (s, 2H), 4.33 (s, 2H), 4.05 (s, 3H), 3.78 (m,

1H), 3.63 (m, 4H), 3.22 (m, 2H), 2.31 (m, 2H), 2.13 (m, 1H), 2.05 (m, 1H), 1.91 (m, 1H), 1.79 (m, 1H);

MS (+ve ESI): 593.24 $(M+H)^+$.

Example 238– Preparation of compound 238 in table 10 - 2-{3-(acetylamino)-4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 236 but starting 2-(3-(acetylamino)-4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide (0.12 g, 0.25 mmol) and (2*R*)-2-(hydroxymethyl) pyrrolidine (0.074 ml, 0.75 mmol) yielded compound 238 in table 10 (0.095 g, 66% yield):

^{1}H-NMR (DMSO d_6 TFA): 8.98 (s, 1H), 8.58 (s, 1H), 8.22 (d, 1H), 7.59 (d, 1H), 7.52 (d, 1H), 8.32 (m, 2H), 7.27 (s, 1H), 6.87 (t, 1H), 5.08 (s, 2H), 4.29 (m, 2H), 3.77 (d, 1H), 3.58 (m, 4H), 3.25 (m, 1H), 3.17 (m, 1H), 2.23 (m, 2H), 2.15 (s, 3H), 2.1 (m, 1H), 2.0 (m, 1H), 1.88 (m, 1H), 1.77 (m, 1H);

MS (+ ve ESI): 577.28 $(M+H)^+$.

Example 239 – Preparation of compound 239 in table 10 – ethyl 1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazole-3-carboxylate

A mixture of ethyl 4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazole-3-carboxylate (0.179g, 0.3 mmol) and (2*R*)-pyrrolidin-2-ylmethanol (0.0910 g, 0.9 mmol) and potassium iodide (0.0996 g, 0.6 mmol) in 1-methyl-2-pyrrolidinone (2 ml) was heated at 80°C for 3 hours under an argon atmosphere. The crude reaction mixture was purified directly by silica gel chromatography eluting with a mixture of 0 to 6% methanol in dichloromethane to yield compound 239 in table 10 (0.133 g, 75% yield):

^{1}H-NMR (DMSOd_6 TFA): 8.99 (s, 1H), 8.49 (d, 1H), 8.44 (s, 1H), 7.58 (m, 2H), 7.39 (q, 1H), 7.33 (m, 2H), 6.93 (t, 1H), 5.28 (s, 2H), 4.33 (t, 2H), 4.26 (q, 2H), 3.8 (m, 1H), 3.63 (m, 4H), 3.27 (m, 1H), 3.19 (m, 1H), 2.28 (m, 2H), 2.14 (m, 1H), 2.05 (m, 1H), 1.91 (m, 1H), 1.79 (m, 1H), 1.17 (t, 3H);

MS (+ ve ESI): 592.28 $(M+H)^+$.

Example 240 – Preparation of compound 240 in table 10 – 1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazole-3-carboxylic acid

A solution of lithium hydroxide (0.0164 g, 0.068 mmol) in water (0.39 ml) was added to a mixture of ethyl 1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazole-3-carboxylate (0.0769 g, 0.13 mmol) in methanol (10 ml) and water (2 ml) and the mixture was heated at 50°C for 1.5 hours. The mixture was evaporated and the residue was purified directly by preperative LCMS on a Thermo Hyersil Beta Basic-18 column eluting with a gradient of water in acetonitrile to give compound 240 in table 10 (0.058 g, 79% yield):
^{1}H-NMR (DMSOd_6 TFA): 9.04 (s, 1H), 8.52 (s, 1H), 8.4 (d, 1H), 7.6 (m, 2H), 7.39 (m, 1H), 7.34 (m, 2H), 6.93 (t, 1H), 5.28 (s, 2H), 4.34 (t, 2H), 3.79 (d, 1H), 3.64 (m, 4H), 3.28 (m, 1H), 3.2 (m, 1H), 2.28 (m, 2H), 2.13 (m, 1H), 2.04 (m, 1H), 1.92 (m, 1H), 1.81 (m, 1H);
MS (+ ve ESI): 564.29 $(M+H)^+$.

Example 241 - Preparation of compound 241 in table 11 - 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](propyl)amino]ethyl dihydrogen phosphate

A solution of 4.0 N hydrochloric acid in dioxane (1.42 ml, 5.7 mmol) was added to a solution of di-*tert*-butyl 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](propyl)amino]ethyl phosphate (720 mg, 0.95 mmol) in dichloromethane (7 ml) and dioxane (20 ml) and the mixture was stirred at ambient temperature for 23 hours. The precipitate was filtered, washed with dichloromethane and diethyl ether and dried *in vacuo* (50 °C, 0.1 mm Hg) to yield compound 241 in table 11 (720 mg, 99.5 % yield):
^{1}H-NMR (DMSO d_6, TFA): 8.96 (s, 1H), 8.43 (s, 1H), 8.22 (s, 1H), 8.02 (s, 1H), 7.75 (m, 1H), 7.37 (s, 1H), 7.21 (m, 2H), 5.26 (s, 2H), 4.28 (m, 4H), 4.04 (s, 3H), 3.51 (m, 2H), 3.39 (m, 2H), 3.21 (m, 2H), 2.31 (m, 2H), 1.74 (m, 2H), 0.96 (t, 3H);
MS (+ve ESI): 650.5 $(M+H)^+$.

Di-*tert*-butyl 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](propyl)amino]ethyl phosphate used as starting material, was obtained as follows:

a) Di-tert-butyl diethylphosphoramidite (486 mg, 1.95 mmol) was added slowly to a solution of *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (740 mg, 1.3 mmol) and tetrazole (228 mg, 3.25 mmol) in dimethylformamide (7.4 ml) under argon. The mixture was stirred at ambient temperature for 45 minutes. Hydrogen peroxide (9 N, 288 µl, 2.6 mmol) was added at 0 °C and the reaction stirred for 1.5 hours at ambient temperature. An additional quantity of hydrogen peroxide (72 µl, 0.65 mmol) was added to the solution to complete the oxidation. The mixture was cooled to 0 °C and a saturated solution of sodium metabisulphite (388 mg, 2 ml) was added slowly with vigorous stirring. The mixture was stirred at ambient temperature for 20 minutes, diluted with water and the pH adjusted to 7 with an aqueous solution of sodium bicarbonate. The mixture was extracted with ethyl acetate (3 x 10 ml), dried and concentrated. Purification by silica gel chromatography, eluting with dichloromethane : methanol (98:2) followed by dichloromethane : methanolic ammonia (3 N) (9:1) yielded di-*tert*-butyl 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](propyl)amino]ethyl phosphate (720 mg, 67 % yield): ^{1}H-NMR (DMSO d_6, TFA): 8.97 (s, 1H), 8.41 (s, 1H), 8.08 (s, 1H), 7.96 (s, 1H), 7.74 (m, 1H), 7.35 (s, 1H), 7.20 (m, 2H), 5.25 (s, 2H), 4.27 (m, 4H), 4.02 (s, 3H), 3.52 (m, 2H), 3.37 (m, 2H), 3.21 (m, 2H), 2.29 (m, 2H), 1.72 (m, 2H), 1.44 (s, 18H), 0.95 (t, 3H), 1.44 (s, 18H); MS (+ve ESI): 762.8 $(M+H)^+$.

Example 242 - Preparation of compound 242 in table 11 - {(2*S*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate

An analogous reaction to that described in example 241, but starting with di-*tert*-butyl {(2*S*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate (502 mg, 0.66 mmol) yielded compound 242 in table 11 (462 mg, 88 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.96 (s, 1H), 8.43 (s, 1H), 8.23 (m, 1H), 8.02 (s, 1H), 7.74 (m, 1H), 7.37 (s, 1H), 7.21 (m, 2H), 5.25 (s, 2H), 4.31 (m, 2H), 4.20 (m, 2H), 4.04 (s, 3H), 3.83

(m, 1H), 3.71 (m, 1H), 3.61 (m, 1H), 3.24 (m, 2H), 2.32 (m, 2H), 2.22 (m, 1H), 2.05 (m, 1H), 1.95 (m, 1H), 1.86 (m, 1H);

MS (+ve ESI): 648.0 $(M+H)^+$.

di-*tert*-butyl {(2*S*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate used as starting material was obtained as follows:

a) An analogous reaction to that described in example 241a, but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (1.08 g, 1.9 mmol) yielded di-*tert*-butyl {(2*S*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate (512 mg, 35 % yield):

^{1}H-NMR (DMSO d_6): 10.32 (s, 1H), 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.77 (m, 2H), 7.73 (m, 1H), 7.21 (m, 2H), 7.15 (s, 1H), 5.16 (s, 2H), 4.16 (m, 2H), 3.95 (s, 3H), 3.77 (m, 1H), 3.57 (m, 1H), 3.08 (m, 1H), 2.93 (m, 1H), 2.67 (m, 1H), 2.47 (m, 1H), 2.21 (m, 1H), 1.95 (m, 2H), 1.86 (m, 1H), 1.69 (m, 2H), 1.6 (m, 1H), 1.36 (s, 18H);

MS (+ve ESI): 760.4 $(M+H)^+$.

Example 243 - Preparation of compound 243 in table 11 - {(2*S*)-1-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate

An analogous reaction to that described in example 241, but starting with di-*tert*-butyl {(2*S*)-1-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate (605 mg, 0.96 mmol) yielded compound 243 in table 11 (595 mg, 76 % yield):

^{1}H-NMR (DMSO d_6, CD_3COOD): 8.93 (s, 1H), 8.45 (s, 1H), 8.30 (m, 1H), 8.05 (s, 1H), 7.62 (m, 1H), 7.39 (s, 1H), 7.36 (m, 2H), 6.91 (m, 1H), 5.17 (s, 2H), 4.31 (m, 2H), 4.24 (m, 2H), 4.05 (s, 3H), 3.84 (m, 1H), 3.71 (m, 1H), 3.61 (m, 1H), 3.33 (m, 1H), 3.25 (m, 1H), 2.34 (m, 2H), 2.23 (m, 1H), 2.06 (m, 1H), 1.97 (m, 1H), 1.89 (m, 1H);

MS (+ve ESI): 530.2 $(M+H)^+$.

di-*tert*-butyl {(2*S*)-1-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate used as starting material was obtained as follows:

a) An analogous reaction to that described in example 241a, but starting with *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (1.12 g, 2.04 mmol) yielded di-*tert*-butyl {(2*S*)-1-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate (618 mg, 41 % yield):

^{1}H-NMR (DMSO d_6): 10.56 (s, 1H), 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.59 (m, 1H), 7.36 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.16 (m, 2H), 3.96 (s, 3H), 3.78 (m, 1H), 3.56 (m, 1H), 3.08 (m, 1H), 2.93 (m, 1H), 2.67 (m, 1H), 2.49 (m, 1H), 2.21 (m, 1H), 1.95 (m, 2H), 1.86 (m, 1H), 1.69 (m, 2H), 1.62 (m, 1H), 1.37 (s, 18H);

MS (+ve ESI): 742.4 $(M+H)^+$.

Example 244 - Preparation of compound 244 in table 11 - 2-{ethyl[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate

An analogous reaction to that described in example 241, but starting with di-*tert*-butyl 2-{ethyl[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate (610 mg, 0.84 mmol) yielded compound 244 in table 11 (589 mg, 89 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.95 (s, 1H), 8.44 (s, 1H), 8.32 (m, 1H), 8.04 (s, 1H), 7.61 (m, 1H), 7.36 (m, 3H), 6.92 (m, 1H), 5.16 (s, 2H), 4.31 (m, 2H), 4.25 (m, 2H), 4.04 (s, 3H), 3.48 (m, 2H), 3.37 (m, 4H), 2.30 (m, 2H), 1.28 (t, 3H);

MS (+ve ESI): 618.1 $(M+H)^+$.

di-*tert*-butyl 2-{ethyl[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate used as starting material was obtained as follows:

a) An analogous reaction to that described in example 241a, but starting with 2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-

yl}-*N*-(3-fluorophenyl)acetamide (645 mg, 1.2 mmol) yielded di-*tert*-butyl 2-{ethyl[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate (620 mg, 71 % yield):

^{1}H-NMR (DMSO d_6): 9.67 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.59 (d, 1H), 7.38 (q, 1H), 7.32 (d, 1H), 7.14 (s, 1H), 6.91 (t, 1H), 5.06 (s, 2H), 4.16 (t, 2H), 3.96 (s, 3H), 3.86 (m, 2H), 2.67 (t, 2H), 2.62 (t, 2H), 2.54 (m, 2H), 1.90 (m, 2H), 0.97 (t, 3H), 1.38 (s, 18H);

MS (+ve ESI): 730.2 $(M+H)^+$.

Example 245 - Preparation of compound 245 in table11 - {(2*R*)-1-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate

An analogous reaction to that described in example 241, but starting with di-*tert*-butyl {(2*R*)-1-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate (477 mg, 0.64 mmol) yielded compound 245 in table 11 (430 mg, 90 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.96 (s, 1H), 8.43 (s, 1H), 8.27 (m, 1H), 8.02 (s, 1H), 7.62 (m, 1H), 7.37 (m, 3H), 6.92 (m, 1H), 5.16 (s, 2H), 4.31 (m, 2H), 4.21 (m, 2H), 4.04 (s, 3H), 3.83 (m, 1H), 3.71 (m, 1H), 3.61 (m, 1H), 3.31 (m, 1H), 3.24 (m, 1H), 2.32 (m, 2H), 2.21 (m, 1H), 2.05 (m, 1H), 1.94 (m, 1H), 1.85 (m, 1H);

MS (+ve ESI): 630.2 $(M+H)^+$.

di-*tert*-butyl {(2*R*)-1-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate used as starting material was obtained as follows:

a) An analogous reaction to that described in example 241a, but starting with *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (588 mg, 1.07 mmol) yielded di-*tert*-butyl {(2*R*)-1-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate (367 mg, 46 % yield):

^{1}H-NMR (DMSO d_6): 10.56 (s, 1H), 9.67 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.59 (d, 1H), 7.37 (q, 1H), 7.32 (d, 1H), 7.15 (s, 1H), 6.91 (t, 1H), 5.06 (s, 1H), 4.17

(m, 2H), 3.96 (s, 3H), 3.56 (m, 1H), 3.08 (m, 1H), 2.94 (m, 1H), 2.67 (m, 1H), 2.21 (m, 1H), 1.95 (m, 2H), 1.86 (m, 1H), 1.69 (m, 2H), 1.62 (m, 1H), 1.37 (s, 18H);
MS (+ve ESI): 742.4 $(M+H)^+$.

Example 246 - Preparation of compound 246 in table 11 - 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](2-methoxyethyl)amino]ethyl dihydrogen phosphate

An analogous reaction to that described in example 241, but starting with di-*tert*-butyl 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](2-methoxyethyl)amino]ethyl phosphate (540 mg, 0.69 mmol) yielded compound 246 in table 11 (462 mg, 90 % yield):
^{1}H-NMR (DMSO d_6, CD_3COOD): 8.87 (s, 1H), 8.44 (s, 1H), 8.31 (s, 1H), 8.07 (s, 1H), 7.74 (m, 1H), 7.48 (s, 1H), 7.18 (m, 2H), 5.25 (s, 2H), 4.34 (m, 2H), 4.25 (m, 2H), 3.77 (s, 3H), 3.76 (m, 2H), 3.52 (m, 2H), 3.46 (m, 2H), 3.42 (m, 2H), 3.34 (s, 3H), 2.30 (m, 2H);
MS (+ve ESI): 666.0 $(M+H)^+$.

di-*tert*-butyl 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](2-methoxyethyl)amino]ethyl phosphate used as starting material was obtained as follows:

a) An analogous reaction to that described in example 241a, but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (640 mg, 1.09 mmol) yielded di-*tert*-butyl 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](2-methoxyethyl)amino]ethyl phosphate (550 mg, 65 % yield):
^{1}H-NMR (DMSO d_6): 9.67 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.73 (m, 1H), 7.21 (m, 2H), 7.14 (s, 1H), 5.15 (s, 2H), 4.16 (t, 2H), 3.96 (s, 3H), 3.85 (m, 2H), 3.38 (t, 2H), 2.73 (t, 2H), 2.68 (m, 4H), 1.90 (m, 2H), 1.38 (s, 18H);
MS (+ve ESI): 778.4 $(M+H)^+$.

Example 247 - Preparation of compound 247 in table 11 - {(2*S*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate

An analogous reaction to that described in example 241, but starting with di-*tert*-butyl {(2*S*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate (593 mg, 0.81 mmol) yielded compound 247 in table 11 (559 mg, 100 % yield):

^{1}H-NMR (DMSO d_6, TFA): 9.00 (s, 1H), 8.71 (d, 1H), 8.42 (s, 1H), 8.01 (s, 1H), 7.74 (m, 1H), 7.51 (dd, 1H), 7.31 (d, 1H), 7.21 (m, 2H), 5.25 (s, 2H), 4.31 (m, 2H), 4.21 (m, 2H), 3.81 (m, 1H), 3.69 (m, 1H), 3.61 (m, 1H), 3.33 (m, 1H), 3.23 (m, 1H), 2.28 (m, 2H), 2.20 (m, 1H), 2.05 (m, 1H), 1.95 (m, 1H), 1.84 (m, 1H);

MS (+ve ESI): 618.2 $(M+H)^+$.

di-*tert*-butyl {(2*S*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate used as starting material was obtained as follows:

a) An analogous reaction to that described in example 241a, but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (698 mg, 1.3 mmol) yielded di-*tert*-butyl {(2*S*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate (665 mg, 70 % yield):

^{1}H-NMR (DMSO d_6, TFA): 9.02 (s, 1H), 8.64 (d, 1H), 8.41 (s, 1H), 7.98 (s, 1H), 7.74 (m, 1H), 7.51 (m, 1H), 7.27 (m, 1H), 7.21 (m, 2H), 5.25 (s, 2H), 4.31 (m, 2H), 4.20 (m, 2H), 3.82 (m, 1H), 3.71 (m, 1H), 3.61 (m, 1H), 3.32 (m, 1H), 3.26 (m, 1H), 2.26 (m, 3H), 2.08 (m, 1H), 1.94 (m, 1H), 1.83 (m, 1H), 1.45 (s, 18H);

MS (+ve ESI): 730.6 $(M+H)^+$.

Example 248 - Preparation of compound 248 in table 11 - {(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate

An analogous reaction to that described in example 241, but starting with di-*tert*-butyl {(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-

yl)amino]quinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate (651 mg, 0.89 mmol) yielded compound 248 in table 11 (608 mg, 97 % yield):

^{1}H-NMR (DMSO d_6, TFA): 9.01 (s, 1H), 8.72 (d, 1H), 8.43 (s, 1H), 8.02 (s, 1H), 7.74 (s, 1H), 7.51 (m, 1H), 7.32 (m, 1H), 7.21 (m, 2H), 5.25 (s, 2H), 4.32 (m, 2H), 4.21 (m, 2H), 3.82 (m, 1H), 3.68 (m, 1H), 3.62 (m, 1H), 3.32 (m, 1H), 3.23 (m, 1H), 2.29 (m, 2H), 2.21 (m, 1H), 2.06 (m, 1H), 1.94 (m, 1H), 1.84 (m, 1H);

MS (+ve ESI): 618.3 $(M+H)^+$.

di-*tert*-butyl {(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate used as starting material was obtained as follows:

a) An analogous reaction to that described in example 241 a), but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (688 mg, 1.3 mmol) yielded di-*tert*-butyl {(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate (665 mg, 70 % yield):

^{1}H-NMR (DMSO d_6, TFA): 9.02 (s, 1H), 8.64 (d, 1H), 8.41 (s, 1H), 7.99 (s, 1H), 7.74 (m, 1H), 7.51 (m, 1H), 7.27 (m, 1H), 7.21 (m, 2H), 5.25 (s, 2H), 4.31 (m, 2H), 4.20 (m, 2H), 3.83 (m, 1H), 3.71 (m, 1H), 3.61 (m, 1H), 3.32 (m, 1H), 3.26 (m, 1H), 2.26 (m, 3H), 2.09 (m, 1H), 1.94 (m, 1H), 1.83 (m, 1H), 1.45 (s, 18H);

MS (+ve ESI): 730.6 $(M+H)^+$.

Example 249 - Preparation of compound 249 in table 11 - {(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate

An analogous reaction to that described in example 241, but starting with di-*tert*-butyl {(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate (840 mg, 1.1 mmol) yielded compound 249 in table 11 (742 mg, 90 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.96 (s, 1H), 8.42 (s, 1H), 8.22 (m, 1H), 8.01 (s, 1H), 7.74 (m, 1H), 7.37 (s, 1H), 7.21 (m, 2H), 5.25 (s, 2H), 4.30 (m, 2H), 4.21 (m, 2H), 4.04 (s, 3H), 3.83 (m, 1H), 3.70 (m, 1H), 3.62 (m, 1H), 3.31 (m, 1H), 3.24 (m, 1H), 2.32 (m, 2H), 2.21 (m, 1H), 2.05 (m, 1H), 1.93 (m, 1H), 1.60 (m, 1H);

MS (+ve ESI): 648.3 $(M+H)^+$.

di-*tert*-butyl {(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate used as starting material was obtained as follows:

a) An analogous reaction to that described in example 241a, but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (777 mg, 1.37 mmol) yielded di-*tert*-butyl {(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate (0.84 g, 76 % yield):

^{1}H-NMR (DMSO d_6): 9.67 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.77 (s, 1H), 7.76 (s, 1H), 7.31 (m, 1H), 7.21 (m, 2H), 7.15 (s, 1H), 5.16 (s, 2H), 4.16 (m, 2H), 3.95 (s, 3H), 3.76 (m, 1H), 3.55 (m, 1H), 3.08 (m, 1H), 2.94 (m, 1H), 2.67 (m, 1H), 2.50 (m, 1H), 2.21 (m, 1H), 1.95 (m, 2H), 1.86 (m, 1H), 1.69 (m, 2H), 1.62 (m, 1H), 1.36 (s, 18H);

MS (+ve ESI): 760.6 $(M+H)^+$.

Example 250 - Preparation of compound 250 in table 11 - 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](ethyl)amino]ethyl dihydrogen phosphate

An analogous reaction to that described in example 241, but starting with di-*tert*-butyl 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](ethyl)amino]ethyl phosphate (773 mg, 0.97 mmol) yielded compound 250 in table 11 (693 mg, 98 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.96 (s, 1H), 8.42 (s, 1H), 8.23 (m, 1H), 8.01 (s, 1H), 7.74 (m, 1H), 7.36 (s, 1H), 7.21 (m, 2H), 5.25 (s, 2H), 4.29 (m, 2H), 4.23 (m, 2H), 4.04 (s, 3H), 3.49 (m, 2H), 3.35 (m, 4H), 2.31 (m, 2H), 1.28 (t, 3H);

MS (+ve ESI): 636.3 $(M+H)^+$.

di-*tert*-butyl 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](ethyl)amino]ethyl phosphate used as starting material was obtained as follows:

a) An analogous reaction to that described in example 241a, but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (790 mg, 1.42 mmol) yielded di-*tert*-butyl 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](ethyl)amino]ethyl phosphate (780 mg, 78 % yield):
^{1}H-NMR (DMSO d_6): 9.67 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.73 (m, 1H), 7.21 (m, 2H), 7.14 (s, 1H), 5.16 (s, 2H), 4.16 (t, 2H), 3.95 (s, 3H), 3.85 (m, 2H), 2.66 (t, 2H), 2.62 (t, 2H), 2.53 (t, 2H), 1.91 (m, 2H), 1.38 (s, 18H), 0.97 (t, 3H), 1.50 (s, 18H);
MS (+ve ESI): 748.5 $(M+H)^+$.

Example 251 - Preparation of compound 251 in table 11 - 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](propyl)amino]ethyl dihydrogen phosphate

An analogous reaction to that described in example 241, but starting with di-*tert*-butyl 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](propyl)amino]ethyl phosphate (510 mg, 0.7 mmol) yielded compound 251 in table 11 (460 mg, 95 % yield):
^{1}H-NMR (DMSO d_6, TFA): 8.98 (s, 1H), 8.67 (d, 1H), 8.39 (s, 1H), 7.98 (s, 1H), 7.71 (m, 1H), 7.49 (d, 1H), 7.28 (s, 1H), 7.17 (m, 2H), 5.22 (s, 2H), 4.29 (m, 2H), 4.22 (m, 2H), 3.47 (m, 2H), 3.36 (m, 2H), 3.14 (m, 2H), 2.25 (m, 2H), 1.71 (m, 2H), 0.92 (t, 3H);
MS (+ve ESI): 620.2 $(M+H)^+$.

di-*tert*-butyl 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](propyl)amino]ethyl phosphate used as starting material was obtained as follows:

a) An analogous reaction to that described in example 241a, but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2 hydroxyethyl)(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (377 mg, 0.7 mmol) yielded di-*tert*-butyl 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](propyl)amino]ethyl phosphate (310 mg, 61 % yield):
^{1}H-NMR (DMSO d_6, TFA): 9.02 (s, 1H), 8.63 (d, 1H), 8.41 (s, 1H), 7.99 (s, 1H), 7.74 (m, 1H), 7.51 (d, 1H), 7.27 (s, 1H), 7.21 (m, 2H), 5.25 (s, 2H), 4.31 (m, 2H), 4.25 (m, 2H), 3.51 (m, 2H), 3.38 (m, 2H), 3.18 (m, 2H), 2.25 (m, 2H), 1.70 (m, 2H), 0.95 (t, 3H), 1.45 (s, 18H);

MS (+ve ESI): 732.5 $(M+H)^+$.

Example 252 - Preparation of compound 252 in table 11 - 2-{cyclobutyl[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate

An analogous reaction to that described in example 241, but starting with di-*tert*-butyl 2-{cyclobutyl[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate (500 mg, 0.65 mmol) yielded compound 252 in table 11 (450 mg, 95 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.92 (s, 1H), 8.42 (s, 1H), 8.31 (m, 1H), 8.03 (s, 1H), 7.72 (m, 1H), 7.35 (s, 1H), 7.19 (m, 1H), 5.23 (s, 2H), 4.27 (m, 2H), 4.21 (m, 2H), 4.02 (s, 3H), 3.92 (m, 1H), 3.37 (m, 2H), 3.25 (m, 2H), 2.34 (m, 2H), 2.24 (m, 4H), 1.74 (m, 1H), 1.65 (m, 1H);
MS (+ve ESI): 662.4 $(M+H)^+$.

di-*tert*-butyl 2-{cyclobutyl[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate used as starting material was obtained as follows:

a) An analogous reaction to that described in example 241a, but starting with 2-{4-[(7-{3-[cyclobutyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide (740 mg, 1.27 mmol) yielded di-*tert*-butyl 2-{cyclobutyl[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate (657 mg, 67 % yield):
^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.73 (m, 1H), 7.21 (m, 2H), 7.15 (s, 1H), 5.16 (s, 2H), 4.15 (t, 2H), 3.95 (s, 3H), 3.84 (m, 2H), 3.16 (m, 1H), 2.65 (t, 2H), 2.59 (t, 2H), 1.96 (m, 2H), 1.88 (m, 2H), 1.77 (m, 2H), 1.55 (m, 2H), 1.39 (s, 18H);
MS (+ve ESI): 774.6 $(M+H)^+$.

Example 253 - Preparation of compound 253 in table 11 - 2-{cyclobutyl[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate

An analogous reaction to that described in example 241, but starting with di-*tert*-butyl 2-{cyclobutyl[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-

methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate (530 mg, 0.7 mmol) yielded compound 253 in table 11 (540 mg, 100 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.93 (s, 1H), 8.42 (s, 1H), 8.21 (m, 1H), 7.98 (s, 1H), 7.58 (d, 1H), 7.34 (m, 3H), 6.89 (m, 1H), 5.13 (s, 2H), 4.27 (m, 2H), 4.19 (m, 2H), 4.01 (s, 3H), 3.93 (m, 1H), 3.36 (m, 2H), 3.25 (m, 2H), 2.35 (m, 2H), 2.25 (m, 4H), 1.75 (m, 1H), 1.68 (m, 1H);

MS (+ve ESI): 644.3 $(M+H)^+$.

di-*tert*-butyl 2-{cyclobutyl[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate used as starting material was obtained as follows:

a) An analogous reaction to that described in example 241a, but starting with 2-{4-[(7-{3-[cyclobutyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide (524 mg, 0.93 mmol) yielded di-*tert*-butyl 2-{cyclobutyl[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate (535 mg, 76 % yield):

^{1}H-NMR (DMSO d_6): 10.55 (s, 1H), 9.67 (s, 1H), 8.48 (s, 1H), 8.34 (s, 1H), 7.78 (s, 1H), 7.75 (s, 1H), 7.59 (d, 1H), 7.38 (q, 1H), 7.31 (d, 1H), 7.14 (s, 1H), 6.91 (m, 1H), 5.06 (s, 2H), 4.15 (t, 2H), 3.95 (s, 3H), 3.85 (m, 2H), 3.16 (m, 1H), 2.64 (t, 2H), 2.59 (t, 2H), 1.96 (m, 2H), 1.88 (m, 2H), 1.77 (m, 2H), 1.56 (m, 2H), 1.38 (s, 18H);

MS (+ve ESI): 756.1 $(M+H)^+$.

Example 254 - Preparation of compound 254 in table 11 - 2-[[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](2-methoxyethyl)amino]ethyl dihydrogen phosphate

An analogous reaction to that described in example 241, but starting with (325 mg, 0.43 mmol) yielded compound 254 in table 11 (329 mg, 100 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.96 (s, 1H), 8.42 (s, 1H), 8.22 (m, 1H), 8.00 (s, 1H), 7.61 (m, 1H), 7.36 (m, 3H), 6.92 (m, 1H), 5.15 (s, 2H), 4.30 (m, 2H), 4.25 (m, 2H), 4.04 (s, 3H), 3.74 (m, 2H), 3.56 (m, 2H), 3.49 (m, 2H), 3.42 (m, 2H), 3.34 (s, 3H), 2.37 (m, 2H);

MS (+ve ESI): 648.7$(M+H)^+$.

di-*tert*-butyl 2-[[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](2-methoxyethyl)amino]ethyl phosphate used as starting material was obtained as follows:

a) An analogous reaction to that described in example 241a, but starting with *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (444 mg, 0.78 mmol) yielded di-*tert*-butyl 2-[[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](2-methoxyethyl)amino]ethyl phosphate (325 mg, 55 % yield):

^{1}H-NMR (DMSO d_6): 10.55 (s, 1H), 9.67 (s, 1H), 8.47 (s, 1H), 8.34 (s, 1H), 7.77 (s, 1H), 7.75 (s, 1H), 7.58 (d, 1H), 7.37 (q, 1H), 7.31 (d, 1H), 7.14 (s, 1H), 6.91 (m, 1H), 5.06 (s, 2H), 4.16 (m, 2H), 3.95 (s, 3H), 3.85 (m, 2H), 3.38 (m, 2H), 3.2 (s, 3H), 2.73 (m, 2H), 2.67 (m, 4H), 1.91 (m, 2H), 1.37 (s, 18H);

MS (+ve ESI): 760.6 $(M+H)^+$.

Example 255 - Preparation of compound 255 in table 11- 2-[[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](propyl)amino]ethyl dihydrogen phosphate

Di-*tert*-butyl diethylphosphoramidite (747 mg, 3 mmol) was added slowly to a solution of *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2 hydroxyethyl)(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (390 mg, 0.75 mmol) and tetrazole (158 mg, 2.25 mmol) in dimethylacetamide (4 ml) under nitrogen. The mixture was stirred at ambient temperature for 1 hour. Hydrogen peroxide (383 µl, 3.38 mmol, 30 % aqueous solution) was added slowly at 0 °C and the reaction mixture stirred for 1.5 hours at ambient temperature. An additional portion of hydrogen peroxide (42 µl, 0.37 mmol) was added to the solution to complete the oxidation. The mixture was cooled to 0 °C and a saturated solution of sodium metabisulphite (7 ml of 0.53 M solution) added slowly with vigorous stirring. The mixture was stirred at ambient temperature for 20 minutes, diluted with water and the pH adjusted to 7 with an aqueous solution of potassium hydrogen carbonate. The reaction mixture was extracted with dichloromethane (3 x 25 ml) and the combined organics dried and concentrated *in vacuo*. Purification by silica gel chromatography, eluting with dichloromethane followed by increased polarity to dichloromethane : methanol : ammonia (20:1:0.1 to 20: 3: 0.2) gave di-*tert*-butyl 2-[[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-

yl)amino]quinazolin-7-yl}oxy)propyl](propyl)amino]ethyl phosphite as a pale yellow oil. This intermediate was dissolved in dioxane (10 ml) and a solution of 4.0 N hydrochloric acid in dioxane (1.12 ml, 4.5 mmol) added. The mixture was stirred at ambient temperature for 18 hours. The solid was filtered, washed with dichloromethane and diethyl ether and dried *in vacuo* for 18 hours (50 °C, 0.1 mm Hg) to yield compound 255 in table 11 as the dihydrochloride salt (375 mg, 70 % yield):

^{1}H-NMR (DMSO d_6, CD_3CO_2D): 8.93 (s, 1H), 8.80 (m, 1H), 8.41 (s, 1H), 8.01 (s, 1H), 7.58 (m, 1H), 7.45 (m, 1H), 7.32 (m, 3H), 6.88 (m, 1H), 5.12 (s, 2H), 4.29 (m, 4H), 3.46 (m, 2H), 3.35 (m, 2H), 3.14 (m, 2H), 2.28 (m, 2H), 1.73 (m, 2H), 0.93 (t, 3H);

MS (+ve ESI): 602 $(M+H)^+$.

Example 256 - Preparation of compound 256 in table 11- 2-{4-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]piperazin-1-yl}ethyl dihydrogen phosphate

An analogous reaction to that described in example 255 but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (363 mg, 0.64 mmol) yielded compound 256 in table 11 (442 mg, 91 % yield):

^{1}H-NMR (DMSO d_6, CD_3CO_2D): 8.94 (s, 1H), 8.84 (m, 1H), 8.42 (s, 1H), 8.04 (s, 1H), 7.70 (m, 1H), 7.47 (m, 1H), 7.36 (m, 1H), 7.17 (m, 2H), 5.22 (s, 2H), 4.33 (m, 2H), 4.27 (m, 2H), 3.72 (m, 8H), 3.51 (m, 2H), 3.41 (m, 2H), 2.33 (m, 2H);

MS (+ve ESI): 647 $(M+H)^+$.

Example 257 - Preparation of compound 257 in table 11- 2-{ethyl[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate

An analogous reaction to that described in example 255 but starting with 2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide (362 mg, 0.71 mmol) yielded compound 257 in table 11 (246 mg, 50 % yield):

^{1}H-NMR (DMSO d_6, CD_3CO_2D): 8.92 (s, 1H), 8.80 (m, 1H), 8.40 (s, 1H), 8.01 (s, 1H), 7.58 (m, 1H), 7.47 (m, 1H), 7.33 (m, 3H), 6.88 (m, 1H), 5.13 (s, 2H), 4.28 (m, 4H), 3.45 (m, 2H), 3.36 (m, 2H), 3.28 (m, 2H), 2.28 (m, 2H), 1.28 (t, 3H);

MS (+ve ESI): 588 $(M+H)^+$.

Example 258 - Preparation of compound 258 in table 11- 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](ethyl)amino]ethyl dihydrogen phosphate

An analogous reaction to that described in example 255 but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (368 mg, 0.70 mmol) yielded compound 258 in table 11 (313 mg, 63 % yield):

^{1}H-NMR (DMSO d_6, CD_3CO_2D): 8.91 (s, 1H), 8.77 (m, 1H), 8.40 (s, 1H), 8.01 (s, 1H), 7.68 (m, 1H), 7.45 (m, 1H), 7.34 (s, 1H), 7.16 (m, 2H), 5.20 (s, 2H), 4.28 (m, 2H), 4.25 (m, 2H), 3.43 (m, 2H), 3.34 (m, 2H), 3.25 (m, 2H), 2.25 (m, 2H), 1.27 (t, 3H);
MS (+ve ESI): 606 $(M+H)^+$.

Example 259 - Preparation of compound 259 in table 11- 3-{[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]amino}-3-methylbutyl dihydrogen phosphate

An analogous reaction to that described in example 255 but starting with *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(3-hydroxy-1,1-dimethylpropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide
(379 mg, 0.72 mmol) yielded compound 259 in table 11 (365 mg, 71 % yield):
^{1}H-NMR (DMSO d_6, CD_3CO_2D): 8.91 (s, 1H), 8.74 (d, 1H), 8.39 (s, 1H), 8.00 (s, 1H), 7.55 (m, 1H), 7.47 (m, 1H), 7.31 (m, 3H), 6.85 (m, 1H), 5.10 (s, 2H), 4.31 (m, 2H), 4.00 (m, 2H), 3.10 (m, 2H), 2.23 (m, 2H), 2.02 (m, 2H), 1.34 (s, 6H);
MS (+ve ESI): 602 $(M+H)^+$.

Example 260 - Preparation of compound 260 in table 11- 3-{[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]amino}-3-methylbutyl dihydrogen phosphate

An analogous reaction to that described in example 255 but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3-hydroxy-1,1 dimethylpropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide
(353 mg, 0.65 mmol) yielded compound 260 in table 11 (310 mg, 65 % yield):

^{1}H-NMR (DMSO d_6, CD_3CO_2D): 9.14 (m, 1H), 8.95 (m, 1H), 8.42 (s, 1H), 8.04 (s, 1H), 7.71 (m, 1H), 7.50 (m, 1H), 7.37 (m, 1H), 7.19 (m, 2H), 5.23 (m, 2H), 4.34 (m, 2H), 4.00 (m, 2H), 3.11 (m, 2H), 2.26 (m, 2H), 2.04 (m, 2H), 1.36 (s, 6H);

MS (+ve ESI): 620 $(M+H)^+$.

Example 261 - Preparation of compound 261 in table 11- {(2*R*)-1-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate

An analogous reaction to that described in example 255 but starting with *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

(397 mg, 0.76 mmol) yielded compound 261 in table 11 (429 mg, 79 % yield):

^{1}H-NMR (DMSO d_6, CD_3CO_2D): 8.92 (m, 1H), 8.76 (m, 1H), 8.40 (s, 1H), 8.00 (s, 1H), 7.56 (m, 1H), 7.46 (m, 1H), 7.31 (m, 2H), 6.85 (m, 1H), 5.10 (s, 2H), 4.29 (m, 2H), 4.20 (m, 2H), 3.78 (m, 1H), 3.64 (m, 1H), 3.59 (m, 1H), 3.29 (m, 1H), 3.18 (m, 1H), 2.27 (m, 2H), 2.18 (m, 1H), 2.01 (m, 1H), 1.94 (m, 1H), 1.80 (m, 1H);

MS (+ve ESI): 600 $(M+H)^+$.

Example 262 – Preparation of compound 262 in table 11 - 2-{4-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]piperazin-1-yl}ethyl dihydrogen phosphate

An analogous reaction to that described in example 255, but starting with *N*-(3-fluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (430 mg, 0.79 mmol) yielded compound 262 in table 11 (352 mg, 61% yield):

^{1}H-NMR (DMSO d_6): 10.83 (br s, 1H), 8.92 (s, 1H), 8.84 (d, 1H), 8.40 (s, 1H), 8.04 (s, 1H), 7.60 (dd, 1H), 7.45 (dd, 1H), 7.30 (m, 3H), 6.90 (m, 1H), 5.15 (s, 2H), 4.30 (t, 2H), 4.20 (m, 2H), 3.35 (m, 12H), 2.25 (m, 2H);

MS (+ve ESI): 629 $(M+H)^+$.

Example 263 – Preparation of compound 263 in table 11 - 3-{[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]amino}propyl dihydrogen phosphate

An analogous reaction to that described in example 255, but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3-hydroxypropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (270 mg, 0.53 mmol) yielded compound 263 in table 11 (140 mg, 38% yield):

^{1}H-NMR (DMSO d_6): 11.98 (br s, 1H), 10.40 (s, 1H), 9.15 (br s, 1H), 8.90 (s, 1H), 8.85 (d, 1H), 8.40 (s, 1H), 8.05 (s, 1H), 7.68 (t, 1H), 7.50 (d, 1H), 7.30 (s, 1H), 7.18 (m, 2H), 5.25 (s, 2H), 4.35 (t, 2H), 4.00 (q, 2H), 3.15 (app. s, 2H), 3.05 (app. s, 2H), 2.30 (quintet, 2H), 2.05 (quintet, 2H);

MS (+ve ESI): 592 $(M+H)^+$.

Example 264 – Preparation of compound 264 in table 11 - 2-{[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate

An analogous reaction to that described in example 255, but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (280 mg, 0.5 mmol) yielded compound 264 in table 11 (180 mg, 47% yield):

^{1}H-NMR (DMSO d_6): 11.96 (br s, 1H), 10.41 (br s, 1H), 8.94 (s, 1H), 8.84 (d, 1H), 8.40 (s, 1H), 8.02 (s, 1H), 7.62 (t, 1H), 7.45 (d, 1H), 7.35 (s, 1H), 7.20 (m, 2H), 5.20 (s, 2H), 4.30 (t, 2H), 4.15 (br q, 2H), 3.20 (m, 4H), 2.20 (br quintet, 2H);

MS (+ve ESI): 578 $(M+H)^+$.

Example 265 – Preparation of compound 265 in table 11 –2-[[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](2-methoxyethyl)amino]ethyl dihydrogen phosphate

An analogous reaction to that described in example 255, but starting with *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (483 mg, 0.9 mmol) yielded compound 265 in table 11 (520 mg, 82% yield):

^{1}H-NMR (DMSOd_6, TFA): 9.01 (s, 1H), 8.69 (d, 1H), 8.42 (s, 1H), 8.0 (s, 1H), 7.6 (d, 1H), 7.52 (d, 1H), 7.38 (m, 1H), 7.33 (m, 2H), 6.92 (m, 1H), 5.15 (s, 2H), 4.31 (t, 2H), 4.26 (m, 2H), 3.73 (m, 2H), 3.54 (m, 2H), 3.48 (m, 2H), 3.41 (m, 2H), 2.28 (m, 2H);
MS (+ve ESI): 618.22 $(M+H)^+$.

Example 266 – Preparation of compound 266 in table 11 - 3-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](ethyl)amino]propyl dihydrogen phosphate

An analogous reaction to that described in example 255, but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[ethyl(3-hydroxypropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (200 mg, 0.37 mmol) yielded compound 266 in table 11 (155 mg, 57% yield):

^{1}H-NMR (DMSO d_6): 11.75 (br s, 1H), 9.98 (s, 1H), 8.92 (d, 1H), 8.84 (s, 1H), 8.42 (s, 1H), 8.05 (s, 1H), 7.70 (m, 1H), 7.45 (m, 2H), 7.10 (m, 2H), 5.15 (s, 2H), 4.42 (t, 2H), 4.05 (m, 2H), 3.25 (m, 6H), 2.30 (m, 2H), 2.05 (m, 2H), 1.25 (t, 3H);
MS (+ve ESI): 620 $(M+H)^+$.

Example 267 – Preparation of compound 267 in table 11 - 3-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](propyl)amino]propyl dihydrogen phosphate

An analogous reaction to that described in example 255, but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3-hydroxypropyl)(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (150 mg, 0.27 mmol) yielded compound 267 in table 11 (60 mg; 30% yield):

^{1}H-NMR (DMSO d_6): 11.75 (br s, 1H), 10.01 (s, 1H), 8.84 (m, 2H), 8.42 (s, 1H), 8.05 (s, 1H), 7.70 (m, 1H), 7.45 (m, 2H), 7.10 (m, 2H), 5.15 (s, 2H), 4.42 (t, 2H), 4.05 (m, 2H), 3.25 (m, 6H), 2.30 (m, 2H), 2.05 (m, 4H), 1.01 (t, 3H);
MS (+ve ESI): 634 $(M+H)^+$.

Example 268 – Preparation of compound 268 in table 11 - 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](propyl)amino]-2-oxoethyl dihydrogen phosphate

An analogous reaction to that described in example 255 but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[glycoloyl(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (0.23 g, 0.416 mmol) yielded compound 268 in table 11 (0.141 g, 46% yield):

^{1}H-NMR (DMSO d_6): 11.90 (br s, 1H), 10.43 (br s, 1H), 8.95 (s, 1H), 8.84 (m, 1H), 8.42 (s, 1H), 8.03 (s, 1H), 7.70 (t, 1H), 7.48 (t, 1H), 7.27 (m, 3H), 5.22 (s, 2H), 4.52 (t, 2H), 4.22 (d, 2H), 3.45 (m, 2H), 3.22 (m, 2H), 2.06 (m, 2H), 1.55 (m, 2H), 0.83 (t, 3H);

MS (+ve ESI): 634 $(M+H)^+$.

Example 269 – Preparation of compound 269 in table 11 - 2-{4-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]piperazin-1-yl}-2-oxoethyl dihydrogen phosphate

An analogous reaction to that described in example 255 but starting with *N*-(2,3-difluorophenyl)-2-[4-({7-[3-(4-glycoloylpiperazin-1-yl)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide (0.18 g, 0.30 mmol) yielded compound 269 in table 11 (0.125 g, 52% yield):

^{1}H-NMR (DMSO d_6): 11.71 (br s, 1H), 10.07 (s, 1H), 8.87 (s, 1H), 8.85 (s, 1H), 8.40 (s, 1H), 8.08 (s, 1H), 7.62 (m, 1H), 7.42 (m, 2H), 7.15 (m, 2H), 5.20 (s, 2H), 4.57 (d, 2H), 4.41 (t, 2H), 3.95 (br s, 2H), 3.65 (s, 2H), 3.31 (m, 6H), 2.37 (m, 2H);

MS (+ve ESI): 661 $(M+H)^+$

MS (-ve ESI): 659 $(M-H)^-$.

Example 270 –Preparation of compound 270 in table 11 - {(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-fluoroquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate

An analogous reaction to that described in example 255 but starting with *N*-(2,3-Difluorophenyl)-2-{4-[(6-fluoro-7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (0.205 g, 0.37mmol) yielded compound 270 in table 11 (0.183 g, 66% yield):

^{1}H-NMR (DMSO d_6): 11.74 (s, 1H), 10.40 (s, 1H), 8.95 (d, 1H), 8.91 (s, 1H), 8.43 (s, 1H), 8.05 (s, 1H), 7.72 (m, 1H), 7.63 (m, 1H), 7.21 (m, 2H), 5.22 (s, 2H), 4.40 (m, 2H), 4.20 (m, 2H), 3.80 (m, 1H), 3.66 (m, 1H), 3.57 (m, 1H), 3.31 (m, 1H), 3.21 (m, 1H), 2.32 (m, 2H), 2.20 (m, 1H), 2.04 (m, 1H), 1.95 (m, 1H), 1.5 (m, 1H).

Example 271 – Preparation of compound 271 in table 11 - 4-((1-(2-((2,3-difluorophenyl)amino)-2-oxoethyl)-1*H*-pyrazol-4-yl)amino)-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-6-yl dihydrogen phosphate

An analogous reaction to that described in example 255 but starting with *N*-(2,3-difluorophenyl)-2-(4-((6-hydroxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-yl)amino)-1*H*-pyrazol-1-yl)acetamide (0.075 g, 0.14 mmol) yielded compound 271 in table 11 (0.045 g, 46% yield):

^{1}H-NMR (DMSO d_6 + acetic acid d_4): 8.70 (s, 1H), 8.47 (s, 1H), 8.29 (s, 1H), 7.85 (s, 1H), 7.68 (m, 1H), 7.07 (m, 3H), 5.16 (s, 2H), 3.78 (d, 2H), 3.40 (m, 2H), 2.91 (t, 2H), 2.72 (s, 3H), 2.05 (m, 3H), 1.60 (m, 2H);

MS (+ve ESI): 604 $(M+H)^+$.

Example 272 – Preparation of compound 272 in table 11 - {(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-5-isopropoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate

An analogous reaction to that described in example 255, but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-5-isopropoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (0.200 g, 0.34 mmol) yielded compound 272 in table 11 (0.150 g, 57% yield):

^{1}H-NMR (DMSO d_6): 10.55 (s, 1H), 10.00 (s, 1H), 8.80 (s, 1H) 8.40 (s, 1H), 7.85 (s, 1H), 7.70 (s, 1H), 7.20 (m, 2H), 7.00 (s, 1H), 6.95 (s, 1H), 5.18 (s, 2H), 5.01 (m, 1H), 4.30 (m, 2H), 4.15 (m, 1H), 3.52 (m, 4H), 3.35 (m, 2H), 2.08 (m, 6H), 1.55 (d, 6H);

MS (+ve ESI): 676 $(M+H)^+$.

Example 273 – Preparation of compound 273 in table 11 - 2-{4-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-5-isopropoxyquinazolin-7-yl}oxy)propyl]piperazin-1-yl}ethyl dihydrogen phosphate

An analogous reaction to that described in example 255, but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy}-5-isopropoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (0.086 g, 0.14 mmol) yielded compound 273 in table 11 (0.075 g, 67% yield):

^{1}H-NMR (DMSO d_6): 10.70 (s, 1H), 10.00 (s, 1H), 8.75 (s, 1H), 8.30 (s, 1H), 7.82 (s, 1H), 7.65 (m, 1H), 7.15 (m, 2H), 6.95 (s, 1H), 6.85 (s, 1H), 5.18 (s, 2H), 5.03 (septet, 1H), 4.35 (t, 2H), 4.20 (m, 2H), 3.15 (m, 4H), 3.20 (m, 4H), 2.35 (m, 4H), 2.20 (m, 2H), 1.52 (d, 6H);
MS (+ve ESI): 705 $(M+H)^+$.

Example 274 – Preparation of compound 274 in table 11 - 2-{[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-5-isopropoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate

An analogous reaction to that described in example 255, but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)amino]propoxy}-5-isopropoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (0.181 g, 0.33 mmol) yielded compound 274 in table 11 (0.170 g, 70% yield):

^{1}H-NMR (DMSO d_6): 10.60 (s, 1H), 10.00 (s, 1H), 8.75 (s, 1H), 8.30 (s, 1H), 7.82 (s, 1H), 7.65 (m, 1H), 7.15 (m, 2H), 6.95 (s, 1H), 6.85 (s, 1H), 5.15 (s, 2H), 4.99 (septet, 1H), 4.35 (t, 2H), 4.20 (m, 2H), 3.23 (t, 2H), 3.20 (t, 2H), 2.20 (m, 2H), 1.52 (d, 6H);
MS (+ve ESI): 636 $(M+H)^+$.

Example 275 – Preparation of compound 275 in table 11 - {(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-5-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate

An analogous reaction to that described in example 255, but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-5-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (0.120 g, 0.21 mmol) yielded compound 275 in table 11 (0.100 g, 66% yield):

^{1}H-NMR (DMSO d_6): 10.40 (s, 1H), 9.98 (s, 1H), 8.65 (s, 1H), 8.25 (s, 1H), 7.88 (s, 1H), 7.68 (m, 1H), 7.18 (m, 2H), 6.92 (s, 1H), 6.82 (s, 1H), 5.15 (s, 2H), 4.30 (m, 2H), 4.18 (dd, 2H), 4.15 (s, 3H), 3.45 (m, 5H), 2.15 (m, 6H);
MS (+ve ESI): 648 $(M+H)^+$.

Example 276 – Preparation of compound 276 in table 11 - {(2*R*)-1-[2-({4-[(1-{2-[(2,3-Difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)ethyl]pyrrolidin-2-yl}methyl dihydrogen phosphate.

An analogous reaction to that described in example 255, but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide gave compound 276 in table 11 (83% yield):

^{1}H-NMR (DMSO-d_6): 12.12 (s, 1H), 10.45 (s, 1H), 8.92 (s, 1H), 8.58 (s, 1H), 8.48 (s, 1H), 8.13 (s, 1H), 7.71 (m, 1H), 7.44 (s, 1H), 7.20 (m, 2H), 5.23 (s, 2H), 4.63 (m, 2H), 4.25 (t, 2H), 4.06 (s, 3H), 3.92 (m, 2H), 3.73 (m, 2H), 3.37 (m, 1H), 2.20 (m, 1H), 2.07 (m, 1H), 1.93 (m, 1H), 1.80 (m, 1H);

MS (+ve ESI): 634 $(M+H)^+$.

Example 277 – Preparation of compound 277 in table 11 - {(2*S*)-1-[2-({4-[(1-{2-[(2,3-Difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)ethyl]pyrrolidin-2-yl}methyl dihydrogen phosphate.

An analogous reaction to that described in example 255, but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide gave compound 277 in table 11 (66% yield):

^{1}H-NMR (DMSO-d_6): 12.12 (s, 1H), 10.45 (s, 1H), 8.92 (s, 1H), 8.58 (s, 1H), 8.48 (s, 1H), 8.13 (s, 1H), 7.71 (m, 1H), 7.44 (s, 1H), 7.20 (m, 2H), 5.23 (s, 2H), 4.63 (m, 2H), 4.25 (t, 2H), 4.06 (s, 3H), 3.92 (m, 2H), 3.73 (m, 2H), 3.37 (m, 1H), 2.20 (m, 1H), 2.07 (m, 1H), 1.93 (m, 1H), 1.80 (m, 1H);

MS (+ve ESI): 634 $(M+H)^+$.

Example 278 – Preparation of compound 278 in table 11 - 2-[[2-({4-[(1-{2-[(2,3-Difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)ethyl](tetrahydro-2*H*-pyran-4-yl)amino]ethyl dihydrogen phosphate.

An analogous reaction to that described in example 255, but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2-hydroxyethyl)(tetrahydro-2*H*-pyran-4-yl)amino]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide gave compound 278 in table 11 (81% yield):

^{1}H-NMR (DMSO-d_6): 12.10 (s, 1H), 10.47 (s, 1H), 8.91 (s, 1H), 8.57 (s, 1H), 8.47 (s, 1H), 8.12 (s, 1H), 7.71 (m, 1H), 7.40 (s, 1H), 7.21 (m, 2H), 5.24 (s, 2H), 4.65 (m, 2H), 4.34 (m, 2H), 4.01 (m, 2H), 3.78 (m, 3H), 3.58 (m, 2H), 3.33 (t, 2H), 2.10 (m, 2H), 1.80 (m, 2H); MS (+ve ESI): 678 $(M+H)^+$.

Example 279 – Preparation of compound 279 in table 11 - 2-{4-[3-({4-[(1-{2-[(2,3-Difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]-2-oxopiperazin-1-yl}ethyl dihydrogen phosphate.

Di-*tert*-butyl 2-{4-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]-2-oxopiperazin-1-yl}ethyl phosphate (210mg, 0.27mmol) and hydrogen chloride (0.5ml of a 4M solution in 1,4-dioxane) in 1,4-dioxane (3.0ml) were stirred at room temperature for 6 hours. The mixture was diluted with diethyl ether and then filtered to give compound 279 in table 11 (206mg, 98%) as a colourless solid: ^{1}H-NMR (DMSO-d_6): 12.00 (s, 1H), 10.44 (s, 1H), 8.96 (s, 1H), 8.91 (d, 1H), 8.44 (s, 1H), 8.06 (s, 1H), 7.70 (m, 1H), 7.47 (dd, 1H), 7.38 (d, 1H), 7.20 (m, 2H), 5.22 (s, 2H), 4.32 (t, 2H), 3.95 (m, 4H), 3.75 (m, 2H), 3.58 (m, 2H), 3.56 (s, 2H), 3.38 (m, 2H), 2.32 (quintet, 2H); MS (+ve ESI): 661 $(M+H)^+$.

di-*tert*-butyl 2-{4-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]-2-oxopiperazin-1-yl}ethyl phosphate used as starting material was prepared as follows:

a) Tetra-n-butylammonium di-*tert*-butyl phosphate (4.0g, 8.87mmol) and 1,2-dibromoethane (5.0g, 26.7mmol) in dimethoxyethane (20ml) were stirred and refluxed for 4hr. then cooled to room temperature and filtered. The filtrate was concentrated, diluted with diethyl ether, washed with 20% aqueous potassium carbonate solution, dried over magnesium sulphate and evaporated to leave a colourless oil. The crude product was purified by silica gel chromatography eluting with a 20-50% mixture of ethyl acetate in iso-hexane to give 2-bromoethyl di-*tert*-butyl phosphate (1.3 g, 46% yield) as a colourless oil: ^{1}H-NMR ($CDCl_3$): 4.22 (q, 2H), 3.53 (t, 2H), 1.49 (s, 18H).

b) 2-Bromoethyl di-*tert*-butyl phosphate (298mg, 0.94mmol) in tetrahydrofuran (1.0ml) was added at room temperature to a stirred suspension of benzyl 3-oxopiperazine-1-carboxylate (200mg, 0.85mmol), powdered potassium hydroxide (57mg, 1.0mmol) and tetra-n-butylammonium bromide (55mg, 0.17mmol) in THF (2.0ml). The reaction mixture was

stirred for 90 minutes and then filtered through Celite and the filtrate evaporated to leave a colourless oil. The crude product was purified by silica gel chromatography eluting with a 2-5% mixture of methanol in dichloromethane to give benzyl 4-{2-[(di-*tert*-butoxyphosphoryl)oxy]ethyl}-3-oxopiperazine-1-carboxylate (220 mg, 55% yield) as a colourless oil:

^{1}H-NMR ($CDCl_3$): 7.34 (m, 5H), 5.16 (s, 2H), 4.15 (s, 2H), 4.11 (m, 2H), 3.71 (m, 2H), 3.65 (m, 2H), 3.53 (m, 2H), 1.47 (s, 18H).

c) Benzyl 4-{2-[(di-*tert*-butoxyphosphoryl)oxy]ethyl}-3-oxopiperazine-1-carboxylate (1.20 g, 2.55 mmol) and 10% palladium on carbon (100 mg) in methanol (25 ml) were stirred at room temperature under an atmosphere of hydrogen for 2 hours and then filtered through Celite. The filtrate was evaporated to give di-*tert*-butyl 2-(2-oxopiperazin-1-yl)ethyl phosphate as a colourless oil which was dissolved in dimethylacetamide(4.0 ml) containing 2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide hydrochloride (326 mg, 0.64 mmol) and potassium iodide (213 mg, 1.28 mmol) and the mixture was then heated at 90°C for 3 hours. The mixture was cooled to room temperature, poured into dilute aqueous sodium hydrogen carbonate solution and then extracted with a solution of 10% isopropanol in dichloromethane. The organic layer was dried over magnesium sulphate and then evaporated to leave an orange oil. The crude product was purified by silica gel chromatography eluting with 5% methanol in dichloromethane containing 0-4% 7N ammonia in methanol to give di-*tert*-butyl 2-{4-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]-2-oxopiperazin-1-yl}ethyl phosphate (211 mg, 43% yield) as a pale yellow solid:
MS (+ve ESI): 773 $(M+H)^+$.

Example 280 – Preparation of compound 280 in table 11 - 2-[[2-({4-[(1-{2-[(2,3-Difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)ethyl](tetrahydro-2*H*-pyran-4-yl)amino]ethyl dihydrogen phosphate.

An analogous reaction to that described in example 255, but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2-hydroxyethyl)(tetrahydro-2*H*-pyran-4-yl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide gave compound 280 in table 11 (2% yield):

^{1}H-NMR (DMSO-d_6): 12.08 (s, 1H), 10.44 (s, 1H), 8.98 (d, 1H), 8.97 (s, 1H), 8.44 (s, 1H), 8.07 (s, 1H), 7.69 (m, 1H), 7.52 (dd, 1H), 7.41 (d, 1H), 7.20 (m, 2H), 5.22 (s, 2H), 4.65 (m,

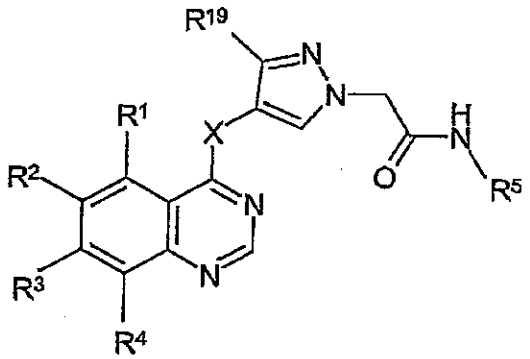
2H), 4.32 (m, 2H), 4.00 (m, 2H), 3.74 (m, 2H), 3.57 (m, 2H), 3.34 (m, 3H), 2.07 (m, 2H), 1.80 (m, 2H);

MS (+ve ESI): 648 $(M+H)^+$.

CLAIMS

What we claim is:

1. A compound of formula (I)



or a salt or ester thereof;

where:

X is O or NR^6;

$\mathbf{R^6}$ is hydrogen or C_{1-4}alkyl;

$\mathbf{R^1}$ is hydrogen, halo, or $-X^1R^{11}$;

$\mathbf{X^1}$ is a direct bond, $-CH_2=CH_2-$, -O-, -NH-, $-N(C_{1-6}alkyl)-$, -C(O)-, -C(O)O-, -OC(O)-, -NHC(O)-, $-N(C_{1-6}alkyl)C(O)-$, -C(O)NH- or $-C(O)N(C_{1-6}alkyl)-$;

$\mathbf{R^{11}}$ is hydrogen, or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, heterocyclyl, heterocyclylC_{1-4}alkyl, heterocyclylC_{2-4}alkenyl and heterocyclylC_{2-4}alkynyl which group is optionally substituted by 1 or 2 substituents independently selected from halo, hydroxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, $-NR^9R^{10}$, $-C(O)R^9$, $-C(O)NR^9R^{10}$ and $-C(O)OR^9$;

$\mathbf{R^2}$ is hydrogen, halo, nitro, cyano or $-X^2R^{12}$;

$\mathbf{X^2}$ is a direct bond, -O-, -NH-, $-N(C_{1-6}alkyl)-$, -OC(O)- or -C(O)O-;

$\mathbf{R^{12}}$ is hydrogen, or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, aryl, arylC_{1-4}alkyl, arylC_{2-4}alkenyl, arylC_{2-4}alkynyl, heterocyclyl, heterocyclylC_{1-4}alkyl, heterocyclylC_{2-4}alkenyl and heterocyclylC_{2-4}alkynyl, which group is optionally substituted by 1, 2 or 3 substituents selected from halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, $-NR^{15}R^{16}$, $-NHC(O)NR^{15}R^{16}$, $-C(O)R^{15}$ and $-C(O)OR^{15}$;

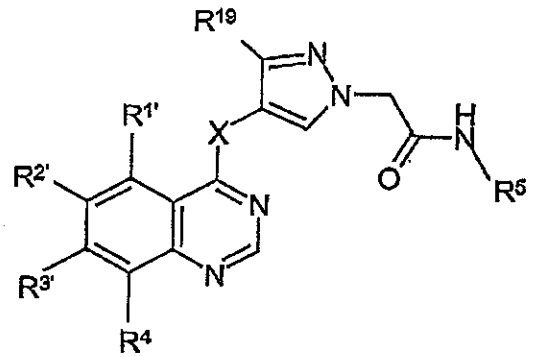
$\mathbf{R^3}$ is hydrogen, halo or $-X^3R^{13}$;

$\mathbf{X^3}$ is a direct bond, $-CH_2=CH_2-$, -O-, -NH-, $-N(C_{1-6}alkyl)-$, -C(O)-, -C(O)O-,

-OC(O)-, -NHC(O)-, -N(C_{1-6}alkyl)C(O)-, -C(O)NH- or -C(O)N(C_{1-6}alkyl)-;
R^{13} is hydrogen or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, aryl, arylC_{1-4}alkyl, arylC_{2-4}alkenyl, arylC_{2-4}alkynyl, heterocyclyl, heterocyclylC_{1-4}alkyl, heterocyclylC_{2-4}alkenyl and heterocyclylC_{2-4}alkynyl which group is optionally substituted by 1 or 2 substituents independently selected from $-NR^7R^8$, $-C(O)NR^7R^8$, halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, hydroxyC_{1-4}alkylcarbonyl, C_{1-4}alkylcarbonyl, aminoC_{1-4}alkylcarbonyl, C_{1-4}alkylaminoC_{1-4}alkylcarbonyl and bis(C_{1-4}alkyl)aminoC_{1-4}alkylcarbonyl;
R^7 and R^8 are independently selected from hydrogen, heterocyclyl, heterocyclylC_{1-4}alkyl, C_{1-4}alkylheterocyclylC_{1-4}alkyl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-4}alkoxyC_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-4}alkyl, hydroxyC_{3-6}cycloalkyl, hydroxyC_{1-4}alkylC_{3-6}cycloalkyl, hydroxyC_{3-6}cycloalkylC_{1-4}alkyl, hydroxyC_{1-4}alkylC_{3-6}cycloalkylC_{1-4}alkyl, C_{1-4}alkoxyC_{3-6}cycloalkyl, C_{1-4}alkoxyC_{3-6}cycloalkylC_{1-4}alkyl, haloC_{1-6}alkyl, haloC_{3-6}cycloalkyl, haloC_{3-6}cycloalkylC_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, cyanoC_{1-4}alkyl, aminoC_{1-6}alkyl, C_{1-4}alkylaminoC_{1-6}alkyl, bis(C_{1-4}alkyl)aminoC_{1-6}alkyl, hydroxyC_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkylcarbonyl, C_{1-4}alkylcarbonyl, aminoC_{1-4}alkylcarbonyl, C_{1-4}alkylaminoC_{1-4}alkylcarbonyl and bis(C_{1-4}alkyl)aminoC_{1-4}alkylcarbonyl;
or R^7 and R^8 together with the nitrogen to which they are attached form a heterocyclic ring which ring is monocyclic or bicyclic and comprises 4 to 7 ring atoms of which one is nitrogen and of which another is optionally selected from N, NH, O, S, SO and SO_2, and which ring is optionally substituted on carbon or nitrogen by 1 or 2 substituents independently selected from C_{1-4}alkyl, hydroxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkoxy, hydroxyC_{1-4}alkylcarbonyl, C_{1-4}alkylcarbonyl, aminoC_{1-4}alkylcarbonyl, C_{1-4}alkylaminoC_{1-4}alkylcarbonyl and bis(C_{1-4}alkyl)aminoC_{1-4}alkylcarbonyl, and where a ring $-CH_2-$ is optionally replaced with $-C(O)-$;
R^4 is selected from hydrogen, halo or $-X^4R^{14}$;
X^4 is a direct bond, -O-, -NH- or $-N(C_{1-6}alkyl)-$;
R^{14} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl;
R^5 is aryl or heteroaryl optionally substituted by 1, 2 or 3 substituents independently selected from halo, hydroxy, cyano, nitro, amino, C_{1-4}alkylamino, bis(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, $-CONHR^{17}$, $-NHCOR^{18}$ $-SR^{17}$, $-S(O)R^{17}$ and $-S(O)OR^{17}$;

R^9, R^{10}, R^{15} and R^{16} are independently selected from hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-4}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-4}alkylaminoC_{1-6}alkyl and bis(C_{1-4}alkyl)aminoC_{1-6}alkyl;
or R^9 and R^{10} together with the nitrogen to which they are attached form a heterocyclic ring which ring is monocyclic or bicyclic and comprises 4 to 7 ring atoms of which one is nitrogen and of which another is optionally selected from N, NH, O, S, SO and SO_2, and which ring is optionally substituted on carbon or nitrogen by 1 or 2 substituents independently selected from C_{1-4}alkyl, hydroxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkoxy, hydroxyC_{1-4}alkylcarbonyl, C_{1-4}alkylcarbonyl, aminoC_{1-4}alkylcarbonyl, C_{1-4}alkylaminoC_{1-4}alkylcarbonyl and bis(C_{1-4}alkyl)aminoC_{1-4}alkylcarbonyl, and where a ring $-CH_2-$ is optionally replaced with $-C(O)-$;
R^{17} and R^{18} are independently selected from hydrogen, C_{1-4}alkyl, C_{3-6}cycloalkyl, C_{2-4}alkenyl and C_{2-4}alkynyl;
R^{19} is hydrogen, hydroxyC_{1-4}alkyl, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-CONR^{20}R^{21}$, $-NHC(O)R^{20}$ or $-NHC(O)OR^{20}$;
R^{20} are R^{21} are independently selected from hydrogen, C_{1-4}alkyl and aryl.

2. A compound of formula (IA)



or a salt or ester thereof
where X, X^1, X^2, X^3, R^4, R^5 and R^{19} are as defined in relation to formula (I) and
$R^{1'}$ is hydrogen, halo, or $-X^1R^{11'}$;
$R^{11'}$ is hydrogen, phosphonooxy or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, heterocyclyl, heterocyclylC_{1-4}alkyl, heterocyclylC_{2-4}alkenyl and heterocyclylC_{2-4}alkynyl which group is optionally

substituted by a substituent selected from halo, hydroxy, phosphonooxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkyl, $-NR^{9'}R^{10'}$, $-C(O)R^{9'}$, $-C(O)NR^{9'}R^{10'}$ and $-C(O)OR^{9'}$;

$R^{2'}$ is hydrogen, halo, nitro, cyano or $-X^2R^{12'}$;

$R^{12'}$ is hydrogen, phosphonooxy or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, aryl, arylC_{1-4}alkyl, arylC_{2-4}alkenyl, arylC_{2-4}alkynyl, heterocyclyl, heterocyclylC_{1-4}alkyl, heterocyclylC_{2-4}alkenyl and heterocyclylC_{2-4}alkynyl, which group is optionally substituted by 1, 2 or 3 substituents selected from halo, hydroxy, phosphonooxy, C_{1-4}alkyl, C_{1-4}alkoxy, $-NR^{15}R^{16}$, $-NHC(O)NR^{15}R^{16}$, $-C(O)R^{15}$ and $-C(O)OR^{15}$;

$R^{3'}$ is hydrogen, halo or $-X^3R^{13'}$;

$R^{13'}$ is hydrogen, phosphonooxy or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, aryl, arylC_{1-4}alkyl, arylC_{2-4}alkenyl, arylC_{2-4}alkynyl, heterocyclyl, heterocyclylC_{1-4}alkyl, heterocyclylC_{2-4}alkenyl and heterocyclylC_{2-4}alkynyl which group is optionally substituted by 1 or 2 substituents independently selected from $-NR^{7'}R^{8'}$, $-C(O)NR^{7'}R^{8'}$, halo, hydroxy, phosphonooxy, C_{1-4}alkyl, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, phosponooxyC_{1-4}alkyl, hydroxyC_{1-4}alkylcarbonyl, phosphonooxyC_{1-4}alkylcarbonyl, C_{1-4}alkylcarbonyl, aminoC_{1-4}alkylcarbonyl, C_{1-4}alkylaminoC_{1-4}alkylcarbonyl and bis(C_{1-4}alkyl)aminoC_{1-4}alkylcarbonyl;

$R^{7'}$ and $R^{8'}$ are independently selected from hydrogen, heterocyclyl, heterocyclylC_{1-4}alkyl, C_{1-4}alkylheterocyclylC_{1-4}alkyl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, phosphonooxyC_{1-6}alkyl, C_{1-4}alkoxyC_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-4}alkyl, hydroxyC_{3-6}cycloalkyl, phosphonooxyC_{3-6}cycloalkyl, hydroxyC_{1-4}alkylC_{3-6}cycloalkyl, phosphonooxyC_{1-4}alkylC_{3-6}cycloalkyl, hydroxyC_{3-6}cycloalkylC_{1-4}alkyl, phosphonooxyC_{3-6}cycloalkylC_{1-4}alkyl, hydroxyC_{1-4}alkylC_{3-6}cycloalkylC_{1-4}alkyl, phosphonooxyC_{1-4}alkylC_{3-6}cycloalkylC_{1-4}alkyl, C_{1-4}alkoxyC_{3-6}cycloalkyl, C_{1-4}alkoxyC_{3-6}cycloalkylC_{1-4}alkyl, haloC_{1-6}alkyl, haloC_{3-6}cycloalkyl, haloC_{3-6}cycloalkylC_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, cyanoC_{1-4}alkyl, aminoC_{1-6}alkyl, C_{1-4}alkylaminoC_{1-6}alkyl, bis(C_{1-4}alkyl)aminoC_{1-6}alkyl, hydroxyC_{1-4}alkoxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkylcarbonyl, phosphonooxyC_{1-4}alkylcarbonyl, C_{1-4}alkylcarbonyl, aminoC_{1-4}alkylcarbonyl, C_{1-4}alkylaminoC_{1-4}alkylcarbonyl and bis(C_{1-4}alkyl)aminoC_{1-4}alkylcarbonyl;

or $R^{7'}$ and $R^{8'}$ together with the nitrogen to which they are attached form a heterocyclic ring which ring is monocyclic or bicyclic and comprises 4 to 7 ring atoms of which one is nitrogen and of which another is optionally selected from N, NH, O, S, SO and SO_2, and which ring is optionally substituted on carbon or nitrogen by 1 or 2 substituents independently selected from C_{1-4}alkyl, hydroxy, phosphonooxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkoxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkoxy, hydroxyC_{1-4}alkylcarbonyl, phosphonooxyC_{1-4}alkylcarbonyl, C_{1-4}alkylcarbonyl, aminoC_{1-4}alkylcarbonyl, C_{1-4}alkylaminoC_{1-4}alkylcarbonyl and bis(C_{1-4}alkyl)aminoC_{1-4}alkylcarbonyl, and where a ring $-CH_2-$ is optionally replaced with $-C(O)-$;

$R^{9'}$, $R^{10'}$, $R^{15'}$ and $R^{16'}$ are independently selected from hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-3}alkyl, hydroxyC_{1-6}alkyl, phosphonooxyC_{1-6}alkyl, haloC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl and bis(C_{1-6}alkyl)aminoC_{1-6}alkyl;

or $R^{9'}$ and $R^{10'}$ together with the nitrogen to which they are attached form a heterocyclic ring which ring is monocyclic or bicyclic and comprises 4 to 7 ring atoms of which one is nitrogen and of which another is optionally selected from N, NH, O, S, SO and SO_2, and which ring is optionally substituted on carbon or nitrogen by 1 or 2 substituents independently selected from C_{1-4}alkyl, hydroxy, phosphonooxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkoxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkoxy, hydroxyC_{1-4}alkylcarbonyl, phosphonooxyC_{1-4}alkylcarbonyl, C_{1-4}alkylcarbonyl, aminoC_{1-4}alkylcarbonyl, C_{1-4}alkylaminoC_{1-4}alkylcarbonyl and bis(C_{1-4}alkyl)aminoC_{1-4}alkylcarbonyl, and where a ring $-CH_2-$ is optionally replaced with $-C(O)-$;

provided that a compound of formula (IA) contains at least one phosphonooxy group.

3. A compound according to claim 2 or a salt or ester thereof containing only one phosphonooxy group.

4. A compound according to claim 1 or a salt or ester thereof wherein R^1 is hydrogen, halo or $-OR^{11}$ and R^{11} is hydrogen or a group selected from C_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-4}alkyl, which group is optionally substituted by a

substituent selected from hydroxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, hydroxyC_{1-4}alkylcarbonyl, aminoC_{1-4}alkylcarbonyl, C_{1-4}alkylaminoC_{1-4}alkylcarbonyl and bis(C_{1-4}alkyl)aminoC_{1-4}alkylcarbonyl.

5. A compound according to claim 4 or a salt or ester thereof wherein R^1 is hydrogen or $-OR^{11}$ and R^{11} is hydrogen, methyl, ethyl, propyl, isopropyl or pyrrolidinylmethyl which pyrrolidinylmethyl is optionally substituted by 2-hydroxyethyl, glycoloyl or N,N-dimethylglycyl.

6. A compound according to claim 4 or a salt or ester thereof wherein R^1 is hydrogen, fluoro, hydroxy, methoxy, isopropoxy, pyrrolidin-2-ylmethoxy, 1-(2-hydroxyethyl)pyrrolidin-2-ylmethoxy, 1-glycoloylpyrrolidin-2-ylmethoxy or 1-(N,N-dimethylglycyl)pyrrolidin-2-ylmethoxy.

7. A compound according to any one of claims 1, 4, 5 or 6 or a salt or ester thereof wherein R^2 is hydrogen, halo, $-OR^{12}$ or $-OC(O)R^{12}$ and R^{12} is hydrogen or a group selected from C_{1-4}alkyl, aryl, heterocyclyl and heterocyclylC_{1-4}alkyl which group is optionally substituted by a substituent selected from C_{1-4}alkyl and C_{1-4}alkoxy.

8. A compound according to claim 7 or a salt or ester thereof wherein R^2 is hydrogen or methoxy.

9. A compound according to claim 8 or a salt or ester thereof wherein R^2 is hydrogen.

10. A compound according to claim 8 or a salt or ester thereof wherein R^2 is methoxy.

11. A compound according to claim 1 or any one of claims 4 to 10 or a salt or ester thereof wherein R^3 is hydrogen or $-X^3R^{13}$ and R^{13} is hydrogen, methyl, ethyl, propyl, heterocyclyl, heterocyclylmethyl, heterocyclylethyl or heterocyclylpropyl which methyl, ethyl or propyl are optionally substituted by $-NR^7R^8$, $-C(O)NR^7R^8$ or 1 or 2 halo, hydroxy or C_{1-4}alkoxy substituents and which heterocyclylmethyl,

heterocyclylethyl or heterocyclylpropyl are optionally substituted on heterocyclyl by hydroxy, C_{1-4}alkyl, hydroxyC_{1-4}alkyl or hydroxyC_{1-4}alkylcarbonyl.

12. A compound according to claim 11 or a salt or ester thereof wherein X^3 is -O- and R^{13} is hydrogen, methyl, ethyl, propyl, heterocyclyl, heterocyclylmethyl, heterocyclylethyl or heterocyclylpropyl which methyl, ethyl or propyl are optionally substituted by $-NR^7R^8$, $-C(O)NR^7R^8$ or 1 or 2 halo, hydroxy or C_{1-4}alkoxy substituents and which heterocyclylmethyl, heterocyclylethyl or heterocyclylpropyl are optionally substituted on heterocyclyl by hydroxy, C_{1-4}alkyl, hydroxyC_{1-4}alkyl or hydroxyC_{1-4}alkylcarbonyl.

13. A compound according to claim 11 or claim 12 or a salt or ester thereof wherein R^7 and R^8 are independently selected from hydrogen, heterocyclyl, heterocyclylC_{1-4}alkyl, C_{1-4}alkylheterocyclylC_{1-4}alkyl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-4}alkyl, hydroxyC_{3-6}cycloalkyl, hydroxyC_{1-4}alkylC_{3-6}cycloalkyl, haloC_{1-6}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, cyanoC_{1-4}alkyl, aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkyl, bis(C_{1-4}alkyl)aminoC_{1-4}alkyl, hydroxyC_{1-4}alkoxyC_{1-4}alkyl and hydroxyC_{1-4}alkylcarbonyl; or R^7 and R^8 together with the nitrogen to which they are attached form a heterocyclic ring selected from azetidine, pyrrolidine, piperidine, morpholine, piperazine, diazepane, 1,4-diazepane and azabicyclo[3.1.0]hexane which ring is optionally substituted on carbon or nitrogen by 1 or 2 substituents independently selected from C_{1-4}alkyl, hydroxy, hydroxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl and hydroxyC_{1-4}alkylcarbonyl, and where a ring $-CH_2-$ is optionally replaced with -C(O)-.

14. A compound according to claim 2 or a salt or ester thereof wherein $R^{1'}$ is hydrogen, halo or $-OR^{11'}$ and $R^{11'}$ is hydrogen, phosphonooxy or a group selected from C_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-4}alkyl, which group is optionally substituted by a substituent selected from hydroxy, phosphonooxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkyl, hydroxyC_{1-4}alkylcarbonyl, phosphonooxyC_{1-4}alkylcarbonyl, aminoC_{1-4}alkylcarbonyl, C_{1-4}alkylaminoC_{1-4}alkylcarbonyl and bis(C_{1-4}alkyl)aminoC_{1-4}alkylcarbonyl.

15. A compound according to claim 2 or claim 14 or a salt or ester thereof wherein $R^{2'}$ is hydrogen, halo, $-OR^{12'}$ or $-OC(O)R^{12'}$ and $R^{12'}$ is hydrogen, phosphonooxy or a group selected from C_{1-4}alkyl, aryl, heterocyclyl and heterocyclylC_{1-4}alkyl which group is optionally substituted by a substituent selected from C_{1-4}alkyl and C_{1-4}alkoxy.

16. A compound according to any one of claims 2, 14 or 15 or a salt or ester thereof wherein $R^{3'}$ is hydrogen, phosponooxy or $-X^3R^{13'}$ and $R^{13'}$ is hydrogen or a group selected from C_{1-6}alkyl, aryl, arylC_{1-4}alkyl, heterocyclyl and heterocyclylC_{1-4}alkyl, which group is optionally substituted by 1 or 2 substituents independently selected from $-NR^{7'}R^{8'}$, $-C(O)NR^{7'}R^{8'}$, halo, hydroxy, phosphonooxy, C_{1-4}alkyl, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkyl, hydroxyC_{1-4}alkylcarbonyl, phosphonooxyC_{1-4}alkylcarbonyl and C_{1-4}alkylcarbonyl.

17. A compound according to claim 16 or a salt or ester thereof wherein $R^{7'}$ and $R^{8'}$ are independently selected from hydrogen, heterocyclyl, heterocyclylC_{1-4}alkyl, C_{1-4}alkylheterocyclylC_{1-4}alkyl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, phosphonooxyC_{1-6}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-4}alkyl, hydroxyC_{3-6}cycloalkyl, phosphonooxyC_{3-6}cycloalkyl, hydroxyC_{1-4}alkylC_{3-6}cycloalkyl, phosphonooxyC_{1-4}alkylC_{3-6}cycloalkyl, haloC_{1-6}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, cyanoC_{1-4}alkyl, aminoC_{1-4}alkyl, bis(C_{1-4}alkyl)aminoC_{1-4}alkyl, hydroxyC_{1-4}alkoxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkylcarbonyl and phosphonooxyC_{1-4}alkylcarbonyl; or $R^{7'}$ and $R^{8'}$ together with the nitrogen to which they are attached form a heterocyclic ring selected from azetidine, pyrrolidine, piperidine, morpholine, piperazine, diazepane, 1,4-diazepane and azabicyclo[3.1.0]hexane which ring is optionally substituted on carbon or nitrogen by 1 or 2 substituents independently selected from C_{1-4}alkyl, hydroxy, phosphonooxy, hydroxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkoxyC_{1-4}alkyl, phosphonooxyC_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl, hydroxyC_{1-4}alkylcarbonyl and phosphonooxyC_{1-4}alkylcarbonyl, and where a ring $-CH_2-$ is optionally replaced with $-C(O)-$.

18. A compound according to any one of the preceding claims or a salt or ester thereof wherein X is NH.

19. A compound according to any one of the preceding claims or a salt or ester thereof wherein R^4 is hydrogen.

20. A compound according to any one of the preceding claims or a salt or ester thereof wherein R^5 is aryl optionally substituted by 1 or 2 halo.

21. A compound according to any one of the preceding claims or a salt or ester thereof wherein R^{19} is hydrogen, hydroxycarbonyl, ethoxycarbonyl, aminocarbonyl and acetylamino.

22. A compound according to claim 18 or a salt or ester thereof wherein R^{19} is hydrogen.

23. A compound of formula (I) selected from:
2-(4-{[7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide;
2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide;
2-(4-{[7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide;
2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide;
2-(4-{[7-(2-chloroethoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide;
2-(4-{[7-(2-chloroethoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide;
N-(2,3-difluorophenyl)-2-(4-{[7-(2,2-dimethoxyethoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;
4-{[7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl]amino}-1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazole-3-carboxamide;
ethyl 4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazole-3-carboxylate;
2-(3-(acetylamino)-4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-[4-(quinazolin-4-ylamino)-1*H*-pyrazol-1-yl]acetamide;
2-(4-{[7-(3-chloropropoxy)-5-isopropoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide;
2-(4-{[7-(3-chloropropoxy)-5-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide;
2-(4-{[7-(3-chloropropoxy)-6-fluoroquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide;
2-(4-{[7-(3-chloropropoxy)-6-fluoroquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide;
N-(3-fluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(isobutyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
N-(3-fluorophenyl)-2-(4-{[6-methoxy-7-(3-piperidin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;
N-(3-fluorophenyl)-2-(4-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;
2-[4-({7-[3-(diethylamino)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(3-fluorophenyl)acetamide;
N-(3-fluorophenyl)-2-(4-{[6-methoxy-7-(3-piperazin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;
N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
2-[4-({7-[3-(cyclopropylamino)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(3-fluorophenyl)acetamide;
2-{4-[(7-{3-[[2-(dimethylamino)ethyl](methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;
N-(3-fluorophenyl)-2-[4-({6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;
N-(3-fluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-[4-({7-[3-(4-hydroxypiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

2-{4-[(7-{3-[bis(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[ethyl(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[[2-(dimethylamino)ethyl](ethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[2-(2-hydroxyethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[(cyclopropylmethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(6-methoxy-7-{3-[methyl(prop-2-yn-1-yl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[allyl(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[isobutyl(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-[4-({7-[3-(3-hydroxypiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[4-(hydroxymethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(6-methoxy-7-{3-[methyl(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[(cyclopropylmethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[[2-(diethylamino)ethyl](methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[[2-(diethylamino)ethyl](ethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-[4-({6-methoxy-7-[3-(4-methyl-1,4-diazepan-1-yl)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(isopropyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[cyclopropyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[cyclobutyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[(cyclopropylmethyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[(cyclobutylmethyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(prop-2-yn-1-yl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[allyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[(2,2-dimethylpropyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(3,3,3-trifluoropropyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-(4-{[7-(3-azetidin-1-ylpropoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide;

2-{4-[(6,7-dimethoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-hydroxy-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(isobutyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
N-(2,3-difluorophenyl)-2-[4-({7-[3-(dimethylamino)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;
N-(2,3-difluorophenyl)-2-(4-{[6-methoxy-7-(3-piperidin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;
N-(2,3-difluorophenyl)-2-(4-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;
N-(2,3-difluorophenyl)-2-(4-{[6-methoxy-7-(3-piperazin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;
N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide
2-[4-({7-[3-(cyclopropylamino)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(2,3-difluorophenyl)acetamide;
N-(2,3-difluorophenyl)-2-{4-[(7-{3-[[2-(dimethylamino)ethyl](methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
N-(2,3-difluorophenyl)-2-[4-({6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;
N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
N-(2,3-difluorophenyl)-2-[4-({7-[3-(4-hydroxypiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;
2-{4-[(7-{3-[bis(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;
N-(2,3-difluorophenyl)-2-{4-[(7-{3-[ethyl(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
N-(2,3-difluorophenyl)-2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
N-(2,3-difluorophenyl)-2-{4-[(7-{3-[[2-(dimethylamino)ethyl](ethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[2-(2-hydroxyethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
N-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
2-{4-[(7-{3-[(cyclopropylmethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;
N-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
N-(2,3-difluorophenyl)-2-{4-[(6-methoxy-7-{3-[methyl(prop-2-yn-1-yl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
N-(2,3-difluorophenyl)-2-{4-[(7-{3-[isobutyl(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
N-(2,3-difluorophenyl)-2-[4-({7-[3-(3-hydroxypiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;
N-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(hydroxymethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
N-(2,3-difluorophenyl)-2-{4-[(6-methoxy-7-{3-[methyl(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
2-{4-[(7-{3-[(cyclopropylmethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;
2-{4-[(7-{3-[[2-(diethylamino)ethyl](methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;
2-{4-[(7-{3-[[2-(diethylamino)ethyl](ethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;
N-(2,3-difluorophenyl)-2-[4-({6-methoxy-7-[3-(4-methyl-1,4-diazepan-1-yl)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;
N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(isopropyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
2-{4-[(7-{3-[cyclopropyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;
N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[cyclobutyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;
2-{4-[(7-{3-[(cyclopropylmethyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;
2-{4-[(7-{3-[(cyclobutylmethyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;
N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(prop-2-yn-1-yl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
2-{4-[(7-{3-[allyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;
N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2,2-dimethylpropyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(3,3,3-trifluoropropyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;
N-(2,3-difluorophenyl)-2-(4-{[7-(2-{4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl}ethoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;
N-(2,3-difluorophenyl)-2-{4-[(7-{2-[2-(hydroxymethyl)piperidin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2-hydroxy-1,1-dimethylethyl)amino]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
N-(2,3-difluorophenyl)-2-{4-[(7-{2-[4-(2-hydroxyethyl)piperazin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(*trans*-4-hydroxycyclohexyl)amino]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
N-(2,3-difluorophenyl)-2-{4-[(7-{2-[3-(hydroxymethyl)piperidin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
N-(2,3-difluorophenyl)-2-(4-{[7-(2-{[1-(hydroxymethyl)cyclopentyl]amino}ethoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;
N-(2,3-difluorophenyl)-2-{4-[(7-{2-[4-(3-hydroxypropyl)piperazin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{2-[cyclohexyl(2-hydroxyethyl)amino]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2-hydroxyethyl)(propyl)amino]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(3-hydroxy-2,2-diethylpropyl)amino]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-[4-({6-methoxy-7-[2-(tetrahydro-2*H*-pyran-4-ylamino)ethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

2-{4-[(7-{2-[cyclobutyl(2-hydroxyethyl)amino]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2-hydroxyethyl)(tetrahydro-2*H*-pyran-4-yl)amino]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2*R*)-2-(2-hydroxyethyl)piperidin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2*S*)-2-(2-hydroxyethyl)piperidin-1-yl]ethoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(isobutyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[cyclopentyl(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(hydroxymethyl)piperidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3-hydroxy-1,1-dimethylpropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[(2-cyanoethyl)(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3-hydroxy-2,2-dimethylpropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3-hydroxypropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3-hydroxypropyl)(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[ethyl(3-hydroxypropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)-3-oxopiperazin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-[4-({7-[3-(propylamino)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(3-piperazin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[glycoloyl(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-[4-({7-[3-(4-glycoloylpiperazin-1-yl)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(3-{[*trans*-2-(hydroxymethyl)cyclohexyl]amino}propoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(1α,5α,6α)-6-(hydroxymethyl)-3-azabicyclo[3.1.0]hex-3-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(3-{[(2*R*)-2-hydroxypropyl]amino}propoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(3-{[(1*S*)-2-hydroxy-1-methylethyl]amino}propoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxy-1,1-dimethylethyl)amino]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2,3-dihydroxypropyl)amino]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(3-{[2-(2-hydroxyethoxy)ethyl]amino}propoxy)quinazolin-4-yl]amino}-1H-pyrazol-1-yl)acetamide;

2-[4-({7-[3-(4-acetylpiperazin-1-yl)propoxy]quinazolin-4-yl}amino)-1H-pyrazol-1-yl]-N-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(tetrahydrofuran-2-ylmethyl)amino]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

2-[4-({7-[3-(allylamino)propoxy]quinazolin-4-yl}amino)-1H-pyrazol-1-yl]-N-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(3-{[1-(hydroxymethyl)-2-methylpropyl]amino}propoxy)quinazolin-4-yl]amino}-1H-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(3-{[(5-methylisoxazol-3-yl)methyl]amino}propoxy)quinazolin-4-yl]amino}-1H-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-[4-({7-[3-(tetrahydro-2H-pyran-4-ylamino)propoxy]quinazolin-4-yl}amino)-1H-pyrazol-1-yl]acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3S)-3-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(3-hydroxypropoxy)quinazolin-4-yl]amino}-1H-pyrazol-1-yl)acetamide;

2-(4-{[7-(3-aminopropoxy)quinazolin-4-yl]amino}-1H-pyrazol-1-yl)-N-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2S,4R)-4-hydroxy-2-(hydroxymethyl)pyrrolidin-1-l]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(3-hydroxy-2,2-dimethylpropyl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{2-[cyclohexyl(2-hydroxyethyl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

2-[4-({7-[2-(cyclopropylamino)ethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(2,3-difluorophenyl)acetamide;

2-[4-({7-[2-(cyclobutylamino)ethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-[4-({7-[2-(tetrahydro-2*H*-pyran-4-ylamino)ethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

2-[4-({7-[2-(cyclopentylamino)ethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2-hydroxyethyl)(tetrahydro-2*H*-pyran-4-yl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{2-[cyclopentyl(2-hydroxyethyl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{2-[cyclopropyl(2-hydroxyethyl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

2-{4-[(7-{2-[cyclobutyl(2-hydroxyethyl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

2-{4-[(7-{2-[cyclopentyl(3-hydroxypropyl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

2-{4-[(7-{2-[cyclopentyl(glycoloyl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(3*S*)-3-(hydroxymethyl)-4-methylpiperazin-1-yl]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2*R*)-2-(hydroxymethyl)-4-methylpiperazin-1-yl]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[4-(hydroxymethyl)piperidin-1-yl]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[4-(2-hydroxyethyl)piperidin-1-yl]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{2-[(2-hydroxyethyl)amino]ethoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(2-{[*trans*-2-(hydroxymethyl)cyclohexyl]amino}ethoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-(4-{[7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(tetrahydro-2H-pyran-4-yl)amino]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2R)-2-(2-hydroxyethyl)piperidin-1-yl]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2S)-2-(2-hydroxyethyl)piperidin-1-yl]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2R)-2-(hydroxymethyl)-4-methylpiperazin-1-yl]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3S)-3-(hydroxymethyl)-4-methylpiperazin-1-yl]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2R)-2-(hydroxymethyl)morpholin-4-yl]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3S)-3-(hydroxymethyl)morpholin-4-yl]propoxy}quinazolin-4-yl)amino]-1H-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-[4-({7-[3-(glycoloylamino)propoxy]quinazolin-4-yl}amino)-1H-pyrazol-1-yl]acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[4-(hydroxymethyl)piperidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(3-hydroxy-1,1-dimethylpropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[2-(2-hydroxyethyl)piperidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(tetrahydrofuran-3-yl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-(4-{[7-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(3-fluorophenyl)-2-[4-({7-[(2*S*)-pyrrolidin-2-ylmethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{[(2*S*)-1-(2-hydroxyethyl)pyrrolidin-2-yl]methoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{[(2*S*)-1-glycoloylpyrrolidin-2-yl]methoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-(4-{[7-(pyrrolidin-3-ylmethoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{[1-(2-hydroxyethyl)pyrrolidin-3-yl]methoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-[4-({7-[(1-glycoloylpyrrolidin-3-yl)methoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-hydroxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2-fluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2-fluorophenyl)acetamide;

2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-phenylacetamide;

2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-phenylacetamide;

N-(2,6-difluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}-6-fluoroquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[(cyclopropylmethyl)(2-hydroxyethyl)amino]propoxy}-6-fluoroquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(6-fluoro-7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(6-fluoro-7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[cyclopentyl(2-hydroxyethyl)amino]propoxy}-6-fluoroquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

2-{4-[(7-{3-[bis(2-hydroxyethyl)amino]propoxy}-5-isopropoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-5-isopropoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy}-5-isopropoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-(4-{[5-isopropoxy-7-(3-piperazin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-5-isopropoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)amino]propoxy}-5-isopropoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-[4-({7-[3-(4-glycoloylpiperazin-1-yl)propoxy]-5-isopropoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-5-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
N-(2,3-difluorophenyl)-2-{4-[(5,7-dimethoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
N-(2,3-difluorophenyl)-2-{4-[(5-hydroxy-7-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
N-(2,3-difluorophenyl)-2-[4-({7-methoxy-5-[(2*R*)-pyrrolidin-2-ylmethoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;
N-(2,3-difluorophenyl)-2-{4-[(5-{[(2*R*)-1-glycoloylpyrrolidin-2-yl]methoxy}-7-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
N-(2,3-difluorophenyl)-2-{4-[(5-{[(2*R*)-1-(*N*,*N*-dimethylglycyl)pyrrolidin-2-yl]methoxy}-7-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
N-(2,3-difluorophenyl)-2-{4-[(5-{[(2*R*)-1-(2-hydroxyethyl)pyrrolidin-2-yl]methoxy}-7-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
N-(2,3-difluorophenyl)-2-{4-[(5-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
N-(2,3-difluorophenyl)-2-{4-[(5-fluoroquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
N-(3-fluorophenyl)-2-(4-{[7-methoxy-6-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;
N-(3-fluorophenyl)-2-[4-({7-methoxy-6-[(1-methylpyrrolidin-3-yl)oxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;
N-(3-fluorophenyl)-2-(4-{[7-methoxy-6-(2-morpholin-4-ylethoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;
2-(4-{[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide;
N-(3-fluorophenyl)-2-{4-[(6-hydroxy-7-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;
4-((1-(2-((2,3-difluorophenyl)amino)-2-oxoethyl)-1*H*-pyrazol-4-yl)amino)-7-((1-methylpiperidn-4-yl)methoxy)quinazolin-6-yl benzoate;
N-(2,3-difluorophenyl)-2-(4-((6-hydroxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-yl)amino)-1*H*-pyrazol-1-yl)acetamide;

1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-4-[(7-{3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazole-3-carboxamide;

1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazole-3-carboxamide;

2-{3-(acetylamino)-4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

ethyl 1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazole-3-carboxylate; and

1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazole-3-carboxylic acid;

or a salt or ester thereof.

24. A compound of formula (IA) selected from:

2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](propyl)amino]ethyl dihydrogen phosphate;

{(2*S*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

{(2*S*)-1-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

2-{ethyl[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate;

{(2*R*)-1-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](2-methoxyethyl)amino]ethyl dihydrogen phosphate;

{(2*S*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

{(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

{(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](ethyl)amino]ethyl dihydrogen phosphate;

2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](propyl)amino]ethyl dihydrogen phosphate;

2-{cyclobutyl[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate;

2-{cyclobutyl[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate;

2-[[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](2-methoxyethyl)amino]ethyl dihydrogen phosphate;

2-[[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](propyl)amino]ethyl dihydrogen phosphate;

2-{4-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]piperazin-1-yl}ethyl dihydrogen phosphate;

2-{ethyl[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate;

2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](ethyl)amino]ethyl dihydrogen phosphate;

3-{[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]amino}-3-methylbutyl dihydrogen phosphate;

3-{[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]amino}-3-methylbutyl dihydrogen phosphate;

{(2*R*)-1-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

2-{4-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]piperazin-1-yl}ethyl dihydrogen phosphate

3-{[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]amino}propyl dihydrogen phosphate;

2-{[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate;

2-[[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](2-methoxyethyl)amino]ethyl dihydrogen phosphate;

3-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](ethyl)amino]propyl dihydrogen phosphate;

3-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](propyl)amino]propyl dihydrogen phosphate;

2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](propyl)amino]-2-oxoethyl dihydrogen phosphate;

2-{4-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]piperazin-1-yl}-2-oxoethyl dihydrogen phosphate;

{(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-fluoroquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

4-((1-(2-((2,3-difluorophenyl)amino)-2-oxoethyl)-1*H*-pyrazol-4-yl)amino)-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-6-yl dihydrogen phosphate;

{(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-5-isopropoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

2-{4-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-5-isopropoxyquinazolin-7-yl}oxy)propyl]piperazin-1-yl}ethyl dihydrogen phosphate;

2-{[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-5-isopropoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate;

{(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-5-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

{(2*R*)-1-[2-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)ethyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

{(2*S*)-1-[2-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)ethyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

2-[[2-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)ethyl](tetrahydro-2*H*-pyran-4-yl)amino]ethyl dihydrogen phosphate;

2-{4-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]qinazolin-7-yl}oxy)propyl]-2-oxopiperazin-1-yl}ethyl dihydrogen phosphate; and

2-[[2-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)ethyl](tetrahydro-2*H*-pyran-4-yl)amino]ethyl dihydrogen phosphate;

or a salt or ester thereof.

25. A compound according to any one of the preceding claims or a salt or ester thereof for use as a medicament.

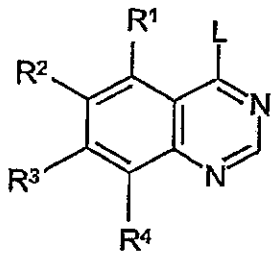
26. The use of a compound according to any one of claim 1 to 24 or a salt or ester thereof, in the preparation of a medicament for the treatment of a hyperproliferative disease.

27. The use according to claim 26 where the hyperproliferative disease is cancer.

28. The use of a compound according to any one of claims 1 to 24, in the preparation of a medicament for the treatment of colorectal, breast, lung, prostate, bladder, renal or pancreatic cancer or leukaemia or lymphoma.

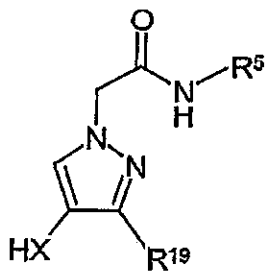
29. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 24, or a pharmaceutically acceptable salt or ester thereof, in association with a pharmaceutically acceptable diluent or carrier.

30. A process for the preparation of a compound according to claim 1 or a pharmaceutically acceptable salt or ester thereof, which process comprises reacting a compound of formula (II)



(II)

where L is a suitable leaving group and R^1, R^2, R^3, R^4 are as defined in claim 1 with a compound of formula (III)



(III)

wherein R^5 and R^{19} are as defined in claim 1
in the presence of hydrochloric acid in dioxane under an inert atmosphere,
and thereafter if necessary:
i) converting a compound of the formula (I) into another compound of the formula (I); and/or
ii) removing any protecting groups; and/or
iii) forming a salt or ester thereof.

31. A process for the preparation of a compound according to claim 2 or a pharmaceutically acceptable salt thereof, which process comprises phosphorylation of a compound according to claim 1, followed by deprotection of the phosphate group to yield a compound according to claim 2.