QUINAZOLINE DERIVATIVES AS ANGIOGENESIS INHIBITORS

The present invention relates to quinazoline derivatives, processes for their preparation, pharmaceutical compositions containing them as active ingredient, methods for the treatment of disease states associated with angiogenesis and/or increased vascular permeability, to their use as medicaments and to their use in the manufacture of medicaments for use in the production of antiangiogenic and/or vascular permeability reducing effects in warm-blooded animals such as humans.

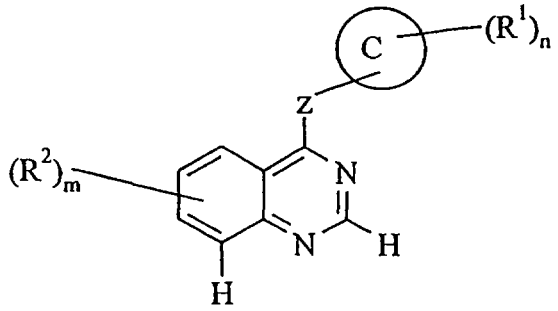
Normal angiogenesis plays an important role in a variety of processes including embryonic development, wound healing and several components of female reproductive function. Undesirable or pathological angiogenesis has been associated with disease states including diabetic retinopathy, psoriasis, cancer, rheumatoid arthritis, atheroma, Kaposi's sarcoma and haemangioma (Fan et al, 1995, Trends Pharmacol. Sci. 16: 57-66; Folkman, 1995, Nature Medicine 1: 27-31). Alteration of vascular permeability is thought to play a role in both normal and pathological physiological processes (Cullinan-Bove et al, 1993, Endocrinology 133: 829-837; Senger et al, 1993, Cancer and Metastasis Reviews, 12: 303-324). Several polypeptides with in vitro endothelial cell growth promoting activity have been identified including, acidic and basic fibroblast growth factors (aFGF & bFGF) and vascular endothelial growth factor (VEGF). By virtue of the restricted expression of its receptors, the growth factor activity of VEGF, in contrast to that of the FGFs, is relatively specific towards endothelial cells. Recent evidence indicates that VEGF is an important stimulator of both normal and pathological angiogenesis (Jakeman et al, 1993, Endocrinology, 133: 848-859; Kolch et al, 1995, Breast Cancer Research and Treatment, 36:139-155) and vascular permeability (Connolly et al, 1989, J. Biol. Chem. 264: 20017-20024). Antagonism of VEGF action by sequestration of VEGF with antibody can result in inhibition of tumour growth (Kim et al, 1993, Nature 362: 841-844). Basic FGF (bFGF) is a potent stimulator of angiogenesis (e.g. Hayek et al, 1987, Biochem. Biophys. Res. Commun. 147: 876-880) and raised levels of FGFs have been found in the serum (Fujimoto et al, 1991, Biochem. Biophys. Res. Commun. 180: 386-392) and urine (Nguyen et al, 1993, J. Natl. Cancer. Inst. 85: 241-242) of patients with cancer.

Receptor tyrosine kinases (RTKs) are important in the transmission of biochemical signals across the plasma membrane of cells. These transmembrane molecules

characteristically consist of an extracellular ligand-binding domain connected through a segment in the plasma membrane to an intracellular tyrosine kinase domain. Binding of ligand to the receptor results in stimulation of the receptor-associated tyrosine kinase activity which leads to phosphorylation of tyrosine residues on both the receptor and other intracellular molecules. These changes in tyrosine phosphorylation initiate a signalling cascade leading to a variety of cellular responses. To date, at least nineteen distinct RTK subfamilies, defined by amino acid sequence homology, have been identified. One of these subfamilies is presently comprised by the fms-like tyrosine kinase receptor, Flt or Flt1, the kinase insert domain-containing receptor, KDR (also referred to as Flk-1), and another fms-like tyrosine kinase receptor, Flt4. Two of these related RTKs, Flt and KDR, have been shown to bind VEGF with high affinity (De Vries et al, 1992, Science 255: 989-991; Terman et al, 1992, Biochem. Biophys. Res. Comm. 1992, 187: 1579-1586). Binding of VEGF to these receptors expressed in heterologous cells has been associated with changes in the tyrosine phosphorylation status of cellular proteins and calcium fluxes.

The present invention is based on the discovery of compounds that surprisingly inhibit the effects of VEGF, a property of value in the treatment of disease states associated with angiogenesis and/or increased vascular permeability such as cancer, diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, excessive scar formation and adhesions, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation. Compounds of the present invention generally possess higher potency against VEGF receptor tyrosine kinase than against epidermal growth factor (EGF) receptor tyrosine kinase. Compounds of the invention which have been tested possess activity against VEGF receptor tyrosine kinase such that they may be used in an amount sufficient to inhibit VEGF receptor tyrosine kinase whilst demonstrating no significant activity against EGF receptor tyrosine kinase. Compounds of the present invention generally possess higher potency against VEGF receptor tyrosine kinase than against FGF R1 receptor tyrosine kinase. Compounds of the invention which have been tested possess activity against VEGF receptor tyrosine kinase such that they may be used in an amount sufficient to inhibit VEGF receptor tyrosine kinase whilst demonstrating no significant activity against FGF R1 receptor tyrosine kinase.

According to one aspect of the present invention there is provided the use of a compound of the formula I:



(I)

wherein:

ring C is an 8, 9, 10, 12 or 13-membered bicyclic or tricyclic moiety which moiety may be saturated or unsaturated, which may be aromatic or non-aromatic, and which optionally may contain 1-3 heteroatoms selected independently from O, N and S;

Z is -O-, -NH-, -S-, $-CH_2-$ or a direct bond;

n is an integer from 0 to 5;

m is an integer from 0 to 3;

R^2 represents hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkylsulphanyl, $-NR^3R^4$ (wherein R^3 and R^4, which may be the same or different, each represents hydrogen or C_{1-3}alkyl), or R^5X^1- (wherein X^1 represents a direct bond, -O-, $-CH_2-$, -OC(O)-, -C(O)-, -S-, -SO-, $-SO_2-$, $-NR^6C(O)-$, $-C(O)NR^7-$, $-SO_2NR^8-$, $-NR^9SO_2-$ or $-NR^{10}-$ (wherein R^6, R^7, R^8, R^9 and R^{10} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl), and R^5 is selected from one of the following twenty-two groups:

1) hydrogen, oxiranylC_{1-4}alkyl or C_{1-5}alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, chloro, bromo and amino;

2) C_{1-5}alkyl$X^2C(O)R^{11}$ (wherein X^2 represents -O- or $-NR^{12}-$ (in which R^{12} represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{11} represents C_{1-3}alkyl, $-NR^{13}R^{14}$ or $-OR^{15}$ (wherein R^{13}, R^{14} and R^{15} which may be the same or different each represents hydrogen, C_{1-5}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

3) C_{1-5}alkylX^3R^{16} (wherein X^3 represents -O-, -S-, -SO-, $-SO_2-$, -OC(O)-, $-NR^{17}C(O)-$, $-C(O)NR^{18}-$, $-SO_2NR^{19}-$, $-NR^{20}SO_2-$ or $-NR^{21}-$ (wherein R^{17}, R^{18}, R^{19}, R^{20} and R^{21} each

independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{16} represents hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl or a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C_{1-3}alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1-4}alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl));

4) C_{1-5}alkylX^4C_{1-5}alkylX^5R^{22} (wherein X^4 and X^5 which may be the same or different are each -O-, -S-, -SO-, -SO_2-, -NR^{23}C(O)-, -C(O)NR^{24}-, -SO_2NR^{25}-, -$NR^{26}SO_2$- or -NR^{27}- (wherein R^{23}, R^{24}, R^{25}, R^{26} and R^{27} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{22} represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl);

5) R^{28} (wherein R^{28} is a 4-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl));

6) C_{1-5}alkylR^{28} (wherein R^{28} is as defined hereinbefore);

7) C_{2-5}alkenylR^{28} (wherein R^{28} is as defined hereinbefore);

8) C_{2-5}alkynylR^{28} (wherein R^{28} is as defined hereinbefore);

9) R^{29} (wherein R^{29} represents a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-3 heteroatoms selected from O, N and S, which pyridone, phenyl or aromatic heterocyclic group may carry up to 5 substituents

selected from hydroxy, halogeno, amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, trifluoromethyl, cyano, -$C(O)NR^{30}R^{31}$, -$NR^{32}C(O)R^{33}$ (wherein R^{30}, R^{31}, R^{32} and R^{33}, which may be the same or different, each represents hydrogen, C_{1-4}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl));

10) C_{1-5}alkylR^{29} (wherein R^{29} is as defined hereinbefore);

11) C_{2-5}alkenylR^{29} (wherein R^{29} is as defined hereinbefore);

12) C_{2-5}alkynylR^{29} (wherein R^{29} is as defined hereinbefore);

13) C_{1-5}alkylX^6R^{29} (wherein X^6 represents -O-, -S-, -SO-, -SO_2-, -$NR^{34}C(O)$-, -$C(O)NR^{35}$-, -SO_2NR^{36}-, -$NR^{37}SO_2$- or -NR^{38}- (wherein R^{34}, R^{35}, R^{36}, R^{37} and R^{38} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{29} is as defined hereinbefore);

14) C_{2-5}alkenylX^7R^{29} (wherein X^7 represents -O-, -S-, -SO-, -SO_2-, -$NR^{39}C(O)$-, -$C(O)NR^{40}$-, -SO_2NR^{41}-, -$NR^{42}SO_2$- or -NR^{43}- (wherein R^{39}, R^{40}, R^{41}, R^{42} and R^{43} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{29} is as defined hereinbefore);

15) C_{2-5}alkynylX^8R^{29} (wherein X^8 represents -O-, -S-, -SO-, -SO_2-, -$NR^{44}C(O)$-, -$C(O)NR^{45}$-, -SO_2NR^{46}-, -$NR^{47}SO_2$- or -NR^{48}- (wherein R^{44}, R^{45}, R^{46}, R^{47} and R^{48} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{29} is as defined hereinbefore);

16) C_{1-4}alkylX^9C_{1-4}alkylR^{29} (wherein X^9 represents -O-, -S-, -SO-, -SO_2-, -$NR^{49}C(O)$-, -$C(O)NR^{50}$-, -SO_2NR^{51}-, -$NR^{52}SO_2$- or -NR^{53}- (wherein R^{49}, R^{50}, R^{51}, R^{52} and R^{53} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{29} is as defined hereinbefore);

17) C_{1-4}alkylX^9C_{1-4}alkylR^{28} (wherein X^9 and R^{28} are as defined hereinbefore);

18) C_{2-5}alkenyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C_{1-4}alkylamino, N,N-di(C_{1-4}alkyl)amino, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl and N,N-di(C_{1-4}alkyl)aminosulphonyl;

19) C_{2-5}alkynyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C_{1-4}alkylamino, N,N-di(C_{1-4}alkyl)amino, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl and N,N-di(C_{1-4}alkyl)aminosulphonyl;

20) C_{2-5}alkenylX^9C_{1-4}alkylR^{28} (wherein X^9 and R^{28} are as defined hereinbefore);

21) C_{2-5}alkynylX^9C_{1-4}alkylR^{28} (wherein X^9 and R^{28} are as defined hereinbefore); and

22) C_{1-4}alkylR^{54}(C_{1-4}alkyl)$_q$(X^9)$_r$$R^{55}$ (wherein X^9 is as defined hereinbefore, q is 0 or 1, r is 0 or 1, and R^{54} and R^{55} are each independently selected from hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl and a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C_{1-3}alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1-4}alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl), with the proviso that R^{54} cannot be hydrogen);

and additionally wherein any C_{1-5}alkyl, C_{2-5}alkenyl or C_{2-5}alkynyl group in R^5X^1- may bear one or more substituents selected from hydroxy, halogeno and amino);

R^1 represents hydrogen, oxo, halogeno, hydroxy, C_{1-4}alkoxy, C_{1-4}alkyl, C_{1-4}alkoxymethyl, C_{1-4}alkanoyl, C_{1-4}haloalkyl, cyano, amino, C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-3}alkanoyloxy, nitro, C_{1-4}alkanoylamino, C_{1-4}alkoxycarbonyl, C_{1-4}alkylsulphanyl, C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl, carbamoyl, N-C_{1-4}alkylcarbamoyl, N,N-di(C_{1-4}alkyl)carbamoyl, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl, N,N-di(C_{1-4}alkyl)aminosulphonyl, N-(C_{1-4}alkylsulphonyl)amino, N-(C_{1-4}alkylsulphonyl)-N-(C_{1-4}alkyl)amino, N,N-di(C_{1-4}alkylsulphonyl)amino, a C_{3-7}alkylene chain joined to two ring C carbon atoms, C_{1-4}alkanoylaminoC_{1-4}alkyl, carboxy or a group $R^{56}X^{10}$ (wherein X^{10} represents a direct bond, -O-, -CH_2-, -OC(O)-, -C(O)-, -S-, -SO-, -SO_2-, -NR^{57}C(O)-, -C(O)NR^{58}-, -SO_2NR^{59}-, -$NR^{60}SO_2$- or -NR^{61}- (wherein R^{57}, R^{58}, R^{59}, R^{60} and R^{61} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl), and R^{56} is selected from one of the following twenty-two groups:

1) hydrogen, oxiranylC_{1-4}alkyl or C_{1-5}alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, chloro, bromo and amino;

2) C_{1-5}alkylX^{11}C(O)R^{62} (wherein X^{11} represents -O- or -NR^{63}- (in which R^{63} represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{62} represents C_{1-3}alkyl, -$NR^{64}R^{65}$ or -OR^{66} (wherein R^{64}, R^{65} and R^{66} which may be the same or different each represents hydrogen, C_{1-5}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

3) C_{1-5}alkyl$X^{12}R^{67}$ (wherein X^{12} represents -O-, -S-, -SO-, $-SO_2$-, -OC(O)-, $-NR^{68}C(O)$-, $-C(O)NR^{69}$-, $-SO_2NR^{70}$-, $-NR^{71}SO_2$- or $-NR^{72}$- (wherein R^{68}, R^{69}, R^{70}, R^{71} and R^{72} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{67} represents hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl or a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C_{1-3}alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1-4}alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl));

4) C_{1-5}alkyl$X^{13}C_{1-5}$alkyl$X^{14}R^{73}$ (wherein X^{13} and X^{14} which may be the same or different are each -O-, -S-, -SO-, $-SO_2$-, $-NR^{74}C(O)$-, $-C(O)NR^{75}$-, $-SO_2NR^{76}$-, $-NR^{77}SO_2$- or $-NR^{78}$- (wherein R^{74}, R^{75}, R^{76}, R^{77} and R^{78} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{73} represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl);

5) R^{79} (wherein R^{79} is a 4-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl));

6) C_{1-5}alkylR^{79} (wherein R^{79} is as defined hereinbefore);

7) C_{2-5}alkenylR^{79} (wherein R^{79} is as defined hereinbefore);

8) C_{2-5}alkynylR^{79} (wherein R^{79} is as defined hereinbefore);

9) R^{80} (wherein R^{80} represents a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-3 heteroatoms selected from O, N and S, which pyridone, phenyl or aromatic heterocyclic group may carry up to 5 substituents selected from hydroxy, halogeno, amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, trifluoromethyl, cyano, -$C(O)NR^{81}R^{82}$, -$NR^{83}C(O)R^{84}$ (wherein R^{81}, R^{82}, R^{83} and R^{84}, which may be the same or different, each represents hydrogen, C_{1-4}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl));

10) C_{1-5}alkylR^{80} (wherein R^{80} is as defined hereinbefore);

11) C_{2-5}alkenylR^{80} (wherein R^{80} is as defined hereinbefore);

12) C_{2-5}alkynylR^{80} (wherein R^{80} is as defined hereinbefore);

13) C_{1-5}alkyl$X^{15}R^{80}$ (wherein X^{15} represents -O-, -S-, -SO-, -SO_2-, -$NR^{85}C(O)$-, -$C(O)NR^{86}$-, -SO_2NR^{87}-, -$NR^{88}SO_2$- or -NR^{89}- (wherein R^{85}, R^{86}, R^{87}, R^{88} and R^{89} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{80} is as defined hereinbefore);

14) C_{2-5}alkenyl$X^{16}R^{80}$ (wherein X^{16} represents -O-, -S-, -SO-, -SO_2-, -$NR^{90}C(O)$-, -$C(O)NR^{91}$-, -SO_2NR^{92}-, -$NR^{93}SO_2$- or -NR^{94}- (wherein R^{90}, R^{91}, R^{92}, R^{93} and R^{94} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{80} is as defined hereinbefore);

15) C_{2-5}alkynyl$X^{17}R^{80}$ (wherein X^{17} represents -O-, -S-, -SO-, -SO_2-, -$NR^{95}C(O)$-, -$C(O)NR^{96}$-, -SO_2NR^{97}-, -$NR^{98}SO_2$- or -NR^{99}- (wherein R^{95}, R^{96}, R^{97}, R^{98} and R^{99} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{80} is as defined hereinbefore);

16) C_{1-4}alkyl$X^{18}C_{1-4}$alkylR^{80} (wherein X^{18} represents -O-, -S-, -SO-, -SO_2-, -$NR^{100}C(O)$-, -$C(O)NR^{101}$-, -SO_2NR^{102}-, -$NR^{103}SO_2$- or -NR^{104}- (wherein R^{100}, R^{101}, R^{102}, R^{103} and R^{104} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{80} is as defined hereinbefore);

17) C_{1-4}alkyl$X^{18}C_{1-4}$alkylR^{79} (wherein X^{18} and R^{79} are as defined hereinbefore);

18) C_{2-5}alkenyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C_{1-4}alkylamino, N,N-di(C_{1-4}alkyl)amino, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl and N,N-di(C_{1-4}alkyl)aminosulphonyl;

19) C_{2-5}alkynyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C_{1-4}alkylamino, N,N-di(C_{1-4}alkyl)amino, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl and N,N-di(C_{1-4}alkyl)aminosulphonyl;

20) C_{2-5}alkenyl$X^{18}C_{1-4}$alkylR^{79} (wherein X^{18} and R^{79} are as defined hereinbefore);

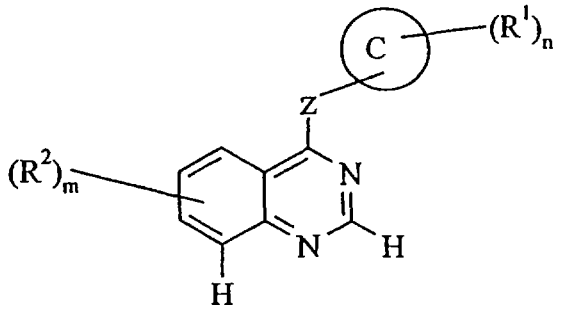
21) C_{2-5}alkynyl$X^{18}C_{1-4}$alkylR^{79} (wherein X^{18} and R^{79} are as defined hereinbefore); and

22) C_{1-4}alkyl$R^{105}(C_{1-4}alkyl)_x(X^{18})_yR^{106}$ (wherein X^{18} is as defined hereinbefore, x is 0 or 1, y is 0 or 1, and R^{105} and R^{106} are each independently selected from hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl and a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C_{1-3}alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1-4}alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl) with the proviso that R^{105} cannot be hydrogen);

and additionally wherein any C_{1-5}alkyl, C_{2-5}alkenyl or C_{2-5}alkynyl group in $R^{56}X^{10}$- may bear one or more substituents selected from hydroxy, halogeno and amino);

or a salt thereof, or a prodrug thereof for example an ester or an amide, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans.

According to another aspect of the present invention there is provided the use of compounds of the formula I:



(I)

wherein:

ring C is a 9-10-membered bicyclic moiety which may be saturated or unsaturated, which may be aromatic or non-aromatic, and which optionally may contain 1-3 heteroatoms selected independently from O, N and S;

Z is -O-, -NH-, -S-, $-CH_2-$ or a direct bond;

R^1 represents hydrogen, oxo, halogeno, hydroxy, C_{1-4}alkoxy, C_{1-4}alkyl, C_{1-4}alkoxymethyl, C_{1-4}alkanoyl, C_{1-4}haloalkyl, cyano, amino, C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-3}alkanoyloxy, nitro, C_{1-4}alkanoylamino, C_{1-4}alkoxycarbonyl, C_{1-4}alkylsulphanyl, C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl, carbamoyl, N-C_{1-4}alkylcarbamoyl, N,N-di(C_{1-4}alkyl)carbamoyl, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl, N,N-di(C_{1-4}alkyl)aminosulphonyl, N-(C_{1-4}alkylsulphonyl)amino, N-(C_{1-4}alkylsulphonyl)-N-(C_{1-4}alkyl)amino, N,N-di(C_{1-4}alkylsulphonyl)amino or a C_{3-7}alkylene chain joined to two ring C carbon atoms;

n is an integer from 0 to 5;

m is an integer from 0 to 3;

R^2 represents hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkylsulphanyl, $-NR^3R^4$ (wherein R^3 and R^4, which may be the same or different, each represents hydrogen or C_{1-3}alkyl), or R^5X^1- (wherein X^1 represents a direct bond, -O-, $-CH_2-$, -OC(O)-, -C(O)-, -S-, -SO-, $-SO_2-$, $-NR^6C(O)-$, $-C(O)NR^7-$, $-SO_2NR^8-$, $-NR^9SO_2-$ or $-NR^{10}-$ (wherein R^6, R^7, R^8, R^9 and R^{10} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl), and R^5 is selected from one of the following twenty-one groups:

1) hydrogen or C_{1-5}alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro and amino;

2) C_{1-5}alkyl$X^2C(O)R^{11}$ (wherein X^2 represents -O- or $-NR^{12}-$ (in which R^{12} represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{11} represents C_{1-3}alkyl, $-NR^{13}R^{14}$ or $-OR^{15}$

(wherein R^{13}, R^{14} and R^{15} which may be the same or different each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

3) C_{1-5}alkylX^3R^{16} (wherein X^3 represents -O-, -S-, -SO-, $-SO_2-$, -OC(O)-, $-NR^{17}C(O)-$, $-C(O)NR^{18}-$, $-SO_2NR^{19}-$, $-NR^{20}SO_2-$ or $-NR^{21}-$ (wherein R^{17}, R^{18}, R^{19}, R^{20} and R^{21} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{16} represents hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C_{1-3}alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1-4}alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl and C_{1-4}alkoxy);

4) C_{1-5}alkylX^4C_{1-5}alkylX^5R^{22} (wherein X^4 and X^5 which may be the same or different are each -O-, -S-, -SO-, $-SO_2-$, $-NR^{23}C(O)-$, $-C(O)NR^{24}-$, $-SO_2NR^{25}-$, $-NR^{26}SO_2-$ or $-NR^{27}-$ (wherein R^{23}, R^{24}, R^{25}, R^{26} and R^{27} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{22} represents hydrogen or C_{1-3}alkyl);

5) R^{28} (wherein R^{28} is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl and C_{1-4}alkylsulphonylC_{1-4}alkyl);

6) C_{1-5}alkylR^{28} (wherein R^{28} is as defined hereinbefore);

7) C_{2-5}alkenylR^{28} (wherein R^{28} is as defined hereinbefore);

8) C_{2-5}alkynylR^{28} (wherein R^{28} is as defined hereinbefore);

9) R^{29} (wherein R^{29} represents a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-3 heteroatoms selected from O, N and S, which pyridone, phenyl or aromatic heterocyclic group may carry up to 5 substituents on an available carbon atom selected from hydroxy, halogeno, amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, trifluoromethyl, cyano, $-C(O)NR^{30}R^{31}$ and $-NR^{32}C(O)R^{33}$ (wherein R^{30}, R^{31}, R^{32} and R^{33}, which may be the same or different, each represents hydrogen, C_{1-4}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

10) C_{1-5}alkylR^{29} (wherein R^{29} is as defined hereinbefore);

11) C_{2-5}alkenylR^{29} (wherein R^{29} is as defined hereinbefore);

12) C_{2-5}alkynylR^{29} (wherein R^{29} is as defined hereinbefore);

13) C_{1-5}alkylX^6R^{29} (wherein X^6 represents -O-, -S-, -SO-, $-SO_2$-, $-NR^{34}C(O)$-, $-C(O)NR^{35}$-, $-SO_2NR^{36}$-, $-NR^{37}SO_2$- or $-NR^{38}$- (wherein R^{34}, R^{35}, R^{36}, R^{37} and R^{38} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{29} is as defined hereinbefore);

14) C_{2-5}alkenylX^7R^{29} (wherein X^7 represents -O-, -S-, -SO-, $-SO_2$-, $-NR^{39}C(O)$-, $-C(O)NR^{40}$-, $-SO_2NR^{41}$-, $-NR^{42}SO_2$- or $-NR^{43}$- (wherein R^{39}, R^{40}, R^{41}, R^{42} and R^{43} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{29} is as defined hereinbefore);

15) C_{2-5}alkynylX^8R^{29} (wherein X^8 represents -O-, -S-, -SO-, $-SO_2$-, $-NR^{44}C(O)$-, $-C(O)NR^{45}$-, $-SO_2NR^{46}$-, $-NR^{47}SO_2$- or $-NR^{48}$- (wherein R^{44}, R^{45}, R^{46}, R^{47} and R^{48} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{29} is as defined hereinbefore);

16) C_{1-3}alkylX^9C_{1-3}alkylR^{29} (wherein X^9 represents -O-, -S-, -SO-, $-SO_2$-, $-NR^{49}C(O)$-, $-C(O)NR^{50}$-, $-SO_2NR^{51}$-, $-NR^{52}SO_2$- or $-NR^{53}$- (wherein R^{49}, R^{50}, R^{51}, R^{52} and R^{53} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{29} is as defined hereinbefore);

17) C_{1-3}alkylX^9C_{1-3}alkylR^{28} (wherein X^9 and R^{28} are as defined hereinbefore);

18) C_{2-5}alkenyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C_{1-4}alkylamino, N,N-di(C_{1-4}alkyl)amino, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl and N,N-di(C_{1-4}alkyl)aminosulphonyl;

19) C_{2-5}alkynyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C_{1-4}alkylamino, N,N-di(C_{1-4}alkyl)amino, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl and N,N-di(C_{1-4}alkyl)aminosulphonyl;

20) C_{2-5}alkenylX^9C_{1-4}alkylR^{28} (wherein X^9 and R^{28} are as defined hereinbefore); and

21) C_{2-5}alkynylX^9C_{1-4}alkylR^{28} (wherein X^9 and R^{28} are as defined hereinbefore);

and salts thereof, and prodrugs thereof for example esters, amides and sulphides, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans.

Preferably ring C is a 9-10-membered aromatic bicyclic moiety which may optionally contain 1-3 heteroatoms selected independently from O, N and S.

More preferably ring C is a 9-10-membered heteroaromatic bicyclic moiety which contains 1-3 heteroatoms selected independently from O, N and S.

Particularly ring C is a 9-10-membered heteroaromatic bicyclic moiety which contains 1 or 2 nitrogen atoms.

According to one aspect of the present invention ring C is a 9-membered heteroaromatic bicyclic moiety which contains 1 or 2 nitrogen atoms, for example indolyl.

According to another aspect of the present invention ring C is a 10-membered heteroaromatic bicyclic moiety which contains 1 or 2 nitrogen atoms, for example quinolinyl.

Especially ring C is indolyl or quinolinyl.

Preferably Z is -O-, -NH-, -S- or a direct bond.

More preferably Z is -O-, -NH- or -S-.

Particularly Z is -O- or -S-, especially -O-.

Advantageously X^{10} represents a direct bond, -O-, -S-, $-NR^{57}C(O)-$, $-NR^{60}SO_2-$ or $-NR^{61}-$ (wherein R^{57}, R^{60} and R^{61} each independently represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

Preferably X^{10} represents a direct bond, -O-, -S-, $-NR^{57}C(O)-$, $-NR^{60}SO_2-$ (wherein R^{57} and R^{60} each independently represents hydrogen or C_{1-2}alkyl) or NH.

More preferably X^{10} represents -O-, -S-, $-NR^{57}C(O)-$ (wherein R^{57} represents hydrogen or C_{1-2}alkyl) or NH.

Particularly X^{10} represents -O- or $-NR^{57}C(O)-$ (wherein R^{57} represents hydrogen or C_{1-2}alkyl), more particularly -O- or -NHC(O)-, especially -O-.

According to another aspect of the present invention X^{10} represents -O- or a direct bond.

Advantageously X^{12} represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{68}C(O)-$, $-NR^{71}SO_2-$ or $-NR^{72}-$ (wherein R^{68}, R^{71} and R^{72} each independently represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

Preferably X^{12} represents -O-, -S-, -SO-, $-SO_2-$ or $-NR^{72}-$ (wherein R^{72} represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

More preferably X^{12} represents -O- or $-NR^{72}-$ (wherein R^{72} represents hydrogen or C_{1-2}alkyl).

According to another aspect of the present invention X^{12} represents -O-, $-SO_2-$, $-NR^{71}SO_2-$ or $-NR^{72}-$ (wherein R^{71} and R^{72} each independently represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

Advantageously X^{18} represents -O-, -S- or $-NR^{104}-$ (wherein R^{104} represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

Preferably X^{18} represents -O- or -NR^{104}- (wherein R^{104} represents hydrogen or C_{1-2}alkyl).

According to another aspect of the present invention X^{18} represents -O-, -$CONR^{101}$- or -NR^{104}- (wherein R^{101} and R^{104} each independently represents hydrogen or C_{1-2}alkyl).

Advantageously R^{67} represents a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-3}cyanoalkyl, C_{1-3}alkyl, C_{1-3}hydroxyalkyl, C_{1-3}alkoxy, C_{1-2}alkoxyC_{1-3}alkyl, C_{1-2}alkylsulphonylC_{1-3}alkyl, C_{1-3}alkoxycarbonyl, C_{1-3}alkylamino, di(C_{1-3}alkyl)amino, C_{1-3}alkylaminoC_{1-3}alkyl, di(C_{1-3}alkyl)aminoC_{1-3}alkyl, C_{1-3}alkylaminoC_{1-3}alkoxy, di(C_{1-3}alkyl)aminoC_{1-3}alkoxy and a group -(-O-)$_f$(C_{1-3}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-3}alkyl).

Preferably R^{67} is pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino or thiomorpholino which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-3}cyanoalkyl, C_{1-3}alkyl, C_{1-3}hydroxyalkyl, C_{1-3}alkoxy, C_{1-2}alkoxyC_{1-3}alkyl, C_{1-2}alkylsulphonylC_{1-3}alkyl, C_{1-3}alkoxycarbonyl, C_{1-3}alkylamino, di(C_{1-3}alkyl)amino, C_{1-3}alkylaminoC_{1-3}alkyl, di(C_{1-3}alkyl)aminoC_{1-3}alkyl, C_{1-3}alkylaminoC_{1-3}alkoxy, di(C_{1-3}alkyl)aminoC_{1-3}alkoxy and a group -(-O-)$_f$(C_{1-3}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino and thiomorpholino, which cyclic group may bear one or more substituents selected from C_{1-3}alkyl).

More preferably R^{67} is pyrrolidinyl, piperazinyl, piperidinyl, azetidinyl, morpholino or thiomorpholino which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-3}cyanoalkyl, C_{1-3}alkyl, C_{1-3}hydroxyalkyl, C_{1-3}alkoxy, C_{1-2}alkoxyC_{1-3}alkyl, C_{1-2}alkylsulphonylC_{1-3}alkyl, C_{1-3}alkoxycarbonyl, C_{1-3}alkylamino, di(C_{1-3}alkyl)amino, C_{1-3}alkylaminoC_{1-3}alkyl, di(C_{1-3}alkyl)aminoC_{1-3}alkyl, C_{1-3}alkylaminoC_{1-3}alkoxy, di(C_{1-3}alkyl)aminoC_{1-3}alkoxy and a group -(-O-)$_f$(C_{1-3}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino).

Particularly R^{67} is pyrrolidinyl, piperazinyl, piperidinyl, azetidinyl, morpholino or thiomorpholino which group may bear 1 or 2 substituents selected from a group -(-O-)$_f$(C_{1-}

$_{3}$alkyl)$_{g}$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino).

Preferably R^{79} is pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino or thiomorpholino which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-3}cyanoalkyl, C_{1-3}alkyl, C_{1-3}hydroxyalkyl, C_{1-3}alkoxy, C_{1-2}alkoxyC_{1-3}alkyl, C_{1-2}alkylsulphonylC_{1-3}alkyl, C_{1-3}alkoxycarbonyl, C_{1-3}alkylamino, di(C_{1-3}alkyl)amino, C_{1-3}alkylaminoC_{1-3}alkyl, di(C_{1-3}alkyl)aminoC_{1-3}alkyl, C_{1-3}alkylaminoC_{1-3}alkoxy, di(C_{1-3}alkyl)aminoC_{1-3}alkoxy and a group -(-O-)$_{f}$(C_{1-3}alkyl)$_{g}$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino and thiomorpholino, which cyclic group may bear one or more substituents selected from C_{1-3}alkyl).

More preferably R^{79} is pyrrolidinyl, piperazinyl, piperidinyl, azetidinyl, morpholino or thiomorpholino which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-3}cyanoalkyl, C_{1-3}alkyl, C_{1-3}hydroxyalkyl, C_{1-3}alkoxy, C_{1-2}alkoxyC_{1-3}alkyl, C_{1-2}alkylsulphonylC_{1-3}alkyl, C_{1-3}alkoxycarbonyl, C_{1-3}alkylamino, di(C_{1-3}alkyl)amino, C_{1-3}alkylaminoC_{1-3}alkyl, di(C_{1-3}alkyl)aminoC_{1-3}alkyl, C_{1-3}alkylaminoC_{1-3}alkoxy, di(C_{1-3}alkyl)aminoC_{1-3}alkoxy and a group -(-O-)$_{f}$(C_{1-3}alkyl)$_{g}$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino).

Particularly R^{79} is pyrrolidinyl, piperazinyl, piperidinyl, azetidinyl, morpholino or thiomorpholino which group may bear 1 or 2 substituents selected from a group -(-O-)$_{f}$(C_{1-3}alkyl)$_{g}$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino).

Advantageously R^{105} and R^{106} are each independently a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-3}cyanoalkyl, C_{1-3}alkyl, C_{1-3}hydroxyalkyl, C_{1-3}alkoxy, C_{1-2}alkoxyC_{1-3}alkyl, C_{1-2}alkylsulphonylC_{1-3}alkyl, C_{1-3}alkoxycarbonyl, C_{1-3}alkylamino, di(C_{1-3}alkyl)amino, C_{1-3}alkylaminoC_{1-3}alkyl, di(C_{1-3}alkyl)aminoC_{1-3}alkyl, C_{1-3}alkylaminoC_{1-3}alkoxy, di(C_{1-3}alkyl)aminoC_{1-3}alkoxy and a group -(-O-)$_{f}$(C_{1-3}alkyl)$_{g}$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-3}alkyl).

Preferably R^{105} and R^{106} are each independently selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino and thiomorpholino which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-3}cyanoalkyl, C_{1-3}alkyl, C_{1-3}hydroxyalkyl, C_{1-3}alkoxy, C_{1-2}alkoxyC_{1-3}alkyl, C_{1-2}alkylsulphonylC_{1-3}alkyl, C_{1-3}alkoxycarbonyl, C_{1-3}alkylamino, di(C_{1-3}alkyl)amino, C_{1-3}alkylaminoC_{1-3}alkyl, di(C_{1-3}alkyl)aminoC_{1-3}alkyl, C_{1-3}alkylaminoC_{1-3}alkoxy, di(C_{1-3}alkyl)aminoC_{1-3}alkoxy and a group -(-O-)$_f$(C_{1-3}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino and thiomorpholino, which cyclic group may bear one or more substituents selected from C_{1-3}alkyl).

More preferably R^{105} and R^{106} are each independently selected from pyrrolidinyl, piperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-3}cyanoalkyl, C_{1-3}alkyl, C_{1-3}hydroxyalkyl, C_{1-3}alkoxy, C_{1-2}alkoxyC_{1-3}alkyl, C_{1-2}alkylsulphonylC_{1-3}alkyl, C_{1-3}alkoxycarbonyl, C_{1-3}alkylamino, di(C_{1-3}alkyl)amino, C_{1-3}alkylaminoC_{1-3}alkyl, di(C_{1-3}alkyl)aminoC_{1-3}alkyl, C_{1-3}alkylaminoC_{1-3}alkoxy, di(C_{1-3}alkyl)aminoC_{1-3}alkoxy and a group -(-O-)$_f$(C_{1-3}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino).

Particularly R^{105} and R^{106} are each independently selected from pyrrolidinyl, piperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino which group may bear 1 or 2 substituents selected from a group -(-O-)$_f$(C_{1-3}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino).

Advantageously R^1 represents oxo, halogeno, hydroxy, C_{1-4}alkoxy, C_{1-4}alkyl, C_{1-4}alkoxymethyl, C_{1-4}alkanoyl, C_{1-4}haloalkyl, cyano, amino, C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-3}alkanoyloxy, nitro, C_{1-4}alkanoylamino, C_{1-4}alkoxycarbonyl, C_{1-4}alkylsulphanyl, C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl, carbamoyl, N-C_{1-4}alkylcarbamoyl, N,N-di(C_{1-4}alkyl)carbamoyl, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl, N,N-di(C_{1-4}alkyl)aminosulphonyl, N-(C_{1-4}alkylsulphonyl)amino, N-(C_{1-4}alkylsulphonyl)-N-(C_{1-4}alkyl)amino, N,N-di(C_{1-4}alkylsulphonyl)amino, a C_{3-7}alkylene chain joined to two ring C

carbon atoms, C_{1-4}alkanoylaminoC_{1-4}alkyl, carboxy or a group $R^{56}X^{10}$ (wherein X^{10} is as defined hereinbefore and R^{56} is selected from one of the following nine groups:

1) C_{1-5}alkyl$X^{12}R^{67}$ (wherein X^{12} and R^{67} are as defined hereinbefore);

2) R^{79} (wherein R^{79} is as defined hereinbefore);

3) C_{1-5}alkylR^{79} (wherein R^{79} is as defined hereinbefore);

4) C_{2-5}alkenylR^{79} (wherein R^{79} is as defined hereinbefore);

5) C_{2-5}alkynylR^{79} (wherein R^{79} is as defined hereinbefore);

6) C_{1-3}alkyl$X^{18}C_{1-3}$alkylR^{79} (wherein X^{18} and R^{79} are as defined hereinbefore);

7) C_{2-5}alkenyl$X^{18}C_{1-4}$alkylR^{79} (wherein X^{18} and R^{79} are as defined hereinbefore);

8) C_{2-5}alkynyl$X^{18}C_{1-4}$alkylR^{79} (wherein X^{18} and R^{79} are as defined hereinbefore); and

9) C_{1-3}alkyl$R^{105}(C_{1-3}alkyl)_x(X^{18})_yR^{106}$ (wherein X^{18}, x, y, R^{105} and R^{106} are as defined hereinbefore;

and additionally wherein any C_{1-5}alkyl, C_{2-5}alkenyl or C_{2-5}alkynyl group in $R^{56}X^{10}$- may bear one or more substituents selected from hydroxy, halogeno and amino,

with the proviso that when X^{10} is a direct bond R^{56} is not R^{79}).

Preferably R^1 represents oxo, halogeno, hydroxy, C_{1-2}alkoxy, C_{1-2}alkyl, C_{1-2}alkoxymethyl, C_{2-3}alkanoyl, C_{1-2}haloalkyl, cyano, amino, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{2-3}alkanoyloxy, nitro, C_{2-3}alkanoylamino, C_{1-2}alkoxycarbonyl, C_{1-2}alkylsulphanyl, C_{1-2}alkylsulphinyl, C_{1-2}alkylsulphonyl, carbamoyl, N-C_{1-2}alkylcarbamoyl, N,N-di(C_{1-2}alkyl)carbamoyl, aminosulphonyl, N-C_{1-2}alkylaminosulphonyl, N,N-di(C_{1-2}alkyl)aminosulphonyl, N-(C_{1-2}alkylsulphonyl)amino, N-(C_{1-2}alkylsulphonyl)-N-(C_{1-2}alkyl)amino or a C_{3-7}alkylene chain joined to two ring C carbon atoms.

More preferably R^1 represents oxo, hydroxy, C_{1-2}alkoxymethyl, amino, halogeno, C_{1-2}alkyl, C_{1-2}alkoxy, trifluoromethyl, cyano, nitro, C_{2-3}alkanoyl.

Particularly R^1 represents methyl, ethyl, trifluoromethyl or halogeno.

Especially R^1 represents methyl, fluoro, chloro or bromo, more especially methyl or fluoro.

Preferably n is an integer from 0 to 3.

More preferably n is 0, 1 or 2.

Preferably m is an integer from 0 to 2, more preferably 1 or 2, most preferably 2.

Advantageously X^1 represents a direct bond, -O-, -S-, -$NR^6C(O)$-, -NR^9SO_2- or -NR^{10}- (wherein R^6, R^9 and R^{10} each independently represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

Preferably X^1 represents a direct bond, -O-, -S-, $-NR^6C(O)-$, $-NR^9SO_2-$ (wherein R^6 and R^9 each independently represents hydrogen or C_{1-2}alkyl) or NH.

More preferably X^1 represents -O-, -S-, $-NR^6C(O)-$ (wherein R^6 represents hydrogen or C_{1-2}alkyl) or NH.

Particularly X^1 represents -O- or $-NR^6C(O)-$ (wherein R^6 represents hydrogen or C_{1-2}alkyl), more particularly -O- or -NHC(O)-, especially -O-.

According to another aspect of the present invention X^1 represents -O- or a direct bond.

Advantageously X^2 represents -O- or NR^{12} (wherein R^{12} represents hydrogen, C_{1-3}alkyl or C_{1-2}alkoxyethyl).

Advantageously X^3 represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{17}C(O)-$, $-NR^{20}SO_2-$ or $-NR^{21}-$ (wherein R^{17}, R^{20} and R^{21} each independently represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

Preferably X^3 represents -O-, -S-, -SO-, $-SO_2-$ or $-NR^{21}-$ (wherein R^{21} represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

More preferably X^3 represents -O- or $-NR^{21}-$ (wherein R^{21} represents hydrogen or C_{1-2}alkyl).

According to another aspect of the present invention X^3 represents -O-, $-SO_2-$, $-NR^{20}SO_2-$ or $-NR^{21}-$ (wherein R^{20} and R^{21} each independently represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

Advantageously X^4 and X^5 which may be the same or different each represents -O-, -S-, -SO-, $-SO_2-$ or $-NR^{27}-$ (wherein R^{27} represents hydrogen, C_{1-3}alkyl or C_{1-2}alkoxyethyl).

Preferably X^4 and X^5 which may be the same or different each represents -O-, -S- or $-NR^{27}-$ (wherein R^{27} represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

More preferably X^4 and X^5 which may be the same or different each represents -O- or -NH-.

Advantageously X^6 represents -O-, -S- or $-NR^{38}-$ (wherein R^{38} represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

Preferably X^6 represents -O- or $-NR^{38}-$ (wherein R^{38} represents hydrogen or C_{1-2}alkyl).

Advantageously X^7 represents -O-, -S- or $-NR^{43}-$ (wherein R^{43} represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

Preferably X^7 represents -O- or $-NR^{43}-$ (wherein R^{43} represents hydrogen or C_{1-2}alkyl).

Advantageously X^8 represents -O-, -S- or -NR^{48}- (wherein R^{48} represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

Preferably X^8 represents -O- or -NR^{48}- (wherein R^{48} represents hydrogen or C_{1-2}alkyl).

Advantageously X^9 represents -O-, -S- or -NR^{53}- (wherein R^{53} represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

Preferably X^9 represents -O- or -NR^{53}- (wherein R^{53} represents hydrogen or C_{1-2}alkyl).

According to another aspect of the present invention X^9 represents -O-, -$CONR^{50}$- or -NR^{53}- (wherein R^{50} and R^{53} each independently represents hydrogen or C_{1-2}alkyl).

Conveniently R^{28} is pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino or thiomorpholino which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-3}cyanoalkyl, C_{1-3}alkyl, C_{1-3}hydroxyalkyl, C_{1-3}alkoxy, C_{1-2}alkoxyC_{1-3}alkyl, C_{1-2}alkylsulphonylC_{1-3}alkyl, C_{1-3}alkoxycarbonyl, C_{1-3}alkylamino, di(C_{1-3}alkyl)amino, C_{1-3}alkylaminoC_{1-3}alkyl, di(C_{1-3}alkyl)aminoC_{1-3}alkyl, C_{1-3}alkylaminoC_{1-3}alkoxy, di(C_{1-3}alkyl)aminoC_{1-3}alkoxy and a group -(-O-)$_f$(C_{1-3}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino and thiomorpholino, which cyclic group may bear one or more substituents selected from C_{1-3}alkyl).

Advantageously R^{28} is pyrrolidinyl, piperazinyl, piperidinyl, azetidinyl, morpholino or thiomorpholino which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-3}cyanoalkyl, C_{1-3}alkyl, C_{1-3}hydroxyalkyl, C_{1-3}alkoxy, C_{1-2}alkoxyC_{1-3}alkyl, C_{1-2}alkylsulphonylC_{1-3}alkyl, C_{1-3}alkoxycarbonyl, C_{1-3}alkylamino, di(C_{1-3}alkyl)amino, C_{1-3}alkylaminoC_{1-3}alkyl, di(C_{1-3}alkyl)aminoC_{1-3}alkyl, C_{1-3}alkylaminoC_{1-3}alkoxy, di(C_{1-3}alkyl)aminoC_{1-3}alkoxy and a group -(-O-)$_f$(C_{1-3}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino).

In one embodiment of the present invention R^{28} is pyrrolidinyl, piperazinyl, piperidinyl, azetidinyl, morpholino or thiomorpholino which group may bear 1 or 2 substituents selected from a group -(-O-)$_f$(C_{1-3}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino).

Particularly R^{28} is pyrrolidinyl, piperazinyl, piperidinyl, azetidinyl, morpholino or thiomorpholino which group may bear 1 or 2 substituents selected from oxo, hydroxy,

halogeno, cyano, C_{1-3}cyanoalkyl, C_{1-3}alkyl, C_{1-3}hydroxyalkyl, C_{1-3}alkoxy, C_{1-2}alkoxyC_{1-3}alkyl and C_{1-2}alkylsulphonylC_{1-3}alkyl.

According to another aspect of the present invention, preferably R^{28} is pyrrolidinyl, piperazinyl, piperidinyl, morpholino or thiomorpholino which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-3}cyanoalkyl, C_{1-3}alkyl, C_{1-3}hydroxyalkyl, C_{1-3}alkoxy, C_{1-2}alkoxyC_{1-3}alkyl and C_{1-2}alkylsulphonylC_{1-3}alkyl.

Where R^{29} is a 5-6-membered aromatic heterocyclic group, it preferably has 1 or 2 heteroatoms, selected from O, N and S, of which more preferably one is N, and may be substituted as hereinbefore defined.

R^{29} is particularly a pyridone, phenyl, pyridyl, imidazolyl, thiazolyl, thienyl, triazolyl or pyridazinyl group which group may be substituted as hereinbefore defined, more particularly a pyridone, pyridyl, imidazolyl, thiazolyl or triazolyl group, especially a pyridone, pyridyl, imidazolyl or triazolyl group which group may be substituted as hereinbefore defined.

In one embodiment of the invention R^{29} represents a pyridone, phenyl or 5-6-membered aromatic heterocyclic group with 1 to 3 heteroatoms selected from O, N and S, which group may preferably carry up to 2 substituents, more preferably up to one substituent, selected from the group of substituents as hereinbefore defined.

In the definition of R^{29}, conveniently substituents are selected from halogeno, C_{1-4}alkyl, C_{1-4}alkoxy, cyano and a group -(-O-)$_f$(C_{1-3}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino and thiomorpholino, which cyclic group may bear one or more substituents selected from C_{1-3}alkyl).

In the definition of R^{29}, more conveniently substituents are selected from chloro, fluoro, methyl, ethyl and a group -(-O-)$_f$(C_{1-3}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino).

According to another emodiment of the present invention in the definition of R^{29}, conveniently substituents are selected from halogeno, C_{1-4}alkyl, C_{1-4}alkoxy and cyano, more conveniently substituents are selected from chloro, fluoro, methyl and ethyl.

Advantageously R^{54} and R^{55} are each independently a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-}

$_3$cyanoalkyl, C_{1-3}alkyl, C_{1-3}hydroxyalkyl, C_{1-3}alkoxy, C_{1-2}alkoxyC_{1-3}alkyl, C_{1-2}alkylsulphonylC_{1-3}alkyl, C_{1-3}alkoxycarbonyl and a group -(-O-)$_f$(C_{1-3}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-3}alkyl).

Preferably R^{54} and R^{55} are each selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino and thiomorpholino which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-3}cyanoalkyl, C_{1-3}alkyl, C_{1-3}hydroxyalkyl, C_{1-3}alkoxy, C_{1-2}alkoxyC_{1-3}alkyl, C_{1-2}alkylsulphonylC_{1-3}alkyl, C_{1-3}alkoxycarbonyl and a group -(-O-)$_f$(C_{1-3}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino and thiomorpholino, which cyclic group may bear one or more substituents selected from C_{1-3}alkyl).

More preferably R^{54} and R^{55} are each selected from pyrrolidinyl, piperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-3}cyanoalkyl, C_{1-3}alkyl, C_{1-3}hydroxyalkyl, C_{1-3}alkoxy, C_{1-2}alkoxyC_{1-3}alkyl, C_{1-2}alkylsulphonylC_{1-3}alkyl, C_{1-3}alkoxycarbonyl and a group -(-O-)$_f$(C_{1-3}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino).

Particularly R^{54} and R^{55} are each selected from pyrrolidinyl, piperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino which group may bear 1 or 2 substituents selected from a group -(-O-)$_f$(C_{1-3}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino).

More particularly R^{54} and R^{55} are each selected from pyrrolidinyl, piperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino which group is unsubstituted.

Conveniently R^2 represents hydroxy, halogeno, cyano, nitro, trifluoromethyl, C_{1-3}alkyl, amino or R^5X^1- [wherein X^1 is as hereinbefore defined and R^5 is selected from one of the following twenty-two groups:

1) oxiranylC_{1-4}alkyl or C_{1-5}alkyl which may be unsubstituted or which may be substituted with one or more groups selected from fluoro, chloro and bromo, or C_{2-5}alkyl which may be unsubstituted or substituted with one or more groups selected from hydroxy and amino;

2) C_{2-3}alkylX^2C(O)R^{11} (wherein X^2 is as hereinbefore defined and R^{11} represents C_{1-3}alkyl, -$NR^{13}R^{14}$ or -OR^{15} (wherein R^{13}, R^{14} and R^{15} which may be the same or different are each C_{1-4}alkyl or C_{1-2}alkoxyethyl));

3) C_{2-4}alkylX^3R^{16} (wherein X^3 is as hereinbefore defined and R^{16} represents hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl or a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C_{1-3}alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1-3}alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl));

4) C_{2-3}alkylX^4C_{2-3}alkylX^5R^{22} (wherein X^4 and X^5 are as hereinbefore defined and R^{22} represents hydrogen or C_{1-3}alkyl);

5) R^{28} (wherein R^{28} is as defined hereinbefore);

6) C_{1-5}alkylR^{107} (wherein R^{107} is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group is linked to C_{1-5}alkyl through a carbon atom and which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl)) or C_{2-5}alkylR^{108} (wherein R^{108} is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, of which one is N and the other may be selected independently from O, S and N, which heterocyclic group is linked to C_{2-5}alkyl

through a nitrogen atom and which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl));

7) C_{3-4}alkenylR^{109} (wherein R^{109} represents R^{107} or R^{108} as defined hereinbefore);

8) C_{3-4}alkynylR^{109} (wherein R^{109} represents R^{107} or R^{108} as defined hereinbefore);

9) R^{29} (wherein R^{29} is as defined hereinbefore);

10) C_{1-5}alkylR^{29} (wherein R^{29} is as defined hereinbefore);

11) C_{3-5}alkenylR^{29} (wherein R^{29} is as defined hereinbefore);

12) C_{3-5}alkynylR^{29} (wherein R^{29} is as defined hereinbefore);

13) C_{1-5}alkylX^6R^{29} (wherein X^6 and R^{29} are as defined hereinbefore);

14) C_{4-5}alkenylX^7R^{29} (wherein X^7 and R^{29} are as defined hereinbefore);

15) C_{4-5}alkynylX^8R^{29} (wherein X^8 and R^{29} are as defined hereinbefore);

16) C_{2-3}alkylX^9C_{1-3}alkylR^{29} (wherein X^9 and R^{29} are as defined hereinbefore);

17) C_{2-3}alkylX^9C_{1-3}alkylR^{28} (wherein X^9 and R^{28} are as defined hereinbefore);

18) C_{2-5}alkenyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C_{1-4}alkylamino, N,N-di(C_{1-4}alkyl)amino, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl and N,N-di(C_{1-4}alkyl)aminosulphonyl;

19) C_{2-5}alkynyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C_{1-4}alkylamino, N,N-di(C_{1-4}alkyl)amino, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl and N,N-di(C_{1-4}alkyl)aminosulphonyl;

20) C_{2-5}alkenylX^9C_{1-3}alkylR^{28} (wherein X^9 and R^{28} are as defined hereinbefore);

21) C_{2-5}alkynylX^9C_{1-3}alkylR^{28} (wherein X^9 and R^{28} are as defined hereinbefore); and

22) C_{1-3}alkylR^{54}(C_{1-3}alkyl)$_q$(X^9)$_r$$R^{55}$ (wherein X^9, q, r, R^{54} and R^{55} are as defined hereinbefore);

and additionally wherein any C_{1-5}alkyl, C_{2-5}alkenyl or C_{2-5}alkynyl group in R^5X^1- may bear one or more substituents selected from hydroxy, halogeno and amino].

Advantageously R^2 represents hydroxy, halogeno, cyano, nitro, trifluoromethyl, C_{1-3}alkyl, amino or R^5X^1- [wherein X^1 is as hereinbefore defined and R^5 is selected from one of the following twenty-two groups:

1) C_{1-4}alkyl which may be unsubstituted or which may be substituted with one or more groups selected from fluoro, chloro and bromo, or C_{2-5}alkyl which may be unsubstituted or substituted with one or more groups selected from hydroxy and amino;

2) C_{2-3}alkylX^2C(O)R^{11} (wherein X^2 is as hereinbefore defined and R^{11} represents -$NR^{13}R^{14}$ or -OR^{15} (wherein R^{13}, R^{14} and R^{15} which may be the same or different are each C_{1-4}alkyl or C_{1-2}alkoxyethyl));

3) C_{2-4}alkylX^3R^{16} (wherein X^3 is as hereinbefore defined and R^{16} is a group selected from C_{1-3}alkyl, cyclopentyl, cyclohexyl, pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl and tetrahydropyranyl, which C_{1-3}alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1-2}alkoxy and which cyclopentyl, cyclohexyl, pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl or tetrahydropyranyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-3}cyanoalkyl, C_{1-3}alkyl, C_{1-3}hydroxyalkyl, C_{1-3}alkoxy, C_{1-2}alkoxyC_{1-3}alkyl, C_{1-2}alkylsulphonylC_{1-3}alkyl, C_{1-3}alkoxycarbonyl, C_{1-3}alkylamino, di(C_{1-3}alkyl)amino, C_{1-3}alkylaminoC_{1-3}alkyl, di(C_{1-3}alkyl)aminoC_{1-3}alkyl, C_{1-3}alkylaminoC_{1-3}alkoxy, di(C_{1-3}alkyl)aminoC_{1-3}alkoxy and a group -(-O-)$_f$(C_{1-3}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino and thiomorpholino, which cyclic group may bear one or more substituents selected from C_{1-3}alkyl));

4) C_{2-3}alkylX^4C_{2-3}alkylX^5R^{22} (wherein X^4 and X^5 are as hereinbefore defined and R^{22} represents hydrogen or C_{1-3}alkyl);

5) R^{28} (wherein R^{28} is as defined hereinbefore);

6) C_{1-4}alkylR^{110} (wherein R^{110} is a group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidin-1-yl, azetidinyl, 1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 1,3-dithiolan-2-yl and 1,3-dithian-2-yl, which group is linked to C_{1-4}alkyl through a carbon atom and which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-3}cyanoalkyl, C_{1-3}alkyl, C_{1-3}hydroxyalkyl, C_{1-3}alkoxy, C_{1-2}alkoxyC_{1-3}alkyl, C_{1-2}alkylsulphonylC_{1-3}alkyl, C_{1-3}alkoxycarbonyl, C_{1-3}alkylamino, di(C_{1-3}alkyl)amino, C_{1-3}alkylaminoC_{1-3}alkyl, di(C_{1-3}alkyl)aminoC_{1-3}alkyl, C_{1-3}alkylaminoC_{1-3}alkoxy, di(C_{1-3}alkyl)aminoC_{1-3}alkoxy and a group -(-

O-)$_f$(C_{1-3}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino and thiomorpholino, which cyclic group may bear one or more substituents selected from C_{1-3}alkyl)) or C_{2-4}alkylR^{111} (wherein R^{111} is a group selected from morpholino, thiomorpholino, azetidin-1-yl, pyrrolidin-1-yl, piperazin-1-yl and piperidino which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-3}cyanoalkyl, C_{1-3}alkyl, C_{1-3}hydroxyalkyl, C_{1-3}alkoxy, C_{1-2}alkoxyC_{1-3}alkyl, C_{1-2}alkylsulphonylC_{1-3}alkyl, C_{1-3}alkoxycarbonyl, C_{1-3}alkylamino, di(C_{1-3}alkyl)amino, C_{1-3}alkylaminoC_{1-3}alkyl, di(C_{1-3}alkyl)aminoC_{1-3}alkyl, C_{1-3}alkylaminoC_{1-3}alkoxy, di(C_{1-3}alkyl)aminoC_{1-3}alkoxy and a group -(-O-)$_f$(C_{1-3}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino and thiomorpholino, which cyclic group may bear one or more substituents selected from C_{1-3}alkyl));

7) C_{3-4}alkenylR^{112} (wherein R^{112} represents R^{110} or R^{111} as defined hereinbefore);

8) C_{3-4}alkynylR^{112} (wherein R^{112} represents R^{110} or R^{111} as defined hereinbefore);

9) R^{29} (wherein R^{29} is as defined hereinbefore);

10) C_{1-4}alkylR^{29} (wherein R^{29} is as defined hereinbefore);

11) 1-R^{29}prop-1-en-3-yl or 1-R^{29}but-2-en-4-yl (wherein R^{29} is as defined hereinbefore with the proviso that when R^5 is 1-R^{29}prop-1-en-3-yl, R^{29} is linked to the alkenyl group via a carbon atom);

12) 1-R^{29}prop-1-yn-3-yl or 1-R^{29}but-2-yn-4-yl (wherein R^{29} is as defined hereinbefore with the proviso that when R^5 is 1-R^{29}prop-1-yn-3-yl, R^{29} is linked to the alkynyl group via a carbon atom);

13) C_{1-5}alkylX^6R^{29} (wherein X^6 and R^{29} are as defined hereinbefore);

14) 1-($R^{29}X^7$)but-2-en-4-yl (wherein X^7 and R^{29} are as defined hereinbefore);

15) 1-($R^{29}X^8$)but-2-yn-4-yl (wherein X^8 and R^{29} are as defined hereinbefore);

16) C_{2-3}alkylX^9C_{1-3}alkylR^{29} (wherein X^9 and R^{29} are as defined hereinbefore);

17) C_{2-3}alkylX^9C_{1-3}alkylR^{28} (wherein X^9 and R^{28} are as defined hereinbefore);

18) C_{2-5}alkenyl which may be unsubstituted or which may be substituted with one or more fluorine atoms or with one or two groups selected from hydroxy, fluoro, amino, C_{1-4}alkylamino, N,N-di(C_{1-4}alkyl)amino, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl and N,N-di(C_{1-4}alkyl)aminosulphonyl;

19) C_{2-5}alkynyl which may be unsubstituted or which may be substituted with one or more fluorine atoms or with one or two groups selected from hydroxy, fluoro, amino, C_{1-4}alkylamino, N,N-di(C_{1-4}alkyl)amino, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl and N,N-di(C_{1-4}alkyl)aminosulphonyl;

20) C_{2-4}alkenylX^9C_{1-3}alkylR^{28} (wherein X^9 and R^{28} are as defined hereinbefore);

21) C_{2-4}alkynylX^9C_{1-3}alkylR^{28} (wherein X^9 and R^{28} are as defined hereinbefore); and

22) C_{1-3}alkyl$R^{54}(C_{1-3}alkyl)_q(X^9)_rR^{55}$ (wherein X^9, q, r, R^{54} and R^{55} are as defined hereinbefore);

and additionally wherein any C_{1-5}alkyl, C_{2-5}alkenyl or C_{2-5}alkynyl group in R^5X^1- may bear one or more substituents selected from hydroxy, halogeno and amino].

Preferably R^2 represents hydroxy, halogeno, nitro, trifluoromethyl, C_{1-3}alkyl, cyano, amino or R^5X^1- [wherein X^1 is as hereinbefore defined and R^5 is selected from one of the following twenty groups:

1) C_{1-3}alkyl which may be unsubstituted or which may be substituted with one or more groups selected from fluoro, chloro and bromo, or C_{2-3}alkyl which may be unsubstituted or substituted with one or more groups selected from hydroxy and amino;

2) 2-(3,3-dimethylureido)ethyl, 3-(3,3-dimethylureido)propyl, 2-(3-methylureido)ethyl, 3-(3-methylureido)propyl, 2-ureidoethyl, 3-ureidopropyl, 2-(N,N-dimethylcarbamoyloxy)ethyl, 3-(N,N-dimethylcarbamoyloxy)propyl, 2-(N-methylcarbamoyloxy)ethyl, 3-(N-methylcarbamoyloxy)propyl, 2-(carbamoyloxy)ethyl, 3-(carbamoyloxy)propyl, or 2-(N-methyl-N-(butoxycarbonyl)amino)ethyl;

3) C_{2-3}alkylX^3R^{16} (wherein X^3 is as hereinbefore defined and R^{16} is a group selected from C_{1-3}alkyl, cyclopentyl, cyclohexyl, pyrrolidinyl, piperidinyl, piperazinyl, azetidinyl, imidazolidinyl and tetrahydropyranyl which group is linked to X^3 through a carbon atom and which C_{1-3}alkyl group may bear 1 or 2 substituents selected from hydroxy, halogeno and C_{1-2}alkoxy and which cyclopentyl, cyclohexyl, pyrrolidinyl, piperidinyl, piperazinyl, azetidinyl, imidazolidinyl or tetrahydropyranyl group may bear one substituent selected from oxo, hydroxy, halogeno, cyano, C_{1-2}cyanoalkyl, C_{1-2}alkyl, C_{1-2}hydroxyalkyl, C_{1-2}alkoxy, C_{1-2}alkoxyC_{1-3}alkyl, C_{1-2}alkylsulphonylC_{1-3}alkyl, C_{1-2}alkoxycarbonyl, C_{1-3}alkylamino, di(C_{1-3}alkyl)amino, C_{1-3}alkylaminoC_{1-3}alkyl, di(C_{1-3}alkyl)aminoC_{1-3}alkyl, C_{1-3}alkylaminoC_{1-3}alkoxy, di(C_{1-3}alkyl)aminoC_{1-3}alkoxy and a group -(-O-)$_f$(C_{1-3}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino));

4) C_{2-3}alkylX^4C_{2-3}alkylX^5R^{22} (wherein X^4 and X^5 are as hereinbefore defined and R^{22} represents hydrogen or C_{1-2}alkyl);

5) R^{28} (wherein R^{28} is as defined hereinbefore);

6) C_{1-3}alkylR^{110} (wherein R^{110} is a group selected from pyrrolidinyl, piperazinyl, piperidinyl, azetidinyl, imidazolidinyl, 1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 1,3-dithiolan-2-yl and 1,3-dithian-2-yl, which group is linked to C_{1-3}alkyl through a carbon atom and which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-2}cyanoalkyl, C_{1-2}alkyl, C_{1-2}hydroxyalkyl, C_{1-2}alkoxy, C_{1-2}alkoxyC_{1-3}alkyl, C_{1-2}alkylsulphonylC_{1-3}alkyl, C_{1-2}alkoxycarbonyl, C_{1-3}alkylamino, di(C_{1-3}alkyl)amino, C_{1-3}alkylaminoC_{1-3}alkyl, di(C_{1-3}alkyl)aminoC_{1-3}alkyl, C_{1-3}alkylaminoC_{1-3}alkoxy, di(C_{1-3}alkyl)aminoC_{1-3}alkoxy and a group -(-O-)$_f$(C_{1-3}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino)) or C_{2-3}alkylR^{111} (wherein R^{111} is a group selected from morpholino, thiomorpholino, azetidin-1-yl, pyrrolidin-1-yl, piperazin-1-yl and piperidino which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-2}cyanoalkyl, C_{1-2}alkyl, C_{1-2}hydroxyalkyl, C_{1-2}alkoxy, C_{1-2}alkoxyC_{1-3}alkyl, C_{1-2}alkylsulphonylC_{1-3}alkyl, C_{1-2}alkoxycarbonyl, C_{1-3}alkylamino, di(C_{1-3}alkyl)amino, C_{1-3}alkylaminoC_{1-3}alkyl, di(C_{1-3}alkyl)aminoC_{1-3}alkyl, C_{1-3}alkylaminoC_{1-3}alkoxy, di(C_{1-3}alkyl)aminoC_{1-3}alkoxy and a group -(-O-)$_f$(C_{1-3}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino));

7) R^{29} (wherein R^{29} is as defined hereinbefore);

8) C_{1-4}alkylR^{29} (wherein R^{29} is as defined hereinbefore);

9) 1-R^{29}but-2-en-4-yl (wherein R^{29} is as defined hereinbefore);

10) 1-R^{29}but-2-yn-4-yl (wherein R^{29} is as defined hereinbefore);

11) C_{1-3}alkylX^6R^{29} (wherein X^6 and R^{29} are as defined hereinbefore);

12) 1-($R^{29}X^7$)but-2-en-4-yl (wherein X^7 and R^{29} are as defined hereinbefore);

13) 1-($R^{29}X^8$)but-2-yn-4-yl (wherein X^8 and R^{29} are as defined hereinbefore);

14) C_{2-3}alkylX^9C_{1-3}alkylR^{29} (wherein X^9 and R^{29} are as defined hereinbefore);

15) C_{2-3}alkylX^9C_{1-3}alkylR^{28} (wherein X^9 and R^{28} are as defined hereinbefore);

16) C_{2-5}alkenyl which may be unsubstituted or which may be substituted with one or more fluorine atoms or with one or two groups selected from hydroxy, fluoro, amino, C_{1-}

$_4$alkylamino, N,N-di(C_{1-4}alkyl)amino, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl and N,N-di(C_{1-4}alkyl)aminosulphonyl;

17) C_{2-5}alkynyl which may be unsubstituted or which may be substituted with one or more fluorine atoms or with one or two groups selected from hydroxy, fluoro, amino, C_{1-4}alkylamino, N,N-di(C_{1-4}alkyl)amino, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl and N,N-di(C_{1-4}alkyl)aminosulphonyl;

18) C_{2-3}alkenylX^9C_{1-3}alkylR^{28} (wherein X^9 and R^{28} are as defined hereinbefore);

19) C_{2-3}alkynylX^9C_{1-3}alkylR^{28} (wherein X^9 and R^{28} are as defined hereinbefore); and

20) C_{1-3}alkyl$R^{54}(C_{1-3}alkyl)_q(X^9)_rR^{55}$ (wherein X^9, q, r, R^{54} and R^{55} are as defined hereinbefore);

and additionally wherein any C_{1-5}alkyl, C_{2-5}alkenyl or C_{2-5}alkynyl group in R^5X^1- may bear one or more substituents selected from hydroxy, halogeno and amino].

More preferably R^2 represents hydroxy, C_{1-3}alkyl, amino or R^5X^1- [wherein X^1 is as hereinbefore defined and R^5 represents methyl, ethyl, benzyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, 2-(methylsulphinyl)ethyl, 2-(methylsulphonyl)ethyl, 2-(ethylsulphinyl)ethyl, 2-(ethylsulphonyl)ethyl, 2-(N,N-dimethylsulphamoyl)ethyl, 2-(N-methylsulphamoyl)ethyl, 2-sulphamoylethyl, 2-(methylamino)ethyl, 3-(methylamino)propyl, 2-(ethylamino)ethyl, 3-(ethylamino)propyl, 2-(N,N-dimethylamino)ethyl, 3-(N,N-dimethylamino)propyl, 2-(N,N-diethylamino)ethyl, 3-(N,N-diethylamino)propyl, 2-(N-methyl-N-methylsulphonylamino)ethyl, 3-(N-methyl-N-methylsulphonylamino)propyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-(methylpiperidino)ethyl, 3-(methylpiperidino)propyl, 2-(ethylpiperidino)ethyl, 3-(ethylpiperidino)propyl, 2-((2-methoxyethyl)piperidino)ethyl, 3-((2-methoxyethyl)piperidino)propyl, 2-((2-methylsulphonyl)ethylpiperidino)ethyl, 3-((2-methylsulphonyl)ethylpiperidino)propyl, piperidin-3-ylmethyl, piperidin-4-ylmethyl, 2-(piperidin-3-yl)ethyl, 2-(piperidin-4-yl)ethyl, 3-(piperidin-3-yl)propyl, 3-(piperidin-4-yl)propyl, 2-(piperidin-2-yl)ethyl, 3-(piperidin-2-yl)propyl, (1-methylpiperidin-3-yl)methyl, (1-methylpiperidin-4-yl)methyl, (1-cyanomethylpiperidin-3-yl)methyl, (1-cyanomethylpiperidin-4-yl)methyl, 2-(methylpiperidin-3-yl)ethyl, 2-(methylpiperidin-4-yl)ethyl, 2-(1-cyanomethylpiperidin-3-yl)ethyl, 2-(1-cyanomethylpiperidin-4-yl)ethyl, 3-(methylpiperidin-3-yl)propyl, 3-(methylpiperidin-4-yl)propyl, 3-(1-cyanomethylpiperidin-3-yl)propyl, 3-(1-cyanomethylpiperidin-4-yl)propyl, 2-(ethylpiperidin-3-yl)ethyl, 2-

(ethylpiperidin-4-yl)ethyl, 3-(ethylpiperidin-3-yl)propyl, 3-(ethylpiperidin-4-yl)propyl, ((2-methoxyethyl)piperidin-3-yl)methyl, ((2-methoxyethyl)piperidin-4-yl)methyl, 2-((2-methoxyethyl)piperidin-3-yl)ethyl, 2-((2-methoxyethyl)piperidin-4-yl)ethyl, 3-((2-methoxyethyl)piperidin-3-yl)propyl, 3-((2-methoxyethyl)piperidin-4-yl)propyl, (1-(2-methylsulphonylethyl)piperidin-3-yl)methyl, (1-(2-methylsulphonylethyl)piperidin-4-yl)methyl, 2-((2-methylsulphonylethyl)piperidin-3-yl)ethyl, 2-((2-methylsulphonylethyl)piperidin-4-yl)ethyl, 3-((2-methylsulphonylethyl)piperidin-3-yl)propyl, 3-((2-methylsulphonylethyl)piperidin-4-yl)propyl, 1-isopropylpiperidin-2-ylmethyl, 1-isopropylpiperidin-3-ylmethyl, 1-isopropylpiperidin-4-ylmethyl, 2-(1-isopropylpiperidin-2-yl)ethyl, 2-(1-isopropylpiperidin-3-yl)ethyl, 2-(1-isopropylpiperidin-4-yl)ethyl, 3-(1-isopropylpiperidin-2-yl)propyl, 3-(1-isopropylpiperidin-3-yl)propyl, 3-(1-isopropylpiperidin-4-yl)propyl, 2-(piperidin-4-yloxy)ethyl, 3-(piperidin-4-yloxy)propyl, 2-(1-(cyanomethyl)piperidin-4-yloxy)ethyl, 3-(1-(cyanomethyl)piperidin-4-yloxy)propyl, 2-(1-(2-cyanoethyl)piperidin-4-yloxy)ethyl, 3-(1-(2-cyanoethyl)piperidin-4-yloxy)propyl, 2-(piperazin-1-yl)ethyl, 3-(piperazin-1-yl)propyl, (pyrrolidin-2-yl)methyl, 2-(pyrrolidin-1-yl)ethyl, 3-(pyrrolidin-1-yl)propyl, (2-oxo-tetrahydro-2*H*-pyrrolidin-5-yl)methyl, 5(*R*)-(2-oxo-tetrahydro-2*H*-pyrrolidin-5-yl)methyl, (5*S*)-(2-oxo-tetrahydro-2*H*-pyrrolidin-5-yl)methyl, (1,3-dioxolan-2-yl)methyl, 2-(1,3-dioxolan-2-yl)ethyl, 2-(2-methoxyethylamino)ethyl, 2-(N-(2-methoxyethyl)-N-methylamino)ethyl, 2-(2-hydroxyethylamino)ethyl, 3-(2-methoxyethylamino)propyl, 3-(N-(2-methoxyethyl)-N-methylamino)propyl, 3-(2-hydroxyethylamino)propyl, 2-methylthiazol-4-ylmethyl, 2-acetamidothiazol-4-ylmethyl, 1-methylimidazol-2-ylmethyl, 2-(imidazol-1-yl)ethyl, 2-(2-methylimidazol-1-yl)ethyl, 2-(2-ethylimidazol-1-yl)ethyl, 3-(2-methylimidazol-1-yl)propyl, 3-(2-ethylimidazol-1-yl)propyl, 2-(1,2,3-triazol-1-yl)ethyl, 2-(1,2,3-triazol-2-yl)ethyl, 2-(1,2,4-triazol-1-yl)ethyl, 2-(1,2,4-triazol-4-yl)ethyl, 4-pyridylmethyl, 2-(4-pyridyl)ethyl, 3-(4-pyridyl)propyl, 2-(4-pyridyloxy)ethyl, 2-(4-pyridylamino)ethyl, 2-(4-oxo-1,4-dihydro-1-pyridyl)ethyl, 2-(2-oxo-imidazolidin-1-yl)ethyl, 3-(2-oxo-imidazolidin-1-yl)propyl, 2-thiomorpholinoethyl, 3-thiomorpholinopropyl, 2-(1,1-dioxothiomorpholino)ethyl, 3-(1,1-dioxothiomorpholino)propyl, 2-(2-methoxyethoxy)ethyl, 2-(4-methylpiperazin-1-yl)ethyl, 3-(4-methylpiperazin-1-yl)propyl, 3-(methylsulphinyl)propyl, 3-(methylsulphonyl)propyl, 3-(ethylsulphinyl)propyl, 3-(ethylsulphonyl)propyl, 2-(5-methyl-1,2,4-triazol-1-yl)ethyl, morpholino, 2-((N-(1-methylimidazol-4-ylsulphonyl)-N-methyl)amino)ethyl, 2-((N-(3-

morpholinopropylsulphonyl)-N-methyl)amino)ethyl, 2-((N-methyl-N-4-pyridyl)amino)ethyl, 3-(4-oxidomorpholino)propyl, 2-(2-(4-methylpiperazin-1-yl)ethoxy)ethyl, 3-(2-(4-methylpiperazin-1-yl)ethoxy)propyl, 2-(2-morpholinoethoxy)ethyl, 3-(2-morpholinoethoxy)propyl, 2-(tetrahydropyran-4-yloxy)ethyl, 3-(tetrahydropyran-4-yloxy)propyl, 2-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)vinyl, 3-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)prop-2-en-1-yl, 1-(2-pyrrolidinylethyl)piperidin-4-ylmethyl, 1-(3-pyrrolidinylpropyl)piperidin-4-ylmethyl, 1-(2-piperidinylethyl)piperidin-4-ylmethyl, 1-(3-piperidinylpropyl)piperidin-4-ylmethyl, 1-(2-morpholinoethyl)piperidin-4-ylmethyl, 1-(3-morpholinopropyl)piperidin-4-ylmethyl, 1-(2-thiomorpholinoethyl)piperidin-4-ylmethyl, 1-(3-thiomorpholinopropyl)piperidin-4-ylmethyl, 1-(2-azetidinylethyl)piperidin-4-ylmethyl, 1-(3-azetidinylpropyl)piperidin-4-ylmethyl, 3-morpholino-2-hydroxypropyl, (2*R*)-3-morpholino-2-hydroxypropyl, (2*S*)-3-morpholino-2-hydroxypropyl, 3-piperidino-2-hydroxypropyl, (2*R*)-3-piperidino-2-hydroxypropyl, (2*S*)-3-piperidino-2-hydroxypropyl, 3-pyrrolidin-1-yl-2-hydroxypropyl, (2*R*)-3-pyrrolidin-1-yl-2-hydroxypropyl, (2*S*)-3-pyrrolidin-1-yl-2-hydroxypropyl, 3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, (2*R*)-3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, (2*S*)-3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, 3-(N,N-diethylamino)-2-hydroxypropyl, (2*R*)-3-(N,N-diethylamino)-2-hydroxypropyl, (2*S*)-3-(N,N-diethylamino)-2-hydroxypropyl, 3-(isopropylamino)-2-hydroxypropyl, (2*R*)-3-(isopropylamino)-2-hydroxypropyl, (2*S*)-3-(isopropylamino)-2-hydroxypropyl, 3-(N,N-diisopropylamino)-2-hydroxypropyl, (2*R*)-3-(N,N-diisopropylamino)-2-hydroxypropyl or (2*S*)-3-(N,N-diisopropylamino)-2-hydroxypropyl].

Particularly R^2 represents C_{1-3}alkyl, amino or R^5X^1- [wherein X^1 is as hereinbefore defined and R^5 represents ethyl, benzyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, 2-(methylsulphinyl)ethyl, 2-(methylsulphonyl)ethyl, 2-(ethylsulphinyl)ethyl, 2-(ethylsulphonyl)ethyl, 2-(N,N-dimethylsulphamoyl)ethyl, 2-(N-methylsulphamoyl)ethyl, 2-sulphamoylethyl, 2-(methylamino)ethyl, 3-(methylamino)propyl, 2-(ethylamino)ethyl, 3-(ethylamino)propyl, 2-(N,N-dimethylamino)ethyl, 3-(N,N-dimethylamino)propyl, 2-(N,N-diethylamino)ethyl, 3-(N,N-diethylamino)propyl, 2-(N-methyl-N-methylsulphonylamino)ethyl, 3-(N-methyl-N-methylsulphonylamino)propyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-(methylpiperidino)ethyl, 3-(methylpiperidino)propyl, 2-(ethylpiperidino)ethyl, 3-(ethylpiperidino)propyl, 2-((2-methoxyethyl)piperidino)ethyl, 3-((2-

methoxyethyl)piperidino)propyl, 2-((2-methylsulphonyl)ethylpiperidino)ethyl, 3-((2-methylsulphonyl)ethylpiperidino)propyl, piperidin-3-ylmethyl, piperidin-4-ylmethyl, 2-(piperidin-3-yl)ethyl, 2-(piperidin-4-yl)ethyl, 3-(piperidin-3-yl)propyl, 3-(piperidin-4-yl)propyl, 2-(piperidin-2-yl)ethyl, 3-(piperidin-2-yl)propyl, (1-methylpiperidin-3-yl)methyl, (1-methylpiperidin-4-yl)methyl, (1-cyanomethylpiperidin-3-yl)methyl, (1-cyanomethylpiperidin-4-yl)methyl, 2-(methylpiperidin-3-yl)ethyl, 2-(methylpiperidin-4-yl)ethyl, 2-(1-cyanomethylpiperidin-3-yl)ethyl, 2-(1-cyanomethylpiperidin-4-yl)ethyl, 3-(methylpiperidin-3-yl)propyl, 3-(methylpiperidin-4-yl)propyl, 3-(1-cyanomethylpiperidin-3-yl)propyl, 3-(1-cyanomethylpiperidin-4-yl)propyl, 2-(ethylpiperidin-3-yl)ethyl, 2-(ethylpiperidin-4-yl)ethyl, 3-(ethylpiperidin-3-yl)propyl, 3-(ethylpiperidin-4-yl)propyl, ((2-methoxyethyl)piperidin-3-yl)methyl, ((2-methoxyethyl)piperidin-4-yl)methyl, 2-((2-methoxyethyl)piperidin-3-yl)ethyl, 2-((2-methoxyethyl)piperidin-4-yl)ethyl, 3-((2-methoxyethyl)piperidin-3-yl)propyl, 3-((2-methoxyethyl)piperidin-4-yl)propyl, (1-(2-methylsulphonylethyl)piperidin-3-yl)methyl, (1-(2-methylsulphonylethyl)piperidin-4-yl)methyl, 2-((2-methylsulphonylethyl)piperidin-3-yl)ethyl, 2-((2-methylsulphonylethyl)piperidin-4-yl)ethyl, 3-((2-methylsulphonylethyl)piperidin-3-yl)propyl, 3-((2-methylsulphonylethyl)piperidin-4-yl)propyl, 1-isopropylpiperidin-2-ylmethyl, 1-isopropylpiperidin-3-ylmethyl, 1-isopropylpiperidin-4-ylmethyl, 2-(1-isopropylpiperidin-2-yl)ethyl, 2-(1-isopropylpiperidin-3-yl)ethyl, 2-(1-isopropylpiperidin-4-yl)ethyl, 3-(1-isopropylpiperidin-2-yl)propyl, 3-(1-isopropylpiperidin-3-yl)propyl, 3-(1-isopropylpiperidin-4-yl)propyl, 2-(piperidin-4-yloxy)ethyl, 3-(piperidin-4-yloxy)propyl, 2-(1-(cyanomethyl)piperidin-4-yloxy)ethyl, 3-(1-(cyanomethyl)piperidin-4-yloxy)propyl, 2-(1-(2-cyanoethyl)piperidin-4-yloxy)ethyl, 3-(1-(2-cyanoethyl)piperidin-4-yloxy)propyl, 2-(piperazin-1-yl)ethyl, 3-(piperazin-1-yl)propyl, (pyrrolidin-2-yl)methyl, 2-(pyrrolidin-1-yl)ethyl, 3-(pyrrolidin-1-yl)propyl, (2-oxo-tetrahydro-2*H*-pyrrolidin-5-yl)methyl, 5(*R*)-(2-oxo-tetrahydro-2*H*-pyrrolidin-5-yl)methyl, (5*S*)-(2-oxo-tetrahydro-2*H*-pyrrolidin-5-yl)methyl, (1,3-dioxolan-2-yl)methyl, 2-(1,3-dioxolan-2-yl)ethyl, 2-(2-methoxyethylamino)ethyl, 2-(N-(2-methoxyethyl)-N-methylamino)ethyl, 2-(2-hydroxyethylamino)ethyl, 3-(2-methoxyethylamino)propyl, 3-(N-(2-methoxyethyl)-N-methylamino)propyl, 3-(2-hydroxyethylamino)propyl, 2-methylthiazol-4-ylmethyl, 2-acetamidothiazol-4-ylmethyl, 1-methylimidazol-2-ylmethyl, 2-(imidazol-1-yl)ethyl, 2-(2-methylimidazol-1-yl)ethyl, 2-(2-ethylimidazol-1-yl)ethyl, 3-(2-methylimidazol-1-yl)propyl, 3-(2-ethylimidazol-1-yl)propyl, 2-

(1,2,3-triazol-1-yl)ethyl, 2-(1,2,3-triazol-2-yl)ethyl, 2-(1,2,4-triazol-1-yl)ethyl, 2-(1,2,4-triazol-4-yl)ethyl, 4-pyridylmethyl, 2-(4-pyridyl)ethyl, 3-(4-pyridyl)propyl, 2-(4-pyridyloxy)ethyl, 2-(4-pyridylamino)ethyl, 2-(4-oxo-1,4-dihydro-1-pyridyl)ethyl, 2-(2-oxo-imidazolidin-1-yl)ethyl, 3-(2-oxo-imidazolidin-1-yl)propyl, 2-thiomorpholinoethyl, 3-thiomorpholinopropyl, 2-(1,1-dioxothiomorpholino)ethyl, 3-(1,1-dioxothiomorpholino)propyl, 2-(2-methoxyethoxy)ethyl, 2-(4-methylpiperazin-1-yl)ethyl, 3-(4-methylpiperazin-1-yl)propyl, 3-(methylsulphinyl)propyl, 3-(methylsulphonyl)propyl, 3-(ethylsulphinyl)propyl, 3-(ethylsulphonyl)propyl, 2-(5-methyl-1,2,4-triazol-1-yl)ethyl, morpholino, 2-((N-(1-methylimidazol-4-ylsulphonyl)-N-methyl)amino)ethyl, 2-((N-(3-morpholinopropylsulphonyl)-N-methyl)amino)ethyl, 2-((N-methyl-N-4-pyridyl)amino)ethyl, 3-(4-oxidomorpholino)propyl, 2-(2-(4-methylpiperazin-1-yl)ethoxy)ethyl, 3-(2-(4-methylpiperazin-1-yl)ethoxy)propyl, 2-(2-morpholinoethoxy)ethyl, 3-(2-morpholinoethoxy)propyl, 2-(tetrahydropyran-4-yloxy)ethyl, 3-(tetrahydropyran-4-yloxy)propyl, 2-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)vinyl, 3-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)prop-2-en-1-yl, 1-(2-pyrrolidinylethyl)piperidin-4-ylmethyl, 1-(3-pyrrolidinylpropyl)piperidin-4-ylmethyl, 1-(2-piperidinylethyl)piperidin-4-ylmethyl, 1-(3-piperidinylpropyl)piperidin-4-ylmethyl, 1-(2-morpholinoethyl)piperidin-4-ylmethyl, 1-(3-morpholinopropyl)piperidin-4-ylmethyl, 1-(2-thiomorpholinoethyl)piperidin-4-ylmethyl, 1-(3-thiomorpholinopropyl)piperidin-4-ylmethyl, 1-(2-azetidinylethyl)piperidin-4-ylmethyl, 1-(3-azetidinylpropyl)piperidin-4-ylmethyl, 3-morpholino-2-hydroxypropyl, (2*R*)-3-morpholino-2-hydroxypropyl, (2*S*)-3-morpholino-2-hydroxypropyl, 3-piperidino-2-hydroxypropyl, (2*R*)-3-piperidino-2-hydroxypropyl, (2*S*)-3-piperidino-2-hydroxypropyl, 3-pyrrolidin-1-yl-2-hydroxypropyl, (2*R*)-3-pyrrolidin-1-yl-2-hydroxypropyl, (2*S*)-3-pyrrolidin-1-yl-2-hydroxypropyl, 3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, (2*R*)-3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, (2*S*)-3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, 3-(N,N-diethylamino)-2-hydroxypropyl, (2*R*)-3-(N,N-diethylamino)-2-hydroxypropyl, (2*S*)-3-(N,N-diethylamino)-2-hydroxypropyl, 3-(isopropylamino)-2-hydroxypropyl, (2*R*)-3-(isopropylamino)-2-hydroxypropyl, (2*S*)-3-(isopropylamino)-2-hydroxypropyl, 3-(N,N-diisopropylamino)-2-hydroxypropyl, (2*R*)-3-(N,N-diisopropylamino)-2-hydroxypropyl or (2*S*)-3-(N,N-diisopropylamino)-2-hydroxypropyl].

More particularly R^2 represents C_{1-3}alkyl, amino or R^5X^1- [wherein X^1 is as hereinbefore defined and R^5 represents ethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2-

hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, 2-(methylsulphinyl)ethyl, 2-(methylsulphonyl)ethyl, 2-(ethylsulphinyl)ethyl, 2-(ethylsulphonyl)ethyl, 2-(N,N-dimethylsulphamoyl)ethyl, 2-(N-methylsulphamoyl)ethyl, 2-sulphamoylethyl, 2-(methylamino)ethyl, 3-(methylamino)propyl, 2-(ethylamino)ethyl, 3-(ethylamino)propyl, 2-(N,N-dimethylamino)ethyl, 3-(N,N-dimethylamino)propyl, 2-(N,N-diethylamino)ethyl, 3-(N,N-diethylamino)propyl, 2-(N-methyl-N-methylsulphonylamino)ethyl, 3-(N-methyl-N-methylsulphonylamino)propyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-(methylpiperidino)ethyl, 3-(methylpiperidino)propyl, 2-(ethylpiperidino)ethyl, 3-(ethylpiperidino)propyl, 2-((2-methoxyethyl)piperidino)ethyl, 3-((2-methoxyethyl)piperidino)propyl, 2-((2-methylsulphonyl)ethylpiperidino)ethyl, 3-((2-methylsulphonyl)ethylpiperidino)propyl, piperidin-3-ylmethyl, piperidin-4-ylmethyl, 2-(piperidin-3-yl)ethyl, 2-(piperidin-4-yl)ethyl, 3-(piperidin-3-yl)propyl, 3-(piperidin-4-yl)propyl, 2-(piperidin-2-yl)ethyl, 3-(piperidin-2-yl)propyl, (1-methylpiperidin-3-yl)methyl, (1-methylpiperidin-4-yl)methyl, (1-cyanomethylpiperidin-3-yl)methyl, (1-cyanomethylpiperidin-4-yl)methyl, 2-(methylpiperidin-3-yl)ethyl, 2-(methylpiperidin-4-yl)ethyl, 2-(1-cyanomethylpiperidin-3-yl)ethyl, 2-(1-cyanomethylpiperidin-4-yl)ethyl, 3-(methylpiperidin-3-yl)propyl, 3-(methylpiperidin-4-yl)propyl, 3-(1-cyanomethylpiperidin-3-yl)propyl, 3-(1-cyanomethylpiperidin-4-yl)propyl, 2-(ethylpiperidin-3-yl)ethyl, 2-(ethylpiperidin-4-yl)ethyl, 3-(ethylpiperidin-3-yl)propyl, 3-(ethylpiperidin-4-yl)propyl, ((2-methoxyethyl)piperidin-3-yl)methyl, ((2-methoxyethyl)piperidin-4-yl)methyl, 2-((2-methoxyethyl)piperidin-3-yl)ethyl, 2-((2-methoxyethyl)piperidin-4-yl)ethyl, 3-((2-methoxyethyl)piperidin-3-yl)propyl, 3-((2-methoxyethyl)piperidin-4-yl)propyl, (1-(2-methylsulphonylethyl)piperidin-3-yl)methyl, (1-(2-methylsulphonylethyl)piperidin-4-yl)methyl, 2-((2-methylsulphonylethyl)piperidin-3-yl)ethyl, 2-((2-methylsulphonylethyl)piperidin-4-yl)ethyl, 3-((2-methylsulphonylethyl)piperidin-3-yl)propyl, 3-((2-methylsulphonylethyl)piperidin-4-yl)propyl, 1-isopropylpiperidin-2-ylmethyl, 1-isopropylpiperidin-3-ylmethyl, 1-isopropylpiperidin-4-ylmethyl, 2-(1-isopropylpiperidin-2-yl)ethyl, 2-(1-isopropylpiperidin-3-yl)ethyl, 2-(1-isopropylpiperidin-4-yl)ethyl, 3-(1-isopropylpiperidin-2-yl)propyl, 3-(1-isopropylpiperidin-3-yl)propyl, 3-(1-isopropylpiperidin-4-yl)propyl, 2-(piperidin-4-yloxy)ethyl, 3-(piperidin-4-yloxy)propyl, 2-(1-(cyanomethyl)piperidin-4-yloxy)ethyl, 3-(1-(cyanomethyl)piperidin-4-yloxy)propyl, 2-(1-(2-cyanoethyl)piperidin-4-yloxy)ethyl, 3-(1-(2-cyanoethyl)piperidin-4-yloxy)propyl, 2-

(piperazin-1-yl)ethyl, 3-(piperazin-1-yl)propyl, (pyrrolidin-2-yl)methyl, 2-(pyrrolidin-1-yl)ethyl, 3-(pyrrolidin-1-yl)propyl, (2-oxo-tetrahydro-2*H*-pyrrolidin-5-yl)methyl, 5(*R*)-(2-oxo-tetrahydro-2*H*-pyrrolidin-5-yl)methyl, (5*S*)-(2-oxo-tetrahydro-2*H*-pyrrolidin-5-yl)methyl, (1,3-dioxolan-2-yl)methyl, 2-(1,3-dioxolan-2-yl)ethyl, 2-(2-methoxyethylamino)ethyl, 2-(N-(2-methoxyethyl)-N-methylamino)ethyl, 2-(2-hydroxyethylamino)ethyl, 3-(2-methoxyethylamino)propyl, 3-(N-(2-methoxyethyl)-N-methylamino)propyl, 3-(2-hydroxyethylamino)propyl, 2-(1,2,3-triazol-1-yl)ethyl, 2-(1,2,3-triazol-2-yl)ethyl, 2-(1,2,4-triazol-1-yl)ethyl, 2-(1,2,4-triazol-4-yl)ethyl, 4-pyridylmethyl, 2-(4-pyridyl)ethyl, 3-(4-pyridyl)propyl, 2-(4-pyridyloxy)ethyl, 2-(4-pyridylamino)ethyl, 2-(4-oxo-1,4-dihydro-1-pyridyl)ethyl, 2-(2-oxo-imidazolidin-1-yl)ethyl, 3-(2-oxo-imidazolidin-1-yl)propyl, 2-thiomorpholinoethyl, 3-thiomorpholinopropyl, 2-(1,1-dioxothiomorpholino)ethyl, 3-(1,1-dioxothiomorpholino)propyl, 2-(2-methoxyethoxy)ethyl, 2-(4-methylpiperazin-1-yl)ethyl, 3-(4-methylpiperazin-1-yl)propyl, 3-(methylsulphinyl)propyl, 3-(methylsulphonyl)propyl, 3-(ethylsulphinyl)propyl, 3-(ethylsulphonyl)propyl, 2-(5-methyl-1,2,4-triazol-1-yl)ethyl, morpholino, 2-((N-(3-morpholinopropylsulphonyl)-N-methyl)amino)ethyl, 2-((N-methyl-N-4-pyridyl)amino)ethyl, 3-(4-oxidomorpholino)propyl, 2-(2-(4-methylpiperazin-1-yl)ethoxy)ethyl, 3-(2-(4-methylpiperazin-1-yl)ethoxy)propyl, 2-(2-morpholinoethoxy)ethyl, 3-(2-morpholinoethoxy)propyl, 2-(tetrahydropyran-4-yloxy)ethyl, 3-(tetrahydropyran-4-yloxy)propyl, 2-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)vinyl, 3-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)prop-2-en-1-yl, 1-(2-pyrrolidinylethyl)piperidin-4-ylmethyl, 1-(3-pyrrolidinylpropyl)piperidin-4-ylmethyl, 1-(2-piperidinylethyl)piperidin-4-ylmethyl, 1-(3-piperidinylpropyl)piperidin-4-ylmethyl, 1-(2-morpholinoethyl)piperidin-4-ylmethyl, 1-(3-morpholinopropyl)piperidin-4-ylmethyl, 1-(2-thiomorpholinoethyl)piperidin-4-ylmethyl, 1-(3-thiomorpholinopropyl)piperidin-4-ylmethyl, 1-(2-azetidinylethyl)piperidin-4-ylmethyl, 1-(3-azetidinylpropyl)piperidin-4-ylmethyl, 3-morpholino-2-hydroxypropyl, (2*R*)-3-morpholino-2-hydroxypropyl, (2*S*)-3-morpholino-2-hydroxypropyl, 3-piperidino-2-hydroxypropyl, (2*R*)-3-piperidino-2-hydroxypropyl, (2*S*)-3-piperidino-2-hydroxypropyl, 3-pyrrolidin-1-yl-2-hydroxypropyl, (2*R*)-3-pyrrolidin-1-yl-2-hydroxypropyl, (2*S*)-3-pyrrolidin-1-yl-2-hydroxypropyl, 3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, (2*R*)-3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, (2*S*)-3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, 3-(N,N-diethylamino)-2-hydroxypropyl, (2*R*)-3-(N,N-diethylamino)-2-hydroxypropyl, (2*S*)-3-(N,N-diethylamino)-2-hydroxypropyl, 3-(isopropylamino)-2-hydroxypropyl, (2*R*)-3-

(isopropylamino)-2-hydroxypropyl, (2*S*)-3-(isopropylamino)-2-hydroxypropyl, 3-(N,N-diisopropylamino)-2-hydroxypropyl, (2*R*)-3-(N,N-diisopropylamino)-2-hydroxypropyl or (2*S*)-3-(N,N-diisopropylamino)-2-hydroxypropyl].

In another aspect R^2 represents ethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, 2-methoxyethoxy, 3-methoxypropoxy, 2-(methylsulphinyl)ethoxy, 2-(methylsulphonyl)ethoxy, 2-(ethylsulphinyl)ethoxy, 2-(ethylsulphonyl)ethoxy, 2-(N,N-dimethylsulphamoyl)ethoxy, 2-(N-methylsulphamoyl)ethoxy, 2-sulphamoylethoxy, 2-(methylamino)ethoxy, 3-(methylamino)propoxy, 2-(ethylamino)ethoxy, 3-(ethylamino)propoxy, 2-(N,N-dimethylamino)ethoxy, 3-(N,N-dimethylamino)propoxy, 2-(N,N-diethylamino)ethoxy, 3-(N,N-diethylamino)propoxy, 2-(N-methyl-N-methylsulphonylamino)ethoxy, 3-(N-methyl-N-methylsulphonylamino)propoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-(methylpiperidino)ethoxy, 3-(methylpiperidino)propoxy, 2-(ethylpiperidino)ethoxy, 3-(ethylpiperidino)propoxy, 2-((2-methoxyethyl)piperidino)ethoxy, 3-((2-methoxyethyl)piperidino)propoxy, 2-((2-methylsulphonyl)ethylpiperidino)ethoxy, 3-((2-methylsulphonyl)ethylpiperidino)propoxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, 2-(piperidin-3-yl)ethoxy, 2-(piperidin-4-yl)ethoxy, 3-(piperidin-3-yl)propoxy, 3-(piperidin-4-yl)propoxy, 2-(piperidin-2-yl)ethoxy, 3-(piperidin-2-yl)propoxy, (1-methylpiperidin-3-yl)methoxy, (1-methylpiperidin-4-yl)methoxy, (1-cyanomethylpiperidin-3-yl)methoxy, (1-cyanomethylpiperidin-4-yl)methoxy, 2-(methylpiperidin-3-yl)ethoxy, 2-(methylpiperidin-4-yl)ethoxy, 2-(1-cyanomethylpiperidin-3-yl)ethoxy, 2-(1-cyanomethylpiperidin-4-yl)ethoxy, 3-(methylpiperidin-3-yl)propoxy, 3-(methylpiperidin-4-yl)propoxy, 3-(1-cyanomethylpiperidin-3-yl)propoxy, 3-(1-cyanomethylpiperidin-4-yl)propoxy, 2-(ethylpiperidin-3-yl)ethoxy, 2-(ethylpiperidin-4-yl)ethoxy, 3-(ethylpiperidin-3-yl)propoxy, 3-(ethylpiperidin-4-yl)propoxy, ((2-methoxyethyl)piperidin-3-yl)methoxy, ((2-methoxyethyl)piperidin-4-yl)methoxy, 2-((2-methoxyethyl)piperidin-3-yl)ethoxy, 2-((2-methoxyethyl)piperidin-4-yl)ethoxy, 3-((2-methoxyethyl)piperidin-3-yl)propoxy, 3-((2-methoxyethyl)piperidin-4-yl)propoxy, (1-(2-methylsulphonylethyl)piperidin-3-yl)methoxy, (1-(2-methylsulphonylethyl)piperidin-4-yl)methoxy, 2-((2-methylsulphonylethyl)piperidin-3-yl)ethoxy, 2-((2-methylsulphonylethyl)piperidin-4-yl)ethoxy, 3-((2-methylsulphonylethyl)piperidin-3-yl)propoxy, 3-((2-methylsulphonylethyl)piperidin-4-yl)propoxy, 1-isopropylpiperidin-2-ylmethoxy, 1-isopropylpiperidin-3-ylmethoxy, 1-isopropylpiperidin-4-ylmethoxy, 2-(1-

isopropylpiperidin-2-yl)ethoxy, 2-(1-isopropylpiperidin-3-yl)ethoxy, 2-(1-isopropylpiperidin-4-yl)ethoxy, 3-(1-isopropylpiperidin-2-yl)propoxy, 3-(1-isopropylpiperidin-3-yl)propoxy, 3-(1-isopropylpiperidin-4-yl)propoxy, 2-(piperidin-4-yloxy)ethoxy, 3-(piperidin-4-yloxy)propoxy, 2-(1-(cyanomethyl)piperidin-4-yloxy)ethoxy, 3-(1-(cyanomethyl)piperidin-4-yloxy)propoxy, 2-(1-(2-cyanoethyl)piperidin-4-yloxy)ethoxy, 3-(1-(2-cyanoethyl)piperidin-4-yloxy)propoxy, 2-(piperazin-1-yl)ethoxy, 3-(piperazin-1-yl)propoxy, (pyrrolidin-2-yl)methoxy, 2-(pyrrolidin-1-yl)ethoxy, 3-(pyrrolidin-1-yl)propoxy, (2-oxo-tetrahydro-2*H*-pyrrolidin-5-yl)methoxy, 5(*R*)-(2-oxo-tetrahydro-2*H*-pyrrolidin-5-yl)methoxy, (5*S*)-(2-oxo-tetrahydro-2*H*-pyrrolidin-5-yl)methoxy, (1,3-dioxolan-2-yl)methoxy, 2-(1,3-dioxolan-2-yl)ethoxy, 2-(2-methoxyethylamino)ethoxy, 2-(N-(2-methoxyethyl)-N-methylamino)ethoxy, 2-(2-hydroxyethylamino)ethoxy, 3-(2-methoxyethylamino)propoxy, 3-(N-(2-methoxyethyl)-N-methylamino)propoxy, 3-(2-hydroxyethylamino)propoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 2-(1,2,3-triazol-2-yl)ethoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 2-(1,2,4-triazol-4-yl)ethoxy, 4-pyridylmethoxy, 2-(4-pyridyl)ethoxy, 3-(4-pyridyl)propoxy, 2-(4-pyridyloxy)ethoxy, 2-(4-pyridylamino)ethoxy, 2-(4-oxo-1,4-dihydro-1-pyridyl)ethoxy, 2-(2-oxo-imidazolidin-1-yl)ethoxy, 3-(2-oxo-imidazolidin-1-yl)propoxy, 2-thiomorpholinoethoxy, 3-thiomorpholinopropoxy, 2-(1,1-dioxothiomorpholino)ethoxy, 3-(1,1-dioxothiomorpholino)propoxy, 2-(2-methoxyethoxy)ethoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 3-(methylsulphinyl)propoxy, 3-(methylsulphonyl)propoxy, 3-(ethylsulphinyl)propoxy, 3-(ethylsulphonyl)propoxy, 2-(5-methyl-1,2,4-triazol-1-yl)ethoxy, 2-((N-(3-morpholinopropylsulphonyl)-N-methyl)amino)ethoxy, 2-((N-methyl-N-4-pyridyl)amino)ethoxy, 3-(4-oxidomorpholino)propoxy, 2-(2-(4-methylpiperazin-1-yl)ethoxy)ethoxy, 3-(2-(4-methylpiperazin-1-yl)ethoxy)propoxy, 2-(2-morpholinoethoxy)ethoxy, 3-(2-morpholinoethoxy)propoxy, 2-(tetrahydropyran-4-yloxy)ethoxy, 3-(tetrahydropyran-4-yloxy)propoxy, 2-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)vinyl, 3-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)prop-2-en-1-yloxy, 1-(2-pyrrolidinylethyl)piperidin-4-ylmethoxy, 1-(3-pyrrolidinylpropyl)piperidin-4-ylmethoxy, 1-(2-piperidinylethyl)piperidin-4-ylmethoxy, 1-(3-piperidinylpropyl)piperidin-4-ylmethoxy, 1-(2-morpholinoethyl)piperidin-4-ylmethoxy, 1-(3-morpholinopropyl)piperidin-4-ylmethoxy, 1-(2-thiomorpholinoethyl)piperidin-4-ylmethoxy, 1-(3-thiomorpholinopropyl)piperidin-4-ylmethoxy, 1-(2-azetidinylethyl)piperidin-4-ylmethoxy, 1-(3-azetidinylpropyl)piperidin-4-ylmethoxy, 3-morpholino-2-hydroxypropoxy,

(2*R*)-3-morpholino-2-hydroxypropoxy, (2*S*)-3-morpholino-2-hydroxypropoxy, 3-piperidino-2-hydroxypropoxy, (2*R*)-3-piperidino-2-hydroxypropoxy, (2*S*)-3-piperidino-2-hydroxypropoxy, 3-pyrrolidin-1-yl-2-hydroxypropoxy, (2*R*)-3-pyrrolidin-1-yl-2-hydroxypropoxy, (2*S*)-3-pyrrolidin-1-yl-2-hydroxypropoxy, 3-(1-methylpiperazin-4-yl)-2-hydroxypropoxy, (2*R*)-3-(1-methylpiperazin-4-yl)-2-hydroxypropoxy, (2*S*)-3-(1-methylpiperazin-4-yl)-2-hydroxypropoxy, 3-(N,N-diethylamino)-2-hydroxypropoxy, (2*R*)-3-(N,N-diethylamino)-2-hydroxypropoxy, (2*S*)-3-(N,N-diethylamino)-2-hydroxypropoxy, 3-(isopropylamino)-2-hydroxypropoxy, (2*R*)-3-(isopropylamino)-2-hydroxypropoxy, (2*S*)-3-(isopropylamino)-2-hydroxypropoxy, 3-(N,N-diisopropylamino)-2-hydroxypropoxy, (2*R*)-3-(N,N-diisopropylamino)-2-hydroxypropoxy or (2*S*)-3-(N,N-diisopropylamino)-2-hydroxypropoxy.

According to another aspect of the present invention conveniently R^2 represents hydroxy, halogeno, nitro, trifluoromethyl, C_{1-3}alkyl, cyano, amino or R^5X^1- [wherein X^1 is as hereinbefore defined and R^5 is selected from one of the following twenty-one groups:

1) C_{1-5}alkyl which may be unsubstituted or substituted with one or more fluorine atoms, or C_{2-5}alkyl which may be unsubstituted or substituted with one or more groups selected from hydroxy and amino;

2) C_{2-3}alkyl$X^2C(O)R^{11}$ (wherein X^2 is as hereinbefore defined and R^{11} represents C_{1-3}alkyl, -$NR^{13}R^{14}$ or -OR^{15} (wherein R^{13}, R^{14} and R^{15} which may be the same or different are each C_{1-2}alkyl or C_{1-2}alkoxyethyl));

3) C_{2-4}alkylX^3R^{16} (wherein X^3 is as hereinbefore defined and R^{16} represents hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C_{1-3}alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1-3}alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl and C_{1-4}alkoxy);

4) C_{2-3}alkylX^4C_{2-3}alkylX^5R^{22} (wherein X^4 and X^5 are as hereinbefore defined and R^{22} represents hydrogen or C_{1-3}alkyl);

5) C_{1-5}alkylR^{129} (wherein R^{129} is a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group is linked to C_{1-5}alkyl through a carbon atom and which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-}

$_4$alkoxy, C_{1-4}alkoxyC_{1-4}alkyl and C_{1-4}alkylsulphonylC_{1-4}alkyl) or C_{2-5}alkylR^{130} (wherein R^{130} is a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms of which one is N and the other is selected independently from O, S and N, which heterocyclic group is linked to C_{2-5}alkyl through a nitrogen atom and which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl and C_{1-4}alkylsulphonylC_{1-4}alkyl);

6) C_{3-4}alkenylR^{131} (wherein R^{131} represents R^{129} or R^{130} as defined hereinbefore);

7) C_{3-4}alkynylR^{131} (wherein R^{131} represents R^{129} or R^{130} as defined hereinbefore);

8) R^{29} (wherein R^{29} is as defined hereinbefore);

9) C_{1-5}alkylR^{29} (wherein R^{29} is as defined hereinbefore);

10) C_{3-5}alkenylR^{29} (wherein R^{29} is as defined hereinbefore);

11) C_{3-5}alkynylR^{29} (wherein R^{29} is as defined hereinbefore);

12) C_{1-5}alkylX^6R^{29} (wherein X^6 and R^{29} are as defined hereinbefore);

13) C_{4-5}alkenylX^7R^{29} (wherein X^7 and R^{29} are as defined hereinbefore);

14) C_{4-5}alkynylX^8R^{29} (wherein X^8 and R^{29} are as defined hereinbefore);

15) C_{2-3}alkylX^9C_{1-2}alkylR^{29} (wherein X^9 and R^{29} are as defined hereinbefore);

16) R^{28} (wherein R^{28} is as defined hereinbefore);

17) C_{2-3}alkylX^9C_{1-2}alkylR^{28} (wherein X^9 and R^{28} are as defined hereinbefore);

18) C_{2-5}alkenyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C_{1-4}alkylamino, N,N-di(C_{1-4}alkyl)amino, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl and N,N-di(C_{1-4}alkyl)aminosulphonyl;

19) C_{2-5}alkynyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C_{1-4}alkylamino, N,N-di(C_{1-4}alkyl)amino, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl and N,N-di(C_{1-4}alkyl)aminosulphonyl;

20) C_{2-5}alkenylX^9C_{1-3}alkylR^{28} (wherein X^9 and R^{28} are as defined hereinbefore); and

21) C_{2-5}alkynylX^9C_{1-3}alkylR^{28} (wherein X^9 and R^{28} are as defined hereinbefore)].

According to another aspect of the present invention advantageously R^2 represents hydroxy, halogeno, nitro, trifluoromethyl, C_{1-3}alkyl, cyano, amino or R^5X^1- [wherein X^1 is as hereinbefore defined and R^5 is selected from one of the following twenty-one groups:

1) C_{1-4}alkyl which may be unsubstituted or substituted with one or more fluorine atoms, or C_{2-4}alkyl which may be unsubstituted or substituted with 1 or 2 groups selected from hydroxy and amino;

2) C_{2-3}alkyl$X^2C(O)R^{11}$ (wherein X^2 is as hereinbefore defined and R^{11} represents $-NR^{13}R^{14}$ or $-OR^{15}$ (wherein R^{13}, R^{14} and R^{15} which may be the same or different are each C_{1-2}alkyl or C_{1-2}alkoxyethyl));

3) C_{2-4}alkylX^3R^{16} (wherein X^3 is as hereinbefore defined and R^{16} is a group selected from C_{1-3}alkyl, cyclopentyl, cyclohexyl, pyrrolidinyl, piperidinyl and tetrahydropyranyl which group is linked to X^3 through a carbon atom and which C_{1-3}alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1-2}alkoxy and which cyclopentyl, cyclohexyl, pyrrolidinyl or piperidinyl group may carry one substituent selected from oxo, hydroxy, halogeno, C_{1-2}alkyl, C_{1-2}hydroxyalkyl and C_{1-2}alkoxy);

4) C_{2-3}alkylX^4C_{2-3}alkylX^5R^{22} (wherein X^4 and X^5 are as hereinbefore defined and R^{22} represents hydrogen or C_{1-3}alkyl);

5) C_{1-4}alkylR^{132} (wherein R^{132} is a group selected from pyrrolidinyl, piperazinyl, piperidinyl, 1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 1,3-dithiolan-2-yl and 1,3-dithian-2-yl, which group is linked to C_{1-4}alkyl through a carbon atom and which group may carry 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-3}cyanoalkyl, C_{1-3}alkyl, C_{1-3}hydroxyalkyl, C_{1-3}alkoxy, C_{1-2}alkoxyC_{1-3}alkyl and C_{1-2}alkylsulphonylC_{1-3}alkyl) or C_{2-4}alkylR^{133} (wherein R^{133} is a group selected from morpholino, thiomorpholino, pyrrolidin-1-yl, piperazin-1-yl and piperidino which group may carry 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-3}cyanoalkyl, C_{1-3}alkyl, C_{1-3}hydroxyalkyl, C_{1-3}alkoxy, C_{1-2}alkoxyC_{1-3}alkyl and C_{1-2}alkylsulphonylC_{1-3}alkyl);

6) C_{3-4}alkenylR^{134} (wherein R^{134} represents R^{132} or R^{133} as defined hereinbefore);

7) C_{3-4}alkynylR^{134} (wherein R^{134} represents R^{132} or R^{133} as defined hereinbefore);

8) R^{29} (wherein R^{29} is as defined hereinbefore);

9) C_{1-4}alkylR^{29} (wherein R^{29} is as defined hereinbefore);

10) 1-R^{29}prop-1-en-3-yl or 1-R^{29}but-2-en-4-yl (wherein R^{29} is as defined hereinbefore with the proviso that when R^5 is 1-R^{29}prop-1-en-3-yl, R^{29} is linked to the alkenyl group via a carbon atom);

11) 1-R^{29}prop-1-yn-3-yl or 1-R^{29}but-2-yn-4-yl (wherein R^{29} is as defined hereinbefore with the proviso that when R^5 is 1-R^{29}prop-1-yn-3-yl, R^{29} is linked to the alkynyl group via a carbon atom);

12) C_{1-5}alkylX^6R^{29} (wherein X^6 and R^{29} are as defined hereinbefore);

13) 1-($R^{29}X^7$)but-2-en-4-yl (wherein X^7 and R^{29} are as defined hereinbefore);

14) 1-($R^{29}X^8$)but-2-yn-4-yl (wherein X^8 and R^{29} are as defined hereinbefore);

15) C_{2-3}alkylX^9C_{1-2}alkylR^{29} (wherein X^9 and R^{29} are as defined hereinbefore);

16) R^{28} (wherein R^{28} is as defined hereinbefore);

17) C_{2-3}alkylX^9C_{1-2}alkylR^{28} (wherein X^9 and R^{28} are as defined hereinbefore);

18) C_{2-5}alkenyl which may be unsubstituted or which may be substituted with one or more fluorine atoms or with one or two groups selected from hydroxy, amino, C_{1-4}alkylamino, N,N-di(C_{1-4}alkyl)amino, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl and N,N-di(C_{1-4}alkyl)aminosulphonyl;

19) C_{2-5}alkynyl which may be unsubstituted or which may be substituted with one or more fluorine atoms or with one or two groups selected from hydroxy, amino, C_{1-4}alkylamino, N,N-di(C_{1-4}alkyl)amino, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl and N,N-di(C_{1-4}alkyl)aminosulphonyl;

20) C_{2-4}alkenylX^9C_{1-3}alkylR^{28} (wherein X^9 and R^{28} are as defined hereinbefore); and

21) C_{2-4}alkynylX^9C_{1-3}alkylR^{28} (wherein X^9 and R^{28} are as defined hereinbefore)].

According to another aspect of the present invention preferably R^2 represents hydroxy, halogeno, nitro, trifluoromethyl, C_{1-3}alkyl, cyano, amino or R^5X^1- [wherein X^1 is as hereinbefore defined and R^5 is selected from one of the following nineteen groups:

1) C_{1-3}alkyl which may be unsubstituted or substituted with one or more fluorine atoms, or C_{2-3}alkyl which may be unsubstituted or substituted with 1 or 2 groups selected from hydroxy and amino;

2) 2-(3,3-dimethylureido)ethyl, 3-(3,3-dimethylureido)propyl, 2-(3-methylureido)ethyl, 3-(3-methylureido)propyl, 2-ureidoethyl, 3-ureidopropyl, 2-(N,N-dimethylcarbamoyloxy)ethyl, 3-(N,N-dimethylcarbamoyloxy)propyl, 2-(N-methylcarbamoyloxy)ethyl, 3-(N-methylcarbamoyloxy)propyl, 2-(carbamoyloxy)ethyl, 3-(carbamoyloxy)propyl;

3) C_{2-3}alkylX^3R^{16} (wherein X^3 is as defined hereinbefore and R^{16} is a group selected from C_{1-2}alkyl, cyclopentyl, cyclohexyl, pyrrolidinyl, piperidinyl and tetrahydropyranyl which group is linked to X^3 through a carbon atom and which C_{1-2}alkyl group may bear 1 or 2 substituents selected from hydroxy, halogeno and C_{1-2}alkoxy and which cyclopentyl, cyclohexyl, pyrrolidinyl or piperidinyl group may carry one substituent selected from oxo, hydroxy, halogeno, C_{1-2}alkyl, C_{1-2}hydroxyalkyl and C_{1-2}alkoxy);

4) C_{2-3}alkylX^4C_{2-3}alkylX^5R^{22} (wherein X^4 and X^5 are as hereinbefore defined and R^{22} represents hydrogen or C_{1-2}alkyl);

5) C_{1-2}alkylR^{132} (wherein R^{132} is a group selected from pyrrolidinyl, piperazinyl, piperidinyl, 1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 1,3-dithiolan-2-yl and 1,3-dithian-2-yl, which group is linked to C_{1-2}alkyl through a carbon atom and which group may carry one substituent selected from oxo, hydroxy, halogeno, cyano, C_{1-3}cyanoalkyl, C_{1-3}alkyl, C_{1-3}hydroxyalkyl, C_{1-3}alkoxy, C_{1-2}alkoxyC_{1-3}alkyl and C_{1-2}alkylsulphonylC_{1-3}alkyl) or C_{2-3}alkylR^{133} (wherein R^{133} is a group selected from morpholino, thiomorpholino, piperidino, piperazin-1-yl and pyrrolidin-1-yl which group may carry one or two substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-3}cyanoalkyl, C_{1-3}alkyl, C_{1-3}hydroxyalkyl, C_{1-3}alkoxy, C_{1-2}alkoxyC_{1-3}alkyl and C_{1-2}alkylsulphonylC_{1-3}alkyl);

6) R^{29} (wherein R^{29} is as defined hereinbefore);

7) C_{1-4}alkylR^{29} (wherein R^{29} is as defined hereinbefore);

8) 1-R^{29}but-2-en-4-yl (wherein R^{29} is as defined hereinbefore);

9) 1-R^{29}but-2-yn-4-yl (wherein R^{29} is as defined hereinbefore);

10) C_{1-5}alkylX^6R^{29} (wherein X^6 and R^{29} are as defined hereinbefore);

11) 1-($R^{29}X^7$)but-2-en-4-yl (wherein X^7 and R^{29} are as defined hereinbefore);

12) 1-($R^{29}X^8$)but-2-yn-4-yl (wherein X^8 and R^{29} are as defined hereinbefore);

13) ethylX^9methylR^{29} (wherein X^9 and R^{29} are as defined hereinbefore);

14) R^{28} (wherein R^{28} is as defined hereinbefore);

15) ethylX^9C_{1-2}alkylR^{28} (wherein X^9 and R^{28} are as defined hereinbefore);

16) C_{2-5}alkenyl which may be unsubstituted or which may be substituted with one or more fluorine atoms or with one or two groups selected from hydroxy, amino, C_{1-4}alkylamino, N,N-di(C_{1-4}alkyl)amino, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl and N,N-di(C_{1-4}alkyl)aminosulphonyl;

17) C_{2-5}alkynyl which may be unsubstituted or which may be substituted with one or more fluorine atoms or with one or two groups selected from hydroxy, amino, C_{1-4}alkylamino, N,N-di(C_{1-4}alkyl)amino, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl and N,N-di(C_{1-4}alkyl)aminosulphonyl;

18) C_{2-3}alkenylX^9C_{1-3}alkylR^{28} (wherein X^9 and R^{28} are as defined hereinbefore); and

19) C_{2-3}alkynylX^9C_{1-3}alkylR^{28} (wherein X^9 and R^{28} are as defined hereinbefore)].

According to another aspect of the present invention more preferably R^2 represents hydroxy, C_{1-3}alkyl, amino or R^5X^1- [wherein X^1 is as hereinbefore defined and R^5 represents methyl, ethyl, benzyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2-hydroxyethyl, 3-hydroxypropyl,

2-methoxyethyl, 3-methoxypropyl, 2-(methylsulphinyl)ethyl, 2-(methylsulphonyl)ethyl, 2-(N,N-dimethylsulphamoyl)ethyl, 2-(N-methylsulphamoyl)ethyl, 2-sulphamoylethyl, 2-(N,N-dimethylamino)ethyl, 3-(N,N-dimethylamino)propyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-(methylpiperidino)ethyl, 3-(methylpiperidino)propyl, 2-(ethylpiperidino)ethyl, 3-(ethylpiperidino)propyl, 2-((2-methoxyethyl)piperidino)ethyl, 3-((2-methoxyethyl)piperidino)propyl, 2-((2-methylsulphonyl)ethylpiperidino)ethyl, 3-((2-methylsulphonyl)ethylpiperidino)propyl, piperidin-3-ylmethyl, piperidin-4-ylmethyl, 2-(piperidin-3-yl)ethyl, 2-(piperidin-4-yl)ethyl, 3-(piperidin-3-yl)propyl, 3-(piperidin-4-yl)propyl, (1-methylpiperidin-3-yl)methyl, (1-methylpiperidin-4-yl)methyl, (1-cyanomethylpiperidin-3-yl)methyl, (1-cyanomethylpiperidin-4-yl)methyl, 2-(methylpiperidin-3-yl)ethyl, 2-(methylpiperidin-4-yl)ethyl, 2-(1-cyanomethylpiperidin-3-yl)ethyl, 2-(1-cyanomethylpiperidin-4-yl)ethyl, 3-(methylpiperidin-3-yl)propyl, 3-(methylpiperidin-4-yl)propyl, 3-(1-cyanomethylpiperidin-3-yl)propyl, 3-(1-cyanomethylpiperidin-4-yl)propyl, 2-(ethylpiperidin-3-yl)ethyl, 2-(ethylpiperidin-4-yl)ethyl, 3-(ethylpiperidin-3-yl)propyl, 3-(ethylpiperidin-4-yl)propyl, ((2-methoxyethyl)piperidin-3-yl)methyl, ((2-methoxyethyl)piperidin-4-yl)methyl, 2-((2-methoxyethyl)piperidin-3-yl)ethyl, 2-((2-methoxyethyl)piperidin-4-yl)ethyl, 3-((2-methoxyethyl)piperidin-3-yl)propyl, 3-((2-methoxyethyl)piperidin-4-yl)propyl, (1-(2-methylsulphonylethyl)piperidin-3-yl)methyl, (1-(2-methylsulphonylethyl)piperidin-4-yl)methyl, 2-((2-methylsulphonylethyl)piperidin-3-yl)ethyl, 2-((2-methylsulphonylethyl)piperidin-4-yl)ethyl, 3-((2-methylsulphonylethyl)piperidin-3-yl)propyl, 3-((2-methylsulphonylethyl)piperidin-4-yl)propyl, 1-isopropylpiperidin-2-ylmethyl, 1-isopropylpiperidin-3-ylmethyl, 1-isopropylpiperidin-4-ylmethyl, 2-(1-isopropylpiperidin-2-yl)ethyl, 2-(1-isopropylpiperidin-3-yl)ethyl, 2-(1-isopropylpiperidin-4-yl)ethyl, 3-(1-isopropylpiperidin-2-yl)propyl, 3-(1-isopropylpiperidin-3-yl)propyl, 3-(1-isopropylpiperidin-4-yl)propyl, 2-(piperazin-1-yl)ethyl, 3-(piperazin-1-yl)propyl, (pyrrolidin-2-yl)methyl, 2-(pyrrolidin-1-yl)ethyl, 3-(pyrrolidin-1-yl)propyl, (2-oxo-tetrahydro-2H-pyrrolidin-5-yl)methyl, (1,3-dioxolan-2-yl)methyl, 2-(1,3-dioxolan-2-yl)ethyl, 2-(2-methoxyethylamino)ethyl, 2-(N-(2-methoxyethyl)-N-methylamino)ethyl, 2-(2-hydroxyethylamino)ethyl, 3-(2-methoxyethylamino)propyl, 3-(N-(2-methoxyethyl)-N-methylamino)propyl, 3-(2-hydroxyethylamino)propyl, 2-methylthiazol-4-ylmethyl, 2-acetamidothiazol-4-ylmethyl, 1-methylimidazol-2-ylmethyl, 2-(imidazol-1-yl)ethyl, 2-(2-methylimidazol-1-yl)ethyl, 2-(2-ethylimidazol-1-yl)ethyl, 3-(2-methylimidazol-1-yl)propyl, 3-

(2-ethylimidazol-1-yl)propyl, 2-(1,2,3-triazol-1-yl)ethyl, 2-(1,2,3-triazol-2-yl)ethyl, 2-(1,2,4-triazol-1-yl)ethyl, 2-(1,2,4-triazol-4-yl)ethyl, 4-pyridylmethyl, 2-(4-pyridyl)ethyl, 3-(4-pyridyl)propyl, 2-(4-pyridyloxy)ethyl, 2-(4-pyridylamino)ethyl, 2-(4-oxo-1,4-dihydro-1-pyridyl)ethyl, 2-thiomorpholinoethyl, 3-thiomorpholinopropyl, 2-(1,1-dioxothiomorpholino)ethyl, 3-(1,1-dioxothiomorpholino)propyl, 2-(2-methoxyethoxy)ethyl, 2-(4-methylpiperazin-1-yl)ethyl, 3-(4-methylpiperazin-1-yl)propyl, 3-(methylsulphinyl)propyl, 3-(methylsulphonyl)propyl, 2-(5-methyl-1,2,4-triazol-1-yl)ethyl, morpholino, 2-((N-(1-methylimidazol-4-ylsulphonyl)-N-methyl)amino)ethyl, 2-((N-(3-morpholinopropylsulphonyl)-N-methyl)amino)ethyl, 2-((N-methyl-N-4-pyridyl)amino)ethyl, 3-(4-oxidomorpholino)propyl, 2-(2-(4-methylpiperazin-1-yl)ethoxy)ethyl, 3-(2-(4-methylpiperazin-1-yl)ethoxy)propyl, 2-(2-morpholinoethoxy)ethyl, 3-(2-morpholinoethoxy)propyl, 2-(tetrahydropyran-4-yloxy)ethyl, 3-(tetrahydropyran-4-yloxy)propyl, 2-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)vinyl or 3-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)prop-2-en-1-yl].

According to another aspect of the present invention particularly R^2 represents C_{1-3}alkyl, amino or R^5X^1- [wherein X^1 is as hereinbefore defined and R^5 represents ethyl, benzyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, 2-(methylsulphinyl)ethyl, 2-(methylsulphonyl)ethyl, 2-(N,N-dimethylsulphamoyl)ethyl, 2-(N-methylsulphamoyl)ethyl, 2-sulphamoylethyl, 2-(N,N-dimethylamino)ethyl, 3-(N,N-dimethylamino)propyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-(methylpiperidino)ethyl, 3-(methylpiperidino)propyl, 2-(ethylpiperidino)ethyl, 3-(ethylpiperidino)propyl, 2-((2-methoxyethyl)piperidino)ethyl, 3-((2-methoxyethyl)piperidino)propyl, 2-((2-methylsulphonyl)ethylpiperidino)ethyl, 3-((2-methylsulphonyl)ethylpiperidino)propyl, piperidin-3-ylmethyl, piperidin-4-ylmethyl, 2-(piperidin-3-yl)ethyl, 2-(piperidin-4-yl)ethyl, 3-(piperidin-3-yl)propyl, 3-(piperidin-4-yl)propyl, (1-methylpiperidin-3-yl)methyl, (1-methylpiperidin-4-yl)methyl, (1-cyanomethylpiperidin-3-yl)methyl, (1-cyanomethylpiperidin-4-yl)methyl, 2-(methylpiperidin-3-yl)ethyl, 2-(methylpiperidin-4-yl)ethyl, 2-(1-cyanomethylpiperidin-3-yl)ethyl, 2-(1-cyanomethylpiperidin-4-yl)ethyl, 3-(methylpiperidin-3-yl)propyl, 3-(methylpiperidin-4-yl)propyl, 3-(1-cyanomethylpiperidin-3-yl)propyl, 3-(1-cyanomethylpiperidin-4-yl)propyl, 2-(ethylpiperidin-3-yl)ethyl, 2-(ethylpiperidin-4-yl)ethyl, 3-(ethylpiperidin-3-yl)propyl, 3-(ethylpiperidin-4-yl)propyl, ((2-methoxyethyl)piperidin-3-

yl)methyl, ((2-methoxyethyl)piperidin-4-yl)methyl, 2-((2-methoxyethyl)piperidin-3-yl)ethyl, 2-((2-methoxyethyl)piperidin-4-yl)ethyl, 3-((2-methoxyethyl)piperidin-3-yl)propyl, 3-((2-methoxyethyl)piperidin-4-yl)propyl, (1-(2-methylsulphonylethyl)piperidin-3-yl)methyl, (1-(2-methylsulphonylethyl)piperidin-4-yl)methyl, 2-((2-methylsulphonylethyl)piperidin-3-yl)ethyl, 2-((2-methylsulphonylethyl)piperidin-4-yl)ethyl, 3-((2-methylsulphonylethyl)piperidin-3-yl)propyl, 3-((2-methylsulphonylethyl)piperidin-4-yl)propyl, 1-isopropylpiperidin-2-ylmethyl, 1-isopropylpiperidin-3-ylmethyl, 1-isopropylpiperidin-4-ylmethyl, 2-(1-isopropylpiperidin-2-yl)ethyl, 2-(1-isopropylpiperidin-3-yl)ethyl, 2-(1-isopropylpiperidin-4-yl)ethyl, 3-(1-isopropylpiperidin-2-yl)propyl, 3-(1-isopropylpiperidin-3-yl)propyl, 3-(1-isopropylpiperidin-4-yl)propyl, 2-(piperazin-1-yl)ethyl, 3-(piperazin-1-yl)propyl, (pyrrolidin-2-yl)methyl, 2-(pyrrolidin-1-yl)ethyl, 3-(pyrrolidin-1-yl)propyl, (2-oxo-tetrahydro-2H-pyrrolidin-5-yl)methyl, (1,3-dioxolan-2-yl)methyl, 2-(1,3-dioxolan-2-yl)ethyl, 2-(2-methoxyethylamino)ethyl, 2-(N-(2-methoxyethyl)-N-methylamino)ethyl, 2-(2-hydroxyethylamino)ethyl, 3-(2-methoxyethylamino)propyl, 3-(N-(2-methoxyethyl)-N-methylamino)propyl, 3-(2-hydroxyethylamino)propyl, 2-methylthiazol-4-ylmethyl, 2-acetamidothiazol-4-ylmethyl, 1-methylimidazol-2-ylmethyl, 2-(imidazol-1-yl)ethyl, 2-(2-methylimidazol-1-yl)ethyl, 2-(2-ethylimidazol-1-yl)ethyl, 3-(2-methylimidazol-1-yl)propyl, 3-(2-ethylimidazol-1-yl)propyl, 2-(1,2,3-triazol-1-yl)ethyl, 2-(1,2,3-triazol-2-yl)ethyl, 2-(1,2,4-triazol-1-yl)ethyl, 2-(1,2,4-triazol-4-yl)ethyl, 4-pyridylmethyl, 2-(4-pyridyl)ethyl, 3-(4-pyridyl)propyl, 2-(4-pyridyloxy)ethyl, 2-(4-pyridylamino)ethyl, 2-(4-oxo-1,4-dihydro-1-pyridyl)ethyl, 2-thiomorpholinoethyl, 3-thiomorpholinopropyl, 2-(1,1-dioxothiomorpholino)ethyl, 3-(1,1-dioxothiomorpholino)propyl, 2-(2-methoxyethoxy)ethyl, 2-(4-methylpiperazin-1-yl)ethyl, 3-(4-methylpiperazin-1-yl)propyl, 3-(methylsulphinyl)propyl, 3-(methylsulphonyl)propyl, 2-(5-methyl-1,2,4-triazol-1-yl)ethyl, morpholino, 2-((N-(1-methylimidazol-4-ylsulphonyl)-N-methyl)amino)ethyl, 2-((N-(3-morpholinopropylsulphonyl)-N-methyl)amino)ethyl, 2-((N-methyl-N-4-pyridyl)amino)ethyl, 3-(4-oxidomorpholino)propyl, 2-(2-(4-methylpiperazin-1-yl)ethoxy)ethyl, 3-(2-(4-methylpiperazin-1-yl)ethoxy)propyl, 2-(2-morpholinoethoxy)ethyl, 3-(2-morpholinoethoxy)propyl, 2-(tetrahydropyran-4-yloxy)ethyl, 3-(tetrahydropyran-4-yloxy)propyl, 2-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)vinyl or 3-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)prop-2-en-1-yl].

According to another aspect of the present invention more particularly R^2 represents C_{1-3}alkyl, amino or R^5X^1- [wherein X^1 is as hereinbefore defined and R^5 represents ethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, 2-(methylsulphinyl)ethyl, 2-(methylsulphonyl)ethyl, 2-(N,N-dimethylsulphamoyl)ethyl, 2-(N-methylsulphamoyl)ethyl, 2-sulphamoylethyl, 2-(N,N-dimethylamino)ethyl, 3-(N,N-dimethylamino)propyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-(methylpiperidino)ethyl, 3-(methylpiperidino)propyl, 2-(ethylpiperidino)ethyl, 3-(ethylpiperidino)propyl, 2-((2-methoxyethyl)piperidino)ethyl, 3-((2-methoxyethyl)piperidino)propyl, 2-((2-methylsulphonyl)ethylpiperidino)ethyl, 3-((2-methylsulphonyl)ethylpiperidino)propyl, piperidin-3-ylmethyl, piperidin-4-ylmethyl, 2-(piperidin-3-yl)ethyl, 2-(piperidin-4-yl)ethyl, 3-(piperidin-3-yl)propyl, 3-(piperidin-4-yl)propyl, (1-methylpiperidin-3-yl)methyl, (1-methylpiperidin-4-yl)methyl, (1-cyanomethylpiperidin-3-yl)methyl, (1-cyanomethylpiperidin-4-yl)methyl, 2-(methylpiperidin-3-yl)ethyl, 2-(methylpiperidin-4-yl)ethyl, 2-(1-cyanomethylpiperidin-3-yl)ethyl, 2-(1-cyanomethylpiperidin-4-yl)ethyl, 3-(methylpiperidin-3-yl)propyl, 3-(methylpiperidin-4-yl)propyl, 3-(1-cyanomethylpiperidin-3-yl)propyl, 3-(1-cyanomethylpiperidin-4-yl)propyl, 2-(ethylpiperidin-3-yl)ethyl, 2-(ethylpiperidin-4-yl)ethyl, 3-(ethylpiperidin-3-yl)propyl, 3-(ethylpiperidin-4-yl)propyl, ((2-methoxyethyl)piperidin-3-yl)methyl, ((2-methoxyethyl)piperidin-4-yl)methyl, 2-((2-methoxyethyl)piperidin-3-yl)ethyl, 2-((2-methoxyethyl)piperidin-4-yl)ethyl, 3-((2-methoxyethyl)piperidin-3-yl)propyl, 3-((2-methoxyethyl)piperidin-4-yl)propyl, (1-(2-methylsulphonylethyl)piperidin-3-yl)methyl, (1-(2-methylsulphonylethyl)piperidin-4-yl)methyl, 2-((2-methylsulphonylethyl)piperidin-3-yl)ethyl, 2-((2-methylsulphonylethyl)piperidin-4-yl)ethyl, 3-((2-methylsulphonylethyl)piperidin-3-yl)propyl, 3-((2-methylsulphonylethyl)piperidin-4-yl)propyl, 1-isopropylpiperidin-2-ylmethyl, 1-isopropylpiperidin-3-ylmethyl, 1-isopropylpiperidin-4-ylmethyl, 2-(1-isopropylpiperidin-2-yl)ethyl, 2-(1-isopropylpiperidin-3-yl)ethyl, 2-(1-isopropylpiperidin-4-yl)ethyl, 3-(1-isopropylpiperidin-2-yl)propyl, 3-(1-isopropylpiperidin-3-yl)propyl, 3-(1-isopropylpiperidin-4-yl)propyl, 2-(piperazin-1-yl)ethyl, 3-(piperazin-1-yl)propyl, (pyrrolidin-2-yl)methyl, 2-(pyrrolidin-1-yl)ethyl, 3-(pyrrolidin-1-yl)propyl, (2-oxo-tetrahydro-2H-pyrrolidin-5-yl)methyl, (1,3-dioxolan-2-yl)methyl, 2-(1,3-dioxolan-2-yl)ethyl, 2-(2-methoxyethylamino)ethyl, 2-(N-(2-methoxyethyl)-N-methylamino)ethyl, 2-(2-hydroxyethylamino)ethyl, 3-(2-methoxyethylamino)propyl, 3-(N-(2-methoxyethyl)-N-

methylamino)propyl, 3-(2-hydroxyethylamino)propyl, 2-thiomorpholinoethyl, 3-thiomorpholinopropyl, 2-(1,1-dioxothiomorpholino)ethyl, 3-(1,1-dioxothiomorpholino)propyl, 2-(2-methoxyethoxy)ethyl, 2-(4-methylpiperazin-1-yl)ethyl, 3-(4-methylpiperazin-1-yl)propyl, 3-(methylsulphinyl)propyl, 3-(methylsulphonyl)propyl, morpholino, 2-((N-(3-morpholinopropylsulphonyl)-N-methyl)amino)ethyl, 2-((N-methyl-N-4-pyridyl)amino)ethyl, 3-(4-oxidomorpholino)propyl, 2-(2-(4-methylpiperazin-1-yl)ethoxy)ethyl, 3-(2-(4-methylpiperazin-1-yl)ethoxy)propyl, 2-(2-morpholinoethoxy)ethyl, 3-(2-morpholinoethoxy)propyl, 2-(tetrahydropyran-4-yloxy)ethyl, 3-(tetrahydropyran-4-yloxy)propyl, 2-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)vinyl or 3-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)prop-2-en-1-yl].

According to another embodiment of the present invention in another aspect R^2 represents methoxy, 2-methoxyethoxy, 2-(2-methoxyethoxy)ethoxy, 3-methoxypropoxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy, benzyloxy, 2-(tetrahydropyran-4-yloxy)ethoxy, 3-(tetrahydropyran-4-yloxy)propoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(imidazol-1-yl)ethoxy, 3-(imidazol-1-yl)propoxy 2-(1,1-dioxothiomorpholino)ethoxy, 3-(1,1-dioxothiomorpholino)propoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 3-(1,2,3-triazol-1-yl)propoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 2-((N-methyl-N-4-pyridyl)amino)ethoxy, 2-(N,N-dimethylamino)ethoxy, 3-(N,N-dimethylamino)propoxy, 2-(N-methoxyacetyl-N-methylamino)ethoxy, 3-(N-methoxyacetyl-N-methylamino)propoxy, 1-methylpiperidin-3-ylmethoxy, 1-methylpiperidin-4-ylmethoxy, (1-cyanomethylpiperidin-3-yl)methoxy, (1-cyanomethylpiperidin-4-yl)methoxy, 2-(1-cyanomethylpiperidin-3-yl)ethoxy, 2-(1-cyanomethylpiperidin-4-yl)ethoxy, 3-(1-cyanomethylpiperidin-3-yl)propoxy, 3-(1-cyanomethylpiperidin-4-yl)propoxy, ((2-methoxyethyl)piperidin-3-yl)methoxy, ((2-methoxyethyl)piperidin-4-yl)methoxy, 2-(N-(2-methoxyethyl)-N-methylamino)ethoxy, 4-(pyrrolidin-1-yl)but-2-en-yloxy, 2-(2-oxopyrrolidin-1-yl)ethoxy, 3-(2-oxopyrrolidin-1-yl)propoxy, (pyrrolidin-2-yl)methoxy, 2-(pyrrolidin-1-yl)ethoxy, 3-(pyrrolidin-1-yl)propoxy, 2-(2-(pyrrolidin-1-yl)ethoxy)ethoxy, (2-oxo-tetrahydro-2*H*-pyrrolidin-5-yl)methoxy, 2-(2-(4-methylpiperazin-1-yl)ethoxy)ethoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-(methylpiperidino)ethoxy, 3-(methylpiperidino)propoxy, 2-(ethylpiperidino)ethoxy, 3-(ethylpiperidino)propoxy, 2-((2-methoxyethyl)piperidino)ethoxy, 3-((2-methoxyethyl)piperidino)propoxy, 1-(2-methylsulphonylethyl)piperidin-3-ylmethoxy, 1-(2-

methylsulphonylethyl)piperidin-4-ylmethoxy, 2-((2-methylsulphonyl)ethylpiperidino)ethoxy, 3-((2-methylsulphonyl)ethylpiperidino)propoxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, 2-(piperidin-3-yl)ethoxy, 2-(piperidin-4-yl)ethoxy, 3-(piperidin-3-yl)propoxy, 3-(piperidin-4-yl)propoxy, 2-(methylpiperidin-3-yl)ethoxy, 2-(methylpiperidin-4-yl)ethoxy, 3-(methylpiperidin-3-yl)propoxy, 3-(methylpiperidin-4-yl)propoxy, 2-(ethylpiperidin-3-yl)ethoxy, 2-(ethylpiperidin-4-yl)ethoxy, 3-(ethylpiperidin-3-yl)propoxy, 3-(ethylpiperidin-4-yl)propoxy, 2-((2-methoxyethyl)piperidin-3-yl)ethoxy, 2-((2-methoxyethyl)piperidin-4-yl)ethoxy, 3-((2-methoxyethyl)piperidin-3-yl)propoxy, 3-((2-methoxyethyl)piperidin-4-yl)propoxy, 2-((2-methylsulphonylethyl)piperidin-3-yl)ethoxy, 2-((2-methylsulphonylethyl)piperidin-4-yl)ethoxy, 3-((2-methylsulphonylethyl)piperidin-3-yl)propoxy, 3-((2-methylsulphonylethyl)piperidin-4-yl)propoxy, 1-isopropylpiperidin-2-ylmethoxy, 1-isopropylpiperidin-3-ylmethoxy, 1-isopropylpiperidin-4-ylmethoxy, 2-(1-isopropylpiperidin-2-yl)ethoxy, 2-(1-isopropylpiperidin-3-yl)ethoxy, 2-(1-isopropylpiperidin-4-yl)ethoxy, 3-(1-isopropylpiperidin-2-yl)propoxy, 3-(1-isopropylpiperidin-3-yl)propoxy, 3-(1-isopropylpiperidin-4-yl)propoxy, 2-(2-(4-methylpiperazin-1-yl)ethoxy)ethoxy, 3-(2-(4-methylpiperazin-1-yl)ethoxy)propoxy, 2-(2-morpholinoethoxy)ethoxy, 3-(2-morpholinoethoxy)propoxy, 2-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)vinyl or 3-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)prop-2-en-1-yl.

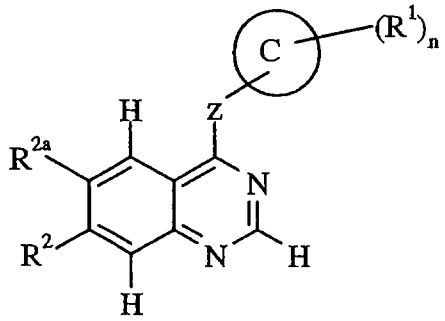
Where one of the R^2 substituents is R^5X^1- the substituent R^5X^1- is preferably at the 6- or 7-position of the quinazoline ring, more preferably at the 7-position of the quinazoline ring.

When one of the R^2 substituents is at the 6-position of the quinazoline ring it is preferably hydrogen, halogeno, C_{1-3}alkyl, trifluoromethyl, C_{1-3}alkoxy, C_{1-3}alkylsulphanyl or -NR^3R^4 (wherein R^3 and R^4 are as defined hereinbefore).

When one of the R^2 substituents is at the 6-position of the quinazoline ring it is more preferably C_{1-3}alkoxy, especially methoxy.

In another aspect of the present invention there is provided the use of compounds of the formula Ia:

(Ia)



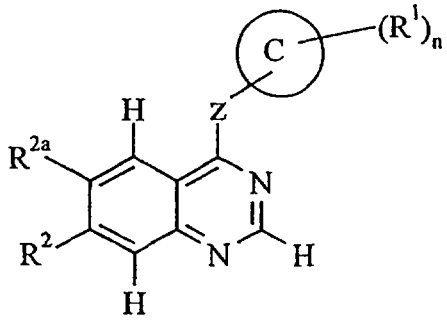
[wherein:

ring C, R^1, R^2, n and Z are as defined hereinbefore with the provisos that R^2 is not hydrogen and that Z is not CH_2 or a direct bond; and

R^{2a} represents hydrogen, halogeno, C_{1-3}alkyl, trifluoromethyl, C_{1-3}alkoxy, C_{1-3}alkylsulphanyl, -$NR^{3a}R^{4a}$ (wherein R^{3a} and R^{4a}, which may be the same or different, each represents hydrogen or C_{1-3}alkyl), or $R^{5a}(CH_2)_{za}X^{1a}$ (wherein R^{5a} is a 4-, 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl), za is an integer from 0 to 4 and X^{1a} represents a direct bond, -O-, -CH_2-, -S-, -SO-, -SO_2-, -NR^{6a}C(O)-, -C(O)NR^{7a}-, -SO_2NR^{8a}-, -$NR^{9a}SO_2$- or -NR^{10a}- (wherein R^{6a}, R^{7a}, R^{8a}, R^{9a} and R^{10a} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

and salts thereof, and prodrugs thereof for example esters and amides, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans.

In another aspect of the present invention there is provided the use of compounds of the formula Ia:



(Ia)

[wherein:

ring C, R^1, R^2, n and Z are as defined hereinbefore with the provisos that R^2 is not hydrogen and that Z is not CH_2 or a direct bond; and

R^{2a} represents hydrogen, halogeno, C_{1-3}alkyl, trifluoromethyl, C_{1-3}alkoxy, C_{1-3}alkylsulphanyl, $-NR^{3a}R^{4a}$ (wherein R^{3a} and R^{4a}, which may be the same or different, each represents hydrogen or C_{1-3}alkyl), or $R^{5a}(CH_2)_{za}X^{1a}$ (wherein R^{5a} is a 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl and C_{1-4}alkoxy, za is an integer from 0 to 4 and X^{1a} represents a direct bond, -O-, $-CH_2-$, -S-, -SO-, $-SO_2-$, $-NR^{6a}C(O)-$, $-C(O)NR^{7a}-$, $-SO_2NR^{8a}-$, $-NR^{9a}SO_2-$ or $-NR^{10a}-$ (wherein R^{6a}, R^{7a}, R^{8a}, R^{9a} and R^{10a} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

and salts thereof, and prodrugs thereof for example esters, amides and sulphides, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans.

Advantageously X^{1a} represents -O-, -S-, $-NR^{6a}C(O)-$, $-NR^{9a}SO_2-$ or $-NR^{10a}-$ (wherein R^{6a}, R^{9a} and R^{10a} each independently represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

Preferably X^{1a} represents -O-, -S-, $-NR^{6a}CO-$, $-NR^{9a}SO_2-$ (wherein R^{6a} and R^{9a} each independently represents hydrogen or C_{1-2}alkyl) or NH.

More preferably X^{1a} represents -O-, -S-, $-NR^{6a}CO-$ (wherein R^{6a} represents hydrogen or C_{1-2}alkyl) or NH.

Particularly X^{1a} represents -O- or $-NR^{6a}CO-$ (wherein R^{6a} represents hydrogen or C_{1-2}alkyl), more particularly -O- or -NHCO-, especially -O-.

Preferably za is an integer from 1 to 3.

Preferably R^{5a} is a group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino and thiomorpholino which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-3}cyanoalkyl, C_{1-3}alkyl, C_{1-3}hydroxyalkyl, C_{1-3}alkoxy, C_{1-2}alkoxyC_{1-3}alkyl, C_{1-2}alkylsulphonylC_{1-3}alkyl, C_{1-3}alkoxycarbonyl, C_{1-3}alkylamino, di(C_{1-3}alkyl)amino, C_{1-3}alkylaminoC_{1-3}alkyl, di(C_{1-3}alkyl)aminoC_{1-3}alkyl, C_{1-3}alkylaminoC_{1-3}alkoxy, di(C_{1-3}alkyl)aminoC_{1-3}alkoxy and a group -(-O-)$_f$(C_{1-3}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino and thiomorpholino, which cyclic group may bear one or more substituents selected from C_{1-3}alkyl).

More preferably R^{5a} is a group selected from pyrrolidinyl, piperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-3}cyanoalkyl, C_{1-3}alkyl, C_{1-3}hydroxyalkyl, C_{1-3}alkoxy, C_{1-2}alkoxyC_{1-3}alkyl, C_{1-2}alkylsulphonylC_{1-3}alkyl, C_{1-3}alkoxycarbonyl, C_{1-3}alkylamino, di(C_{1-3}alkyl)amino, C_{1-3}alkylaminoC_{1-3}alkyl, di(C_{1-3}alkyl)aminoC_{1-3}alkyl, C_{1-3}alkylaminoC_{1-3}alkoxy, di(C_{1-3}alkyl)aminoC_{1-3}alkoxy and a group -(-O-)$_f$(C_{1-3}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino).

Particularly R^{5a} is pyrrolidinyl, piperazinyl, piperidinyl, azetidinyl, morpholino or thiomorpholino which group may bear 1 or 2 substituents selected from a group -(-O-)$_f$(C_{1-3}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino).

According to another aspect of the present invention preferably R^{5a} is a group selected from pyrrolidinyl, piperazinyl, piperidinyl, morpholino and thiomorpholino which group may carry 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-2}alkyl, C_{1-2}hydroxyalkyl and C_{1-2}alkoxy.

Advantageously R^{2a} represents C_{1-3}alkyl, C_{1-3}alkoxy, amino or $R^{5a}(CH_2)_{za}X^{1a}$ (wherein R^{5a}, X^{1a} and za are as defined hereinbefore). Another advantageous value of R^{2a} is hydrogen.

Preferably R^{2a} is methyl, ethyl, methoxy, ethoxy or $R^{5a}(CH_2)_{za}X^{1a}$ (wherein R^{5a}, X^{1a} and za are as defined hereinbefore). Another preferred value of R^{2a} is hydrogen.

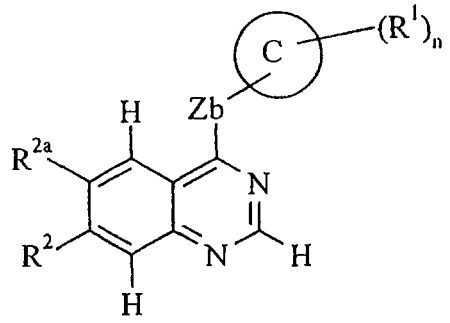
More preferably R^{2a} is methyl, ethyl, methoxy, ethoxy or $R^{5a}(CH_2)_{za}X^{1a}$ (wherein R^{5a} is a group selected from pyrrolidinyl, piperazinyl, piperidinyl, morpholino and thiomorpholino

which group may carry 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-2}alkyl, C_{1-2}hydroxyalkyl and C_{1-2}alkoxy, X^{1a} is -O-, -S-, $-NR^{6a}C(O)-$, $-NR^{9a}SO_2-$ (wherein R^{6a} and R^{9a} each independently represents hydrogen or C_{1-2}alkyl) or NH, and za is an integer from 1 to 3).

Particularly R^{2a} represents methyl, methoxy or $R^{5a}(CH_2)_{za}X^{1a}$ (wherein R^{5a}, X^{1a} and za are as defined hereinbefore).

More particularly R^{2a} represents methoxy.

In a further aspect of the present invention there is provided the use of compounds of the formula Ib:



(Ib)

[wherein:

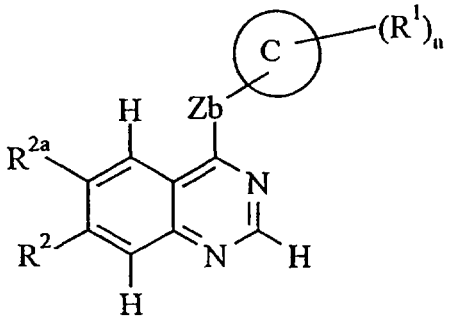
ring C, R^1, R^2, R^{2a} and n are as defined hereinbefore with the proviso that R^2 is not hydrogen; and

Zb is -O- or -S-;

and salts thereof, and prodrugs thereof for example esters, amides and sulphides, preferably esters and amides, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans.

Preferably Zb is -O-.

According to another aspect of the present invention there are provided compounds of the formula II:



(II)

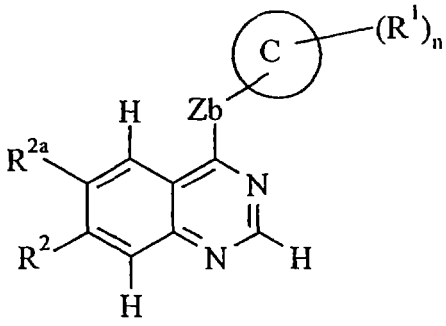
[wherein:

ring C, R^1, R^2, R^{2a}, Zb and n are as defined hereinbefore with the proviso that R^2 is not hydrogen and excluding the compounds:

6,7-dimethoxy-4-(1-naphthylsulphanyl)quinazoline, 6,7-dimethoxy-4-(2-naphthylsulphanyl)quinazoline, 6,7-dimethoxy-4-(1-naphthyloxy)quinazoline and 6,7-dimethoxy-4-(2-naphthyloxy)quinazoline;

and salts thereof, and prodrugs thereof for example esters, amides and sulphides, preferably esters and amides.

According to another aspect of the present invention there are provided compounds of the formula IIa:



(IIa)

[wherein:

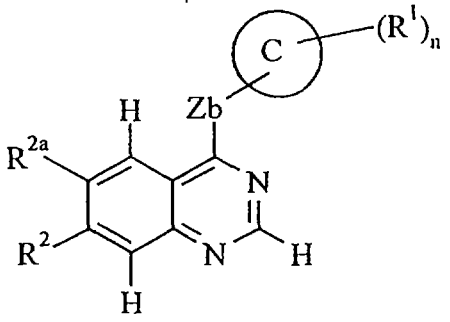
ring C, R^1, R^2, R^{2a}, Zb and n are as defined hereinbefore with the proviso that R^2 does not have any of the following values:

hydrogen, substituted or unsubstituted C_{1-5}alkyl, halogeno or phenoxy and excluding the compounds:

6,7-dimethoxy-4-(1-naphthylsulphanyl)quinazoline, 6,7-dimethoxy-4-(2-naphthylsulphanyl)quinazoline, 6,7-dimethoxy-4-(1-naphthyloxy)quinazoline and 6,7-dimethoxy-4-(2-naphthyloxy)quinazoline;

and salts thereof, and prodrugs thereof for example esters, amides and sulphides, preferably esters and amides.

According to another aspect of the present invention there are provided compounds of the formula IIb:



(IIb)

[wherein:

ring C, R^1, R^2, R^{2a}, Zb and n are as defined hereinbefore with the proviso that R^2 does not have any of the following values:

hydrogen, substituted or unsubstituted C_{1-5}alkyl, halogeno, C_{1-5}alkoxy, C_{2-5}alkenyl, phenoxy or phenylC_{1-5}alkoxy;

and salts thereof, and prodrugs thereof for example esters, amides and sulphides, preferably esters and amides.

Preferred compounds of the present invention include

6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)-4-(2-naphthyloxy)quinazoline,

6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)-4-(quinolin-7-yloxy)quinazoline,

7-(3-(1,1-dioxothiomorpholino)propoxy)-6-methoxy-4-(quinolin-7-yloxy)quinazoline.

6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)-4-(quinolin-7-yloxy)quinazoline,
6-methoxy-7-((1-methylpiperidin-3-yl)methoxy)-4-(quinolin-7-yloxy)quinazoline,
4-(4-chloroquinolin-7-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)-4-(4-methylquinolin-7-yloxy)quinazoline,
6-methoxy-4-(4-methylquinolin-7-yloxy)-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline,
6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-4-(quinolin-7-yloxy)quinazoline,
6-methoxy-7-((1-(2-methylsulphonylethyl)piperidin-4-yl)methoxy)-4-(quinolin-7-yloxy)quinazoline,
4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline,
4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,
6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)-4-(2-trifluoromethylindol-5-yloxy)quinazoline,
6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)-4-(2-trifluoromethylindol-5-yloxy)quinazoline,
(*R*,*S*)-4-(3-fluoroquinolin-7-yloxy)-6-methoxy-7-((1-methylpiperidin-3-yl)methoxy)quinazoline,
4-(indol-5-yloxy)-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline,
7-(3-N,N-dimethylaminopropoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(2-morpholinoethoxy)ethoxy)quinazoline,
7-(2-(N,N-diethylamino)ethoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,
6-methoxy-7-(3-piperidinopropoxy)-4-(quinolin-7-yloxy)quinazoline,
4-(2-methylindol-5-yloxy)-7-(3-morpholinopropoxy)quinazoline,
4-(2-methylindol-5-yloxy)-7-(2-(piperidin-1-yl)ethoxy)quinazoline,
4-(2-methylindol-5-yloxy)-7-(2-(1*H*-1,2,4-triazol-1-yl)ethoxy)quinazoline,
6-methoxy-7-(3-piperidinopropoxy)-4-(6-trifluoromethylindol-5-yloxy)quinazoline,
7-(3-(methylsulphonyl)propoxy)-4-(2-methylindol-5-yloxy)quinazoline,
7-(3-(N,N-dimethylamino)propoxy)-4-(2,3-dimethylindol-5-yloxy)-6-methoxyquinazoline,
4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(1-methylpiperidin-3-ylmethoxy)quinazoline,
7-(2-(N,N-diethylamino)ethoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline,
4-(indol-5-yloxy)-6-methoxy-7-(2-(piperidin-2-yl)ethoxy)quinazoline,
4-(indol-5-yloxy)-6-methoxy-7-(2-(piperidin-1-yl)ethoxy)quinazoline,
4-(indol-6-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
7-(3-(ethylsulphonyl)propoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,

6-methoxy-4-(3-methylindol-5-yloxy)-7-(3-piperidinopropoxy)quinazoline,
7-(2-hydroxy-3-piperidinopropoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,
7-(2-hydroxy-3-(4-methylpiperazin-1-yl)propoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(N-methylamino)ethoxy)quinazoline, and
7-(2-hydroxy-3-(isopropylamino)propoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline, and salts thereof especially hydrochloride salts thereof and prodrugs thereof for example esters and amides.

Especially preferred compounds of the present invention include
6-methoxy-7-(3-morpholinopropoxy)-4-(quinolin-7-yloxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-((1-methylpiperidin-4-yl)methoxy)quinazoline,
4-(indol-5-yloxy)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline,
4-(indol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(3-methylsulphonylpropoxy)quinazoline,
7-((1-cyanomethyl)piperidin-4-ylmethoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-morpholinoethoxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-pyrrolidin-1-ylethoxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(1-methylpiperidin-3-ylmethoxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-piperidinoethoxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(N-methyl-N-(4-pyridyl)amino)ethoxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(3-morpholinopropoxy)quinazoline,
6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-4-(2-methylindol-5-yloxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(1*H*-1,2,4-triazol-1-yl)ethoxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(2-(4-methylpiperazin-1-yl)ethoxy)ethoxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(3-piperidinopropoxy)quinazoline,
4-(indol-5-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline
6-methoxy-7-(1-(2-methoxyethyl)piperidin-4-ylmethoxy)-4-(2-methylindol-5-yloxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-((2-(2-pyrrolidin-1-ylethyl)carbamoyl)vinyl)quinazoline,

6-methoxy-4-(2-methylindol-5-yloxy)-7-(3-(4-methypiperazin-1-yl)propoxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(piperidin-4-ylmethoxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(piperidin-4-yloxy)ethoxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(N-methyl-N-methylsulphonylamino)ethoxy)quinazoline,
7-(2-(1-(2-cyanoethyl)piperidin-4-yloxy)ethoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,
4-(2-methylindol-5-yloxy)-7-(3-(pyrrolidin-yl)propoxy)quinazoline,
4-(2-methylindol-5-yloxy)-7-(3-(1,1-dioxothiomorpholino)propoxy)quinazoline,
4-(2-methylindol-5-yloxy)-7-(piperidin-4-ylmethoxy)quinazoline,
4-(indol-5-yloxy)-6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)quinazoline,
7-(3-(N,N-dimethylamino)propoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline,
7-(3-(N,N-diethylamino)propoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline,
7-(3-(1,1-dioxothiomorpholino)propoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline,
4-(indol-5-yloxy)-6-methoxy-7-(2-(4-pyridyloxy)ethoxy)quinazoline,
4-(indol-6-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,
7-(1-(2-methoxyethyl)piperidin-4-ylmethoxy)-4-(2-methylindol-5-yloxy)quinazoline,
7-(2-hydroxy-3-morpholinopropoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,
7-(2-(1-(2-methoxyethyl)piperidin-4-yl)ethoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,
7-(2-hydroxy-3-pyrrolidin-1-ylpropoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,
7-(3-(N,N-diethylamino)-2-hydroxypropoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,
7-(3-(1,1-dioxothiomorpholino)propoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(4-pyridyloxy)ethoxy)quinazoline,
4-(indol-5-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
(2*R*)-6-methoxy-(2-methyl-1*H*-indol-5-yloxy)-7-(2-hydroxy-3-piperidinopropoxy)quinazoline,
(5*R*)-6-methoxy-4-(2-methyl-1*H*-indol-5-yloxy)-7-(2-oxopyrrolidin-5-ylmethoxy)quinazoline,
4-(4-bromoindol-5-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(1-(2-(pyrrolidin-1-yl)ethyl)-piperidin-4-ylmethoxy)quinazoline.

(2*R*)-7-(2-hydroxy-3-(pyrrolidin-1-yl)propoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline,
(2*R*)-7-(2-hydroxy-3-morpholinopropoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline,
(2*R*)-7-(2-hydroxy-3-piperidinopropoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline,
(2*S*)-7-(2-hydroxy-3-((N,N-diisopropyl)amino)propoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline,
(2*S*)-7-(2-hydroxy-3-piperidinopropoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline,
(2*R*)-7-(2-hydroxy-3-piperidinopropoxy)-6-methoxy-4-(3-methylindol-5-yloxy)quinazoline,
(2*R*)-7-(2-hydroxy-3-(pyrrolidin-1-yl)propoxy)-6-methoxy-4-(3-methylindol-5-yloxy)quinazoline,
(2*R*)-7-(2-hydroxy-3-(pyrrolidin-1-yl)propoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,
(2*R*)-7-(2-hydroxy-3-(4-methylpiperazin-1-yl)propoxy)–6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(1-(2-morpholinoethyl)piperidin-4-ylmethoxy)quinazoline,
4-(3-fluoro-quinolin-7-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,
4-(3-fluoro-quinolin-7-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline,
6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)quinazoline,
(2*S*)-6-methoxy-(2-methyl-1*H*-indol-5-yloxy)-7-(2-hydroxy-3-piperidinopropoxy)quinazoline,
and
4-(6-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline,
and salts thereof especially hydrochloride salts thereof and prodrugs thereof for example esters and amides.

More especially preferred compounds of the present invention include
6-methoxy-4-(2-methylindol-5-yloxy)-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline,
4-(4-fluoroindol-5-yloxy)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline,
4-(4-fluoroindol-5-yloxy)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline,
4-(6-fluoroindol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline,
4-(4-fluoroindol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline,
4-(4-fluoroindol-5-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,
4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline,
4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,

4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline,

4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline,

4-(4-fluoroindol-5-yloxy)-6-methoxy-7-(2-(1-methylpiperidin-4-yl)ethoxy)quinazoline,

(2*R*)-7-(2-hydroxy-3-(pyrrolidin-1-yl)propoxy)-4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxyquinazoline, and

4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(2-(1-methylpiperidin-4-yl)ethoxy)quinazoline,

and salts thereof especially hydrochloride salts thereof and prodrugs thereof for example esters and amides.

Thus preferred compounds of the present invention include those, the preparation of which is described in Examples 23, 10, 5, 176, 7, 22, 13, 15, 177, 12, 35, 47, 44, 45, 157, 52, 62, 66, 75, 159, 87, 88, 89, 167, 83, 97, 101, 108, 113, 114, 121, 124, 178, 162, 165, 150 and 166, and salts thereof especially hydrochloride salts thereof and prodrugs thereof for example esters and amides.

Thus especially preferred compounds of the present invention include those, the preparation of which is described in Examples 2, 11, 34, 36, 186, 151, 57, 54, 55, 58, 56, 60, 61, 64, 65, 67, 68, 71, 72, 74, 70, 77, 79, 80, 82, 86, 122, 107, 110, 112, 117, 118, 119, 123, 161, 147, 163, 164, 63, 78, 115, 320, 318, 290, 252, 292, 293, 294, 301, 299, 279, 280, 305, 269, 246, 266, 267, 182, 321 and 250,

and salts thereof especially hydrochloride salts thereof and prodrugs thereof for example esters and amides.

Thus more especially preferred compounds of the present invention include those, the preparation of which is described in Examples 9, 243, 251, 245, 247, 249, 240, 238, 237, 239, 241, 258 and 322,

and salts thereof especially hydrochloride salts thereof and prodrugs thereof for example esters and amides.

In another embodiment, preferred compounds of the present invention include

6-methoxy-7-(3-morpholinopropoxy)-4-(quinolin-6-yloxy)quinazoline,

(S)-6-methoxy-7-((1-methylpiperidin-3-yl)methoxy)-4-(quinolin-7-yloxy)quinazoline.

6-methoxy-7-(3-morpholinopropoxy)-4-(1-naphthyloxy)quinazoline,

4-(1*H*-indazol-5-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
6,7-dimethoxy-4-(quinolin-7-yloxy)quinazoline,
6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)-4-(2,2,4-trimethyl-1,2-dihydroquinolin-6-yloxy)quinazoline,
6-methoxy-7-((2-piperidin-1-yl)ethoxy)-4-(quinolin-7-yloxy)quinazoline,
6-methoxy-4-(2-methylquinolin-7-yloxy)-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,
6-methoxy-4-(2-methylquinolin-7-yloxy)-7-((1-(2-methylsulphonylethyl)piperidin-4-yl)methoxy)quinazoline,
6-methoxy-4-(2-methylquinolin-7-yloxy)-7-((1-methylpiperidin-4-yl)methoxy)quinazoline,
4-(2-chloro-1*H*-benzimidazol-5-yloxy)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline,
4-(2,4-dimethylquinolin-7-yloxy)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline,
4-(1*H*-indazol-6-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
4-(1,3-benzothiazol-6-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)-4-(3-oxo-2*H*-4*H*-1,4-benzoxazin-6-yloxy)quinazoline,
7-hydroxy-6-methoxy-4-(quinolin-7-yloxy)quinazoline,
6-methoxy-4-(2-methyl-1,3-benzothiazol-5-yloxy)-7-(3-methylsulphonylpropoxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(tetrahydropyran-4-yloxy)ethoxy)quinazoline,
6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)-4-(1,2-cycloheptanebenzimidazol-5-yloxy)quinazoline,
6-methoxy-7-(3-morpholinopropoxy)-4-(quinolin-2-yloxy)quinazoline,
6-methoxy-7-(3-morpholinopropoxy)-4-(3-oxo-1,2-dihydro-3*H*-indazol-1-yl)quinazoline,
4-(2,3-dihydro-1*H*-indan-5-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
6-methoxy-4-(2-methyl-4-oxo-4*H*-chromen-7-yloxy)-7-((1-methylpiperidin-4-yl)methoxy)quinazoline,
6-methoxy-4-(4-methyl-4*H*-1,4-benzoxazin-6-yloxy)-7-((1-methylpiperidin-4-yl)methoxy)quinazoline,
6-methoxy-4-(2-methyl-4-oxo-4*H*-chromen-7-yloxy)-7-((3-pyrrolidin-1-yl)propoxy)quinazoline,

6-methoxy-4-(4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-6-yloxy)-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,

7-benzyloxy-6-methoxy-4-(quinolin-7-yloxy)quinazoline,

4-(2,4-dimethylquinolin-7-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,

6-methoxy-7-(3-methylsulphonylpropoxy)-4-(2-trifluoromethylindol-5-yloxy)quinazoline,

6-methoxy-4-(2-methylquinolin-7-yloxy)-7-(3-methylsulphonylpropoxy)quinazoline,

6-methoxy-7-(3-morpholinopropoxy)-4-(quinazolin-7-yloxy)quinazoline,

6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)-4-(3-oxo-2*H*-4*H*-1,4-benzoxazin-6-yloxy)quinazoline,

7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,

6,7-dimethoxy-4-(2-methyl-1*H*-benzimidazol-5-yloxy)quinazoline,

and salts thereof especially hydrochloride salts thereof and prodrugs thereof for example esters, amides and sulphides, preferably esters and amides.

In another embodiment more preferred compounds of the present invention include

6-methoxy-4-(4-methylquinolin-7-yloxy)-7-(3-morpholinopropoxy)quinazoline,

6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)-4-(quinolin-6-yloxy)quinazoline,

6-methoxy-4-(2-methyl-1,3-benzothiazol-5-yloxy)-7-(3-morpholinopropoxy)quinazoline,

(R)-6-methoxy-7-((1-methylpiperidin-3-yl)methoxy)-4-(quinolin-7-yloxy)quinazoline,

6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)-4-(2,2,4-trimethyl-1,2-dihydroquinolin-6-yloxy)quinazoline,

6-methoxy-7-(2-morpholinoethoxy)-4-(quinolin-7-yloxy)quinazoline,

6-methoxy-4-(2-methylindol-5-yloxy)-7-((1-(2-methylsulphonylethyl)piperidin-4-yl)methoxy)quinazoline,

6-methoxy-4-(2-methylindol-5-ylamino)-7-((1-methylpiperidin-4-yl)methoxy)quinazoline,

6-methoxy-4-(2-methylindol-5-ylamino)-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,

4-(4-chloroquinolin-7-yloxy)-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline,

4-(7-hydroxy-2-naphthyloxy)-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline,

6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)-4-(2-trifluoromethylindol-5-yloxy)quinazoline,

7-(2-(N,N-dimethylamino)ethoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,

6-methoxy-7-(2-(N-(2-methoxyethyl)-N-methylamino)ethoxy)-4-(2-methylindol-5-yloxy)quinazoline,

4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline,

4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,

(S)-6-methoxy-7-((2-oxo-tetrahydro-2*H*-pyrrolidin-5-yl)methoxy)-4-(quinolin-7-yloxy)quinazoline,

and salts thereof especially hydrochloride salts thereof and prodrugs thereof for example esters, amides and sulphides, preferably esters and amides.

In another embodiment especially preferred compounds of the present invention include

6-methoxy-4-(2-methylindol-5-yloxy)-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,

4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,

6-methoxy-4-(2-methylindol-5-yloxy)-7-(3-methylsulphonylpropoxy)quinazoline,

6-methoxy-4-(2-methylindol-5-yloxy)-7-((1-methylpiperidin-3-yl)methoxy)quinazoline,

6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(piperidin-1-yl)ethoxy)quinazoline,

6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)-4-(quinolin-7-yloxy)quinazoline,

6-methoxy-7-((1-methylpiperidin-3-yl)methoxy)-4-(quinolin-7-yloxy)quinazoline,

6-methoxy-4-(2-methylindol-5-yloxy)-7-((1-methylpiperidin-4-yl)methoxy)quinazoline,

4-(indol-5-yloxy)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline,

4-(indol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,

6-methoxy-7-(3-methylsulphonylpropoxy)-4-(quinolin-7-yloxy)quinazoline,

6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(pyrrolidin-1-yl)ethoxy)quinazoline,

6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(N-methyl-N-(4-pyridyl)amino)ethoxy)quinazoline,

6-methoxy-4-(2-methylindol-5-yloxy)-7-(3-morpholinopropoxy)quinazoline,

6-methoxy-7-(3-morpholinopropoxy)-4-(quinolin-7-yloxy)quinazoline,

6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)-4-(2-naphthyloxy)quinazoline,

7-(3-(1,1-dioxothiomorpholino)propoxy)-6-methoxy-4-(quinolin-7-yloxy)quinazoline,

6-methoxy-7-(3-(1-methylpiperazin-4-yl)propoxy)-4-(quinolin-7-yloxy)quinazoline,

4-(4-chloroquinolin-7-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,

6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)-4-(4-methylquinolin-7-yloxy)quinazoline,

6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-4-(quinolin-7-yloxy)quinazoline,

6-methoxy-7-((1-(2-methylsulphonylethyl)piperidin-4-yl)methoxy)-4-(quinolin-7-yloxy)-quinazoline,

7-((1-cyanomethylpiperidin-4-yl)methoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,
6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)-4-(2-trifluoromethylindol-5-yloxy)quinazoline,
4-(3-fluoroquinolin-7-yloxy)-6-methoxy-7-((1-methylpiperidin-3-yl)methoxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-morpholinoethoxy)quinazoline,
6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-4-(2-methylindol-5-yloxy)quinazoline,
7-(3-(N,N-dimethylamino)propoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,
7-(3-(1,1-dioxothiomorpholino)propoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(2-(1-methylpiperazin-4-yl)ethoxy)ethoxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(2-morpholinoethoxy)ethoxy)quinazoline,
6-methoxy-4-(4-methylquinolin-7-yloxy)-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(1,2,4-triazol-1-yl)ethoxy)quinazoline,
4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline,
4-(indol-5-yloxy)-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline,
and salts thereof especially hydrochloride salts thereof and prodrugs thereof for example esters, amides and sulphides, preferably esters and amides.

In another aspect of the present invention preferred compounds include
6-methoxy-7-((1-(2-methoxyethyl)piperidin-4-yl)methoxy)-4-(2-methylindol-5-yloxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(2-(pyrrolidin-1-yl)ethylcarbamoyl)vinyl)quinazoline,
4-(3-cyanoquinolin-7-yloxy)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline,
6-methoxy-7-((1-methylpiperidin-3-yl)methoxy)-4-(4-trifluoromethylquinolin-7-yloxy)quinazoline,
6-methoxy-4-(2-methyl-1*H*-benzimidazol-5-yloxy)-7-((1-methylpiperidin-4-yl)methoxy)quinazoline,
4-(3-carbamoylquinolin-7-yloxy)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(3-(1-methylpiperazin-4-yl)propoxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(piperidin-4-ylmethoxy)quinazoline,

and salts thereof especially hydrochloride salts thereof and prodrugs thereof for example esters, amides and sulphides, preferably esters and amides.

An especially preferred compound of the present invention is

6-methoxy-4-(2-methylindol-5-yloxy)-7-(3-pyrrolidin-1-ylpropoxy)quinazoline

and salts thereof especially hydrochloride salts thereof and prodrugs thereof for example esters, amides and sulphides, preferably esters and amides.

For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined' or 'defined hereinbefore' the said group encompasses the first occurring and broadest definition as well as each and all of the preferred definitions for that group.

In this specification unless stated otherwise the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. An analogous convention applies to other generic terms. Unless otherwise stated the term "alkyl" advantageously refers to chains with 1-6 carbon atoms, preferably 1-4 carbon atoms. The term "alkoxy" as used herein, unless stated otherwise includes "alkyl"-O- groups in which "alkyl" is as hereinbefore defined. The term "aryl" as used herein unless stated otherwise includes reference to a C_{6-10} aryl group which may, if desired, carry one or more substituents selected from halogeno, alkyl, alkoxy, nitro, trifluoromethyl and cyano, (wherein alkyl and alkoxy are as hereinbefore defined). The term "aryloxy" as used herein unless otherwise stated includes "aryl"-O-groups in which "aryl" is as hereinbefore defined. The term "sulphonyloxy" as used herein refers to alkylsulphonyloxy and arylsulphonyloxy groups in which "alkyl" and "aryl" are as hereinbefore defined. The term "alkanoyl" as used herein unless otherwise stated includes formyl and alkylC=O groups in which "alkyl" is as defined hereinbefore, for example C_2alkanoyl is ethanoyl and refers to $CH_3C{=}O$, C_1alkanoyl is formyl and refers to CHO. In this specification unless stated otherwise the term "alkenyl" includes both straight and branched chain alkenyl groups but references to individual alkenyl groups such as 2-butenyl are specific for the straight chain version only. Unless otherwise stated the term "alkenyl" advantageously refers to chains with 2-5 carbon atoms, preferably 3-4 carbon atoms. In this specification unless stated otherwise the term "alkynyl" includes both straight and branched chain alkynyl groups but references to individual alkynyl groups such as 2-butynyl are specific for the straight chain version only. Unless otherwise stated the term "alkynyl" advantageously refers to chains with 2-5 carbon

atoms, preferably 3-4 carbon atoms. Unless stated otherwise the term "haloalkyl" refers to an alkyl group as defined hereinbefore which bears one or more halogeno groups, such as for example trifluoromethyl.

For the avoidance of any doubt, where R^2 has a value of substituted or unsubstituted C_{1-5}alkyl, R^2 has been selected from C_{1-3}alkyl or from a group R^5X^1 wherein X^1 is a direct bond or $-CH_2-$ and R^5 is C_{1-5}alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, chloro, bromo and amino.

Within the present invention it is to be understood that a compound of the formula I 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 inhibits VEGF receptor tyrosine kinase activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings. The formulae drawings within this specification can represent only one of the possible tautomeric forms and it is to be understood that the specification encompasses all possible tautomeric forms of the compounds drawn not just those forms which it has been possible to show graphically herein.

It will be appreciated that compounds of the formula I or a salt thereof may possess an asymmetric carbon atom. Such an asymmetric carbon atom is also involved in the tautomerism described above, and it is to be understood that the present invention encompasses any chiral form (including both pure enantiomers, scalemic and racemic mixtures) as well as any tautomeric form which inhibits VEGF receptor tyrosine kinase activity, and is not to be limited merely to any one tautomeric form or chiral form utilised within the formulae drawings. It is to be understood that the invention encompasses all optical and diastereomers which inhibit VEGF receptor tyrosine kinase activity. It is further to be understood that in the names of chiral compounds (*R*,*S*) denotes any scalemic or racemic mixture while (*R*) and (*S*) denote the enantiomers. In the absence of (*R*,*S*), (*R*) or (*S*) in the name it is to be understood that the name refers to any scalemic or racemic mixture, wherein a scalemic mixture contains *R* and *S* enantiomers in any relative proportions and a racemic mixture contains *R* and *S* enantiomers in the ration 50:50.

It is also to be understood that certain compounds of the formula I 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 inhibit VEGF receptor tyrosine kinase activity.

For the avoidance of any doubt, it is to be understood that when X^1 is, for example, a group of formula $-NR^6C(O)-$, it is the nitrogen atom bearing the R^6 group which is attached to the quinazoline ring and the carbonyl (C(O)) group is attached to R^5, whereas when X^1 is, for example, a group of formula $-C(O)NR^7-$, it is the carbonyl group which is attached to the quinazoline ring and the nitrogen atom bearing the R^7 group is attached to R^5. A similar convention applies to the other two atom X^1 linking groups such as $-NR^9SO_2-$ and $-SO_2NR^8-$. When X^1 is $-NR^{10}-$ it is the nitrogen atom bearing the R^{10} group which is linked to the quinazoline ring and to R^5. An analogous convention applies to other groups. It is further to be understood that when X^1 represents $-NR^{10}-$ and R^{10} is $C_{1-3}alkoxyC_{2-3}alkyl$ it is the $C_{2-3}alkyl$ moiety which is linked to the nitrogen atom of X^1 and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that in a compound of the formula I when R^5 is, for example, a group of formula $C_{1-3}alkylX^9C_{1-3}alkylR^{29}$, it is the terminal $C_{1-3}alkyl$ moiety which is linked to X^1, similarly when R^5 is, for example, a group of formula $C_{2-5}alkenylR^{28}$ it is the $C_{2-5}alkenyl$ moiety which is linked to X^1 and an analogous convention applies to other groups. When R^5 is a group $1-R^{29}prop-1-en-3-yl$ it is the first carbon to which the group R^{29} is attached and it is the third carbon which is linked to X^1 and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that in a compound of the formula I when R^5 is, for example, R^{28} and R^{28} is a pyrrolidinyl ring which bears a group $-(-O-)_f(C_{1-4}alkyl)_gringD$, it is the -O- or $C_{1-4}alkyl$ which is linked to the pyrrolidinyl ring, unless f and g are both 0 when it is ring D which is linked to the pyrrolidinyl ring and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that when R^{29} carries a $C_{1-4}aminoalkyl$ substituent it is the $C_{1-4}alkyl$ moiety which is attached to R^{29} whereas when R^{29} carries a $C_{1-4}alkylamino$ substituent it is the amino moiety which is attached to R^{29} and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that when R^{28} carries a $C_{1-4}alkoxyC_{1-4}alkyl$ substituent it is the $C_{1-4}alkyl$ moiety which is attached to R^{28} and an analogous convention applies to other groups.

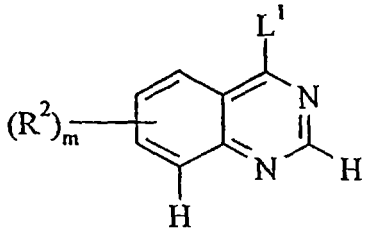
The present invention relates to the compounds of formula I as hereinbefore defined as well as to the salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula I and their pharmaceutically acceptable salts. Pharmaceutically acceptable salts of the invention may, for example, include acid addition salts of the compounds of formula I as hereinbefore defined which are sufficiently basic to form such salts. Such acid addition salts include for example salts with inorganic or organic acids affording pharmaceutically acceptable anions such as with hydrogen halides (especially hydrochloric or hydrobromic acid of which hydrochloric acid is particularly preferred) or with sulphuric or phosphoric acid, or with trifluoroacetic, citric or maleic acid. In addition where the compounds of formula I are sufficiently acidic, pharmaceutically acceptable salts may be formed with an inorganic or organic base which affords a pharmaceutically acceptable cation. Such salts with inorganic or organic bases include for example an alkali metal salt, such as a sodium or potassium salt, an alkaline earth metal salt such as a calcium or magnesium salt, an ammonium salt or for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

A compound of the formula I, or salt thereof, and other compounds of the invention (as hereinafter defined) may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes include, for example, those illustrated in European Patent Applications Publication Nos. 0520722, 0566226, 0602851 and 0635498. Such processes also include, for example, solid phase synthesis. Such processes, are provided as a further feature of the invention and are as described hereinafter. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described within the accompanying non-limiting Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

Thus, the following processes (a) to (f) and (i) to (vi) constitute further features of the present invention.

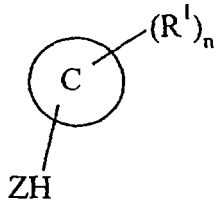
Synthesis of Compounds of Formula I

(a) Compounds of the formula I and salts thereof may be prepared by the reaction of a compound of the formula III:



(III)

(wherein R^2 and m are as defined hereinbefore and L^1 is a displaceable moiety), with a compound of the formula IV:



(IV)

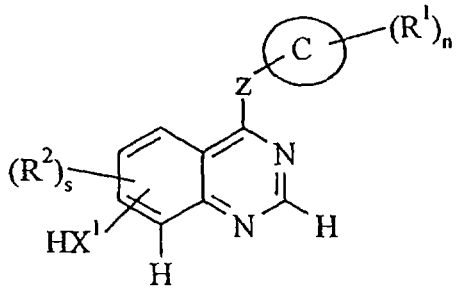
(wherein ring C, R^1, Z and n are as defined hereinbefore) to obtain compounds of the formula I and salts thereof. A convenient displaceable moiety L^1 is, for example, a halogeno, alkoxy (preferably C_{1-4}alkoxy), aryloxy, alkylsulphanyl, arylsulphanyl, alkoxyalkylsulphanyl or sulphonyloxy group, for example a chloro, bromo, methoxy, phenoxy, methylsulphanyl, 2-methoxyethylsulphanyl, methanesulphonyloxy or toluene-4-sulphonyloxy group.

The reaction is advantageously effected in the presence of a base. Such a base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, tetramethylguanidine or for example, an alkali metal or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide. Alternatively such a base is, for example, an alkali metal hydride, for example sodium hydride, or an alkali metal or alkaline earth metal amide, for example sodium amide, sodium bis(trimethylsilyl)amide, potassium amide or potassium bis(trimethylsilyl)amide. The reaction is preferably effected in the presence of an inert solvent or diluent, for example an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic hydrocarbon solvent such as toluene, or a dipolar aprotic solvent such

as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethyl sulphoxide. The reaction is conveniently effected at a temperature in the range, for example, 10 to 150°C, preferably in the range 20 to 90°C.

When it is desired to obtain the acid salt, the free base may be treated with an acid such as a hydrogen halide, for example hydrogen chloride, sulphuric acid, a sulphonic acid, for example methane sulphonic acid, or a carboxylic acid, for example acetic or citric acid, using a conventional procedure.

(b) Production of those compounds of formula I and salts thereof wherein at least one R^2 is R^5X^1 wherein R^5 is as defined hereinbefore and X^1 is -O-, -S-, -OC(O)- or -NR^{10}- (wherein R^{10} independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) can be achieved by the reaction, conveniently in the presence of a base (as defined hereinbefore in process (a)) of a compound of the formula V:



(V)

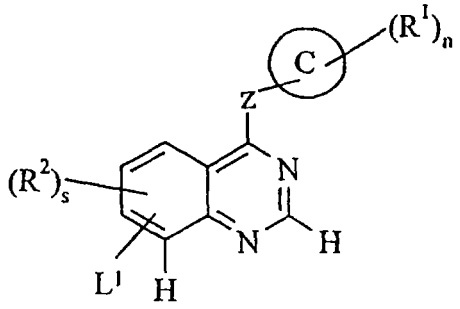
(wherein ring C, Z, R^1, R^2 and n are as hereinbefore defined and X^1 is as hereinbefore defined in this section and s is an integer from 0 to 2) with a compound of formula VI:

$$R^5\text{-}L^1 \qquad \text{(VI)}$$

(wherein R^5 and L^1 are as hereinbefore defined), L^1 is a displaceable moiety for example a halogeno or sulphonyloxy group such as a bromo, methanesulphonyloxy or toluene-4-sulphonyloxy group, or L^1 may be generated in situ from an alcohol under standard Mitsunobu conditions ("Organic Reactions", John Wiley & Sons Inc, 1992, vol 42, chapter 2, David L Hughes). The reaction is preferably effected in the presence of a base (as defined hereinbefore in process (a)) and advantageously in the presence of an inert solvent or diluent

(as defined hereinbefore in process (a)), advantageously at a temperature in the range, for example 10 to 150°C, conveniently at about 50°C.

(c) Compounds of the formula I and salts thereof wherein at least one R^2 is R^5X^1 wherein R^5 is as defined hereinbefore and X^1 is -O-, -S-, -OC(O)- or -NR^{10}- (wherein R^{10} represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) may be prepared by the reaction of a compound of the formula VII:



(VII)

with a compound of the formula VIII:

R^5-X^1-H (VIII)

(wherein L^1, R^1, R^2, R^5, ring C, Z, n and s are all as hereinbefore defined and X^1 is as hereinbefore defined in this section). The reaction may conveniently be effected in the presence of a base (as defined hereinbefore in process (a)) and advantageously in the presence of an inert solvent or diluent (as defined hereinbefore in process (a)), advantageously at a temperature in the range, for example 10 to 150°C, conveniently at about 100°C.

(d) Compounds of the formula I and salts thereof wherein at least one R^2 is R^5X^1 wherein X^1 is as defined hereinbefore and R^5 is C_{1-5}alkylR^{113}, wherein R^{113} is selected from one of the following six groups:

1) $X^{19}C_{1-3}$alkyl (wherein X^{19} represents -O-, -S-, -SO_2-, -NR^{114}C(O)- or –$NR^{115}SO_2$- (wherein R^{114} and R^{115} which may be the same or different are each hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl);

2) $NR^{116}R^{117}$ (wherein R^{116} and R^{117} which may be the same or different are each hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl);

3) $X^{20}C_{1-5}alkylX^5R^{22}$ (wherein X^{20} represents -O-, -S-, $-SO_2-$, $-NR^{118}C(O)-$, $-NR^{119}SO_2-$ or $-NR^{120}-$ (wherein R^{118}, R^{119}, and R^{120} which may be the same or different are each hydrogen, $C_{1-3}alkyl$ or $C_{1-3}alkoxyC_{2-3}alkyl$) and X^5 and R^{22} are as defined hereinbefore);

4) R^{28} (wherein R^{28} is as defined hereinbefore);

5) $X^{21}R^{29}$ (wherein X^{21} represents -O-, -S-, $-SO_2-$, $-NR^{121}C(O)-$, $-NR^{122}SO_2-$, or $-NR^{123}-$ (wherein R^{121}, R^{122}, and R^{123} which may be the same or different are each hydrogen, $C_{1-3}alkyl$ or $C_{1-3}alkoxyC_{2-3}alkyl$) and R^{29} is as defined hereinbefore); and

6) $X^{22}C_{1-3}alkylR^{29}$ (wherein X^{22} represents -O-, -S-, $-SO_2-$, $-NR^{124}C(O)-$, $-NR^{125}SO_2-$ or $-NR^{126}-$ (wherein R^{124}, R^{125} and R^{126} each independently represents hydrogen, $C_{1-3}alkyl$ or $C_{1-3}alkoxyC_{2-3}alkyl$) and R^{29} is as defined hereinbefore);

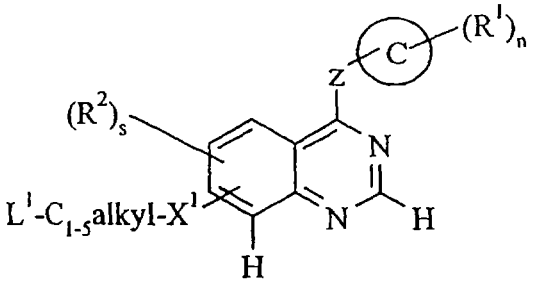
and additionally R^{113} may be selected from the following three groups:

7) R^{29} (wherein R^{29} is as defined hereinbefore);

8) $X^{22}C_{1-4}alkylR^{28}$ (wherein X^{22} and R^{28} are as defined hereinbefore); and

9) $R^{54}(C_{1-4}alkyl)_q(X^9)_rR^{55}$ (wherein q, r, X^9, R^{54} and R^{55} are as defined hereinbefore);

may be prepared by reacting a compound of the formula IX:



(IX)

(wherein L^1, X^1, R^1, R^2, ring C, Z, n and s are as hereinbefore defined) with a compound of the formula X:

$$R^{113}\text{-}H \qquad (X)$$

(wherein R^{113} is as defined hereinbefore) to give a compound of the formula I or salt thereof. The reaction may conveniently be effected in the presence of a base (as defined hereinbefore

in process (a)) and advantageously in the presence of an inert solvent or diluent (as defined hereinbefore in process (a)), and at a temperature in the range, for example 0 to 150°C, conveniently at about 50°C.

Processes (a) and (b) are preferred over processes (c) and (d).

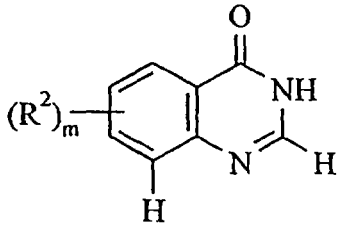
Process (a) is preferred over processes (b), (c) and (d).

(e) The production of those compounds of the formula I and salts thereof wherein one or more of the substituents $(R^2)_m$ is represented by $-NR^{127}R^{128}$, where one (and the other is hydrogen) or both of R^{127} and R^{128} are C_{1-3}alkyl, may be effected by the reaction of compounds of formula I wherein the substituent $(R^2)_m$ is an amino group and an alkylating agent, preferably in the presence of a base as defined hereinbefore. Such alkylating agents are C_{1-3}alkyl moieties bearing a displaceable moiety as defined hereinbefore such as C_{1-3}alkyl halides for example C_{1-3}alkyl chloride, bromide or iodide. The reaction is preferably effected in the presence of an inert solvent or diluent (as defined hereinbefore in process (a)) and at a temperature in the range, for example, 10 to 100°C, conveniently at about ambient temperature. The production of compounds of formula I and salts thereof wherein one or more of the substituents R^2 is an amino group may be effected by the reduction of a corresponding compound of formula I wherein the substituent(s) at the corresponding position(s) of the quinazoline group is/are a nitro group(s). The reduction may conveniently be effected as described in process (i) hereinafter. The production of a compound of formula I and salts thereof wherein the substituent(s) at the corresponding position(s) of the quinazoline group is/are a nitro group(s) may be effected by the processes described hereinbefore and hereinafter in processes (a-d) and (i-v) using a compound selected from the compounds of the formulae (I-XXII) in which the substituent(s) at the corresponding position(s) of the quinazoline group is/are a nitro group(s).

(f) Compounds of the formula I and salts thereof wherein X^1 is -SO- or $-SO_2-$ may be prepared by oxidation from the corresponding compound in which X^1 is -S- or -SO- (when X^1 is $-SO_2-$ is required in the final product). Conventional oxidation conditions and reagents for such reactions are well known to the skilled chemist.

Synthesis of Intermediates

(i) The compounds of formula III and salts thereof in which L^1 is halogeno may for example be prepared by halogenating a compound of the formula XI:

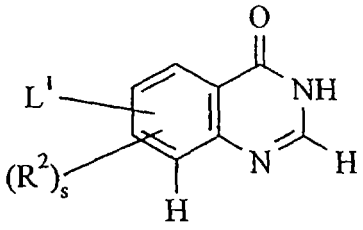


(XI)

wherein R^2 and m are as hereinbefore defined).

Convenient halogenating agents include inorganic acid halides, for example thionyl chloride, phosphorus(III)chloride, phosphorus(V)oxychloride and phosphorus(V)chloride. The halogenation reaction may be effected in the presence of an inert solvent or diluent such as for example a halogenated solvent such as methylene chloride, trichloromethane or carbon tetrachloride, or an aromatic hydrocarbon solvent such as benzene or toluene, or the reaction may be effected without the presence of a solvent. The reaction is conveniently effected at a temperature in the range, for example 10 to 150°C, preferably in the range 40 to 100°C.

The compounds of formula XI and salts thereof may, for example, be prepared by reacting a compound of the formula XII:

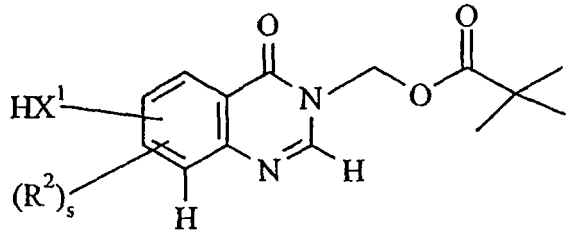


(XII)

(wherein R^2, s and L^1 are as hereinbefore defined) with a compound of the formula VIII as hereinbefore defined. The reaction may conveniently be effected in the presence of a base (as defined hereinbefore in process (a)) and advantageously in the presence of an inert solvent or diluent (as defined hereinbefore in process (a)), advantageously at a temperature in the range, for example 10 to 150°C, conveniently at about 100°C.

Compounds of formula XI and salts thereof wherein at least one R^2 is R^5X^1 and wherein X^1 is -O-, -S-, -SO-, $-SO_2-$, -C(O)-, $-C(O)NR^7-$, $-SO_2NR^8-$ or $-NR^{10}-$ (wherein R^7, R^8

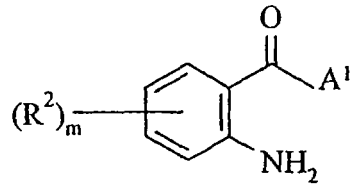
and R^{10} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl), may for example also be prepared by the reaction of a compound of the formula XIII:



(XIII)

(wherein R^2 and s are as hereinbefore defined and X^1 is as hereinbefore defined in this section) with a compound of the formula VI as hereinbefore defined. The reaction may for example be effected as described for process (b) hereinbefore. The pivaloyloxymethyl group can then be cleaved by reacting the product with a base such as, for example, aqueous ammonia, triethylamine in water, an alkali metal or alkaline earth metal hydroxide or alkoxide, preferably aqueous ammonia, aqueous sodium hydroxide or aqueous potassium hydroxide, in a polar protic solvent such as an alcohol, for example methanol or ethanol. The reaction is conveniently effected at a temperature in the range 20 to 100°C, preferably in the range 20 to 50°C.

The compounds of formula XI and salts thereof may also be prepared by cyclising a compound of the formula XIV:

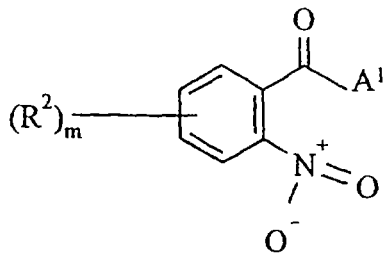


(XIV)

(wherein R^2 and m, are as hereinbefore defined, and A^1 is an hydroxy, alkoxy (preferably C_{1-4}alkoxy) or amino group) whereby to form a compound of formula XI or salt thereof. The cyclisation may be effected by reacting a compound of the formula XIV, where A^1 is an hydroxy or alkoxy group, with formamide or an equivalent thereof effective to cause cyclisation whereby a compound of formula XI or salt thereof is obtained, such as [3-

(dimethylamino)-2-azaprop-2-enylidene]dimethylammonium chloride. The cyclisation is conveniently effected in the presence of formamide as solvent or in the presence of an inert solvent or diluent such as an ether for example 1,4-dioxan. The cyclisation is conveniently effected at an elevated temperature, preferably in the range 80 to 200°C. The compounds of formula XI may also be prepared by cyclising a compound of the formula XIV, where A^1 is an amino group, with formic acid or an equivalent thereof effective to cause cyclisation whereby a compound of formula XI or salt thereof is obtained. Equivalents of formic acid effective to cause cyclisation include for example a tri-C_{1-4}alkoxymethane, for example triethoxymethane and trimethoxymethane. The cyclisation is conveniently effected in the presence of a catalytic amount of an anhydrous acid, such as a sulphonic acid for example p-toluenesulphonic acid, and in the presence of an inert solvent or diluent such as for example a halogenated solvent such as methylene chloride, trichloromethane or carbon tetrachloride, an ether such as diethyl ether or tetrahydrofuran, or an aromatic hydrocarbon solvent such as toluene. The cyclisation is conveniently effected at a temperature in the range, for example 10 to 100°C, preferably in the range 20 to 50°C.

Compounds of formula XIV and salts thereof may for example be prepared by the reduction of the nitro group in a compound of the formula XV:

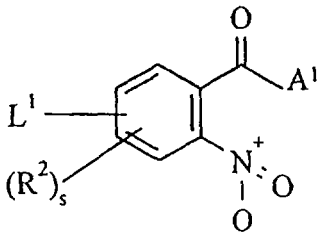


(XV)

(wherein R^2, m and A^1 are as hereinbefore defined) to yield a compound of formula XIV as hereinbefore defined. The reduction of the nitro group may conveniently be effected by any of the procedures known for such a transformation. The reduction may be carried out, for example, by stirring a solution of the nitro compound under hydrogen at 1 to 4 atmospheres pressure in the presence of an inert solvent or diluent as defined hereinbefore in the presence of a metal effective to catalyse hydrogenation reactions such as palladium or platinum. A

further reducing agent is, for example, an activated metal such as activated iron (produced for example by washing iron powder with a dilute solution of an acid such as hydrochloric acid). Thus, for example, the reduction may be effected by heating the nitro compound under hydrogen at 2 atmospheres pressure in the presence of the activated metal and a solvent or diluent such as a mixture of water and alcohol, for example methanol or ethanol, at a temperature in the range, for example 50 to 150°C, conveniently at about 70°C.

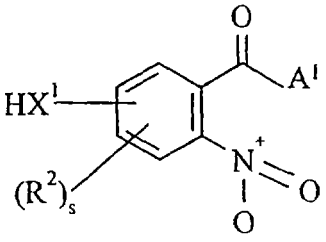
Compounds of the formula XV and salts thereof may for example be prepared by the reaction of a compound of the formula XVI:



(XVI)

(wherein R^2, s, L^1 and A^1 are as hereinbefore defined) with a compound of the formula VIII as hereinbefore defined to give a compound of the formula XV. The reaction of the compounds of formulae XVI and VIII is conveniently effected under conditions as described for process (c) hereinbefore.

Compounds of formula XV and salts thereof wherein at least one R^2 is R^5X^1 and wherein X^1 is -O-, -S-, -SO_2-, -C(O)-, -C(O)NR^7-, -SO_2NR^8- or -NR^{10}- (wherein R^7, R^8 and R^{10} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl), may for example also be prepared by the reaction of a compound of the formula XVII:



(XVII)

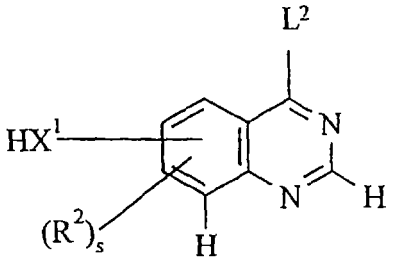
(wherein R^2, s and A^1 are as hereinbefore defined and X^1 is as hereinbefore defined in this section) with a compound of the formula VI as hereinbefore defined to yield a compound of formula XV as hereinbefore defined. The reaction of the compounds of formulae XVII and VI is conveniently effected under conditions as described for process (b) hereinbefore.

The compounds of formula III and salts thereof wherein at least one R^2 is R^5X^1 and wherein X^1 is $-CH_2-$ may be prepared for example as described above from a compound of the formula XV (in which R^2 is $-CH_3$) or XIII (in which HX^1- is $-CH_3$), by radical bromination or chlorination to give a $-CH_2Br$ or $-CH_2Cl$ group which may then be reacted with a compound of the formula R^5-H under standard conditions for such substitution reactions.

The compounds of formula III and salts thereof wherein at least one R^2 is R^5X^1 and wherein X^1 is a direct bond may be prepared for example as described above from a compound of the formula XI, wherein the R^5 group is already present in the intermediate compounds (for example in a compound of the formula XV) used to prepare the compound of formula XI.

The compounds of formula III and salts thereof wherein at least one R^2 is R^5X^1 and wherein X^1 is $-NR^6C(O)-$ or $-NR^9SO_2-$ may be prepared for example from a compound of the formula XIII in which HX^1- is an $-NHR^6-$ or $-NHR^9-$ group (prepared for example from an amino group (later functionalised if necessary) by reduction of a nitro group) which is reacted with an acid chloride or sulfonyl chloride compound of the formula R^5COCl or R^5SO_2Cl.

The compounds of formula III and salts thereof wherein at least one R^2 is R^5X^1 and wherein X^1 is -O-, -S-, $-SO_2-$, -OC(O)-, $-C(O)NR^7-$, $-SO_2NR^8-$ or $-NR^{10}-$ (wherein R^7, R^8 and R^{10} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl), may also be prepared for example by reacting a compound of the formula XVIII:

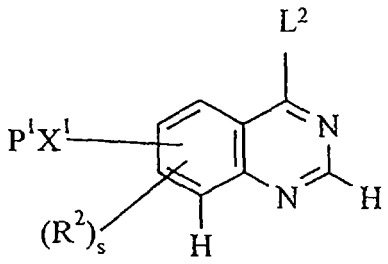


(XVIII)

(wherein R^2 and s are as hereinbefore defined, X^1 is as hereinbefore defined in this section and L^2 represents a displaceable protecting moiety) with a compound of the formula VI as hereinbefore defined, whereby to obtain a compound of formula III in which L^1 is represented by L^2.

A compound of formula XVIII is conveniently used in which L^2 represents a phenoxy group which may if desired carry up to 5 substituents, preferably up to 2 substituents, selected from halogeno, nitro and cyano. The reaction may be conveniently effected under conditions as described for process (b) hereinbefore.

The compounds of formula XVIII and salts thereof may for example be prepared by deprotecting a compound of the formula XIX:



(XIX)

(wherein R^2, s and L^2 are as hereinbefore defined, P^1 is a protecting group and X^1 is as hereinbefore defined in the section describing compounds of the formula XVIII). The choice of protecting group P^1 is within the standard knowledge of an organic chemist, for example those included in standard texts such as "Protective Groups in Organic Synthesis" T.W. Greene and R.G.M.Wuts, 2nd Ed. Wiley 1991, including N-sulphonyl derivatives (for example, p-toluenesulphonyl), carbamates (for example, t-butyl carbonyl), N-alkyl derivatives (for example, 2-chloroethyl, benzyl) and amino acetal derivatives (for example benzyloxymethyl). The removal of such a protecting group may be effected by any of the procedures known for such a transformation, including those reaction conditions indicated in standard texts such as that indicated hereinbefore, or by a related procedure. Deprotection may be effected by techniques well known in the literature, for example where P^1 represents a benzyl group deprotection may be effected by hydrogenolysis or by treatment with trifluoroacetic acid.

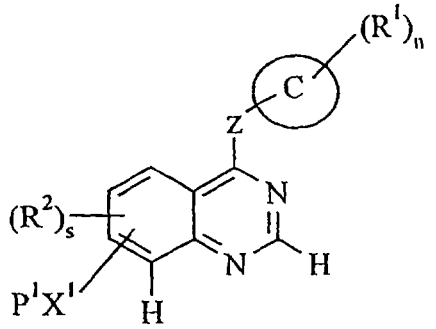
One compound of formula III may if desired be converted into another compound of formula III in which the moiety L^1 is different. Thus for example a compound of formula III in which L^1 is other than halogeno, for example optionally substituted phenoxy, may be converted to a compound of formula III in which L^1 is halogeno by hydrolysis of a compound of formula III (in which L^1 is other than halogeno) to yield a compound of formula XI as hereinbefore defined, followed by introduction of halide to the compound of formula XI, thus obtained as hereinbefore defined, to yield a compound of formula III in which L^1 represents halogen.

(ii) Compounds of formula IV and salts thereof in which ring C is an indolyl may be prepared by any of the methods known in the art, such as for example those described in "Indoles Part I", "Indoles Part II", 1972 John Wiley & Sons Ltd and "Indoles Part III" 1979, John Wiley & Sons Ltd, edited by W. J. Houlihan.

Examples of the preparation of indoles are given in the Examples hereinafter, such as Examples 48, 237, 242, 250 and 291.

Compounds of formula IV and salts thereof in which ring C is a quinolinyl may be prepared by any of the methods known in the art, such as for example those described in "The Chemistry of Heterocyclic Compounds: Quinolines Parts I, II and III", 1982 (Interscience publications) John Wiley & Sons Ltd, edited by G. Jones, and in "Comprehensive Heterocyclic Chemistry Vol II by A. R. Katritzky", 1984 Pergamon Press, edited by A. J. Boulton and A McKillop.

(iii) Compounds of formula V as hereinbefore defined and salts thereof may be made by deprotecting the compound of formula XX:

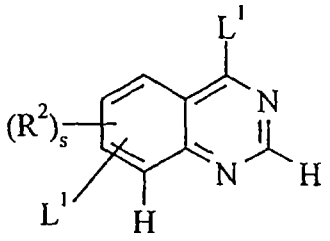


(XX)

(wherein ring C, Z, R^1, R^2, P^1, n and s are as hereinbefore defined and X^1 is as hereinbefore defined in the section describing compounds of the formula V) by a process for example as described in (i) above.

Compounds of the formula XX and salts thereof may be made by reacting compounds of the formulae XIX and IV as hereinbefore defined, under the conditions described in (a) hereinbefore, to give a compound of the formula XX or salt thereof.

(iv) Compounds of the formula VII and salts thereof may be made by reacting a compound of the formula XXI:



(XXI)

(wherein R^2, s and each L^1 are as hereinbefore defined and the L^1 in the 4-position and the other L^1 in a further position on the quinazoline ring may be the same or different) with a compound of the formula IV as hereinbefore defined, the reaction for example being effected by a process as described in (a) above.

(v) Compounds of formula IX as defined hereinbefore and salts thereof may for example be made by the reaction of compounds of formula V as defined hereinbefore with compounds of the formula XXII:

$$L^1\text{-}C_{1\text{-}5}\text{alkyl-}L^1 \qquad \text{(XXII)}$$

(wherein L^1 is as hereinbefore defined) to give compounds of formula IX or salts thereof. The reaction may be effected for example by a process as described in (b) above.

(vi) Intermediate compounds wherein X^1 is -SO- or -SO_2- may be prepared by oxidation from the corresponding compound in which X^1 is -S- or -SO- (when X^1 is -SO_2- is required in the final product). Conventional oxidation conditions and reagents for such reactions are well known to the skilled chemist.

When a pharmaceutically acceptable salt of a compound of the formula I is required, it may be obtained, for example, by reaction of said compound with, for example, an acid using a conventional procedure, the acid having a pharmaceutically acceptable anion.

Many of the intermediates defined herein, for example, those of the formulae V, VII, IX and XX are novel and these are provided as a further feature of the invention. The preparation of these compounds is as described herein and/or is by methods well known to persons skilled in the art of organic chemistry.

The identification of compounds which potently inhibit the tyrosine kinase activity associated with VEGF receptors such as Flt and/or KDR and which inhibit angiogenesis and/or increased vascular permeability is desirable and is the subject of the present invention. These properties may be assessed, for example, using one or more of the procedures set out below:

(a) In Vitro Receptor Tyrosine Kinase Inhibition Test

This assay determines the ability of a test compound to inhibit tyrosine kinase activity. DNA encoding VEGF, FGF or EGF receptor cytoplasmic domains may be obtained by total gene synthesis (Edwards M, International Biotechnology Lab 5(3), 19-25, 1987) or by cloning. These may then be expressed in a suitable expression system to obtain polypeptide with tyrosine kinase activity. For example VEGF, FGF and EGF receptor cytoplasmic domains, which were obtained by expression of recombinant protein in insect cells, were found to display intrinsic tyrosine kinase activity. In the case of the VEGF receptor Flt (Genbank accession number X51602), a 1.7kb DNA fragment encoding most of the cytoplasmic domain, commencing with methionine 783 and including the termination codon, described by Shibuya et al (Oncogene, 1990, 5: 519-524), was isolated from cDNA and cloned into a baculovirus transplacement vector (for example pAcYM1 (see The Baculovirus Expression System: A Laboratory Guide, L.A. King and R. D. Possee, Chapman and Hall, 1992) or pAc360 or pBlueBacHis (available from Invitrogen Corporation)). This recombinant construct was co-transfected into insect cells (for example Spodoptera frugiperda 21(Sf21)) with viral DNA (eg Pharmingen BaculoGold) to prepare recombinant baculovirus. (Details of the methods for the assembly of recombinant DNA molecules and the preparation and use of recombinant baculovirus can be found in standard texts for example Sambrook et al, 1989, Molecular cloning - A Laboratory Manual, 2nd edition, Cold Spring Harbour Laboratory Press and O'Reilly et al, 1992, Baculovirus Expression Vectors - A Laboratory Manual, W. H.

Freeman and Co, New York). For other tyrosine kinases for use in assays, cytoplasmic fragments starting from methionine 806 (KDR, Genbank accession number L04947), methionine 668 (EGF receptor, Genbank accession number X00588) and methionine 399 (FGF R1 receptor, Genbank accession number X51803) may be cloned and expressed in a similar manner.

For expression of cFlt tyrosine kinase activity, Sf21 cells were infected with plaque-pure cFlt recombinant virus at a multiplicity of infection of 3 and harvested 48 hours later. Harvested cells were washed with ice cold phosphate buffered saline solution (PBS) (10mM sodium phosphate pH7.4, 138mM sodium chloride, 2.7mM potassium chloride) then resuspended in ice cold HNTG/PMSF (20mM Hepes pH7.5, 150mM sodium chloride, 10% v/v glycerol, 1% v/v Triton X100, 1.5mM magnesium chloride, 1mM ethylene glycol-bis(βaminoethyl ether) N,N,N',N'-tetraacetic acid (EGTA), 1mM PMSF (phenylmethylsulphonyl fluoride); the PMSF is added just before use from a freshly-prepared 100mM solution in methanol) using 1ml HNTG/PMSF per 10 million cells. The suspension was centrifuged for 10 minutes at 13,000 rpm at 4°C, the supernatant (enzyme stock) was removed and stored in aliquots at -70°C. Each new batch of stock enzyme was titrated in the assay by dilution with enzyme diluent (100mM Hepes pH 7.4, 0.2mM sodium orthovanadate, 0.1% v/v Triton X100, 0.2mM dithiothreitol). For a typical batch, stock enzyme is diluted 1 in 2000 with enzyme diluent and 50µl of dilute enzyme is used for each assay well.

A stock of substrate solution was prepared from a random copolymer containing tyrosine, for example Poly (Glu, Ala, Tyr) 6:3:1 (Sigma P3899), stored as 1 mg/ml stock in PBS at -20°C and diluted 1 in 500 with PBS for plate coating.

On the day before the assay 100µl of diluted substrate solution was dispensed into all wells of assay plates (Nunc maxisorp 96-well immunoplates) which were sealed and left overnight at 4°C.

On the day of the assay the substrate solution was discarded and the assay plate wells were washed once with PBST (PBS containing 0.05% v/v Tween 20) and once with 50mM Hepes pH7.4.

Test compounds were diluted with 10% dimethylsulphoxide (DMSO) and 25µl of diluted compound was transferred to wells in the washed assay plates. "Total" control wells contained 10% DMSO instead of compound. Twenty five microlitres of 40mM manganese(II)chloride containing 8µM adenosine-5'-triphosphate (ATP) was added to all test

wells except "blank" control wells which contained manganese(II)chloride without ATP. To start the reactions 50µl of freshly diluted enzyme was added to each well and the plates were incubated at room temperature for 20 minutes. The liquid was then discarded and the wells were washed twice with PBST. One hundred microlitres of mouse IgG anti-phosphotyrosine antibody (Upstate Biotechnology Inc. product 05-321), diluted 1 in 6000 with PBST containing 0.5% w/v bovine serum albumin (BSA), was added to each well and the plates were incubated for 1 hour at room temperature before discarding the liquid and washing the wells twice with PBST. One hundred microlitres of horse radish peroxidase (HRP)-linked sheep anti-mouse Ig antibody (Amersham product NXA 931), diluted 1 in 500 with PBST containing 0.5% w/v BSA, was added and the plates were incubated for 1 hour at room temperature before discarding the liquid and washing the wells twice with PBST. One hundred microlitres of 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid) (ABTS) solution, freshly prepared using one 50mg ABTS tablet (Boehringer 1204 521) in 50ml freshly prepared 50mM phosphate-citrate buffer pH5.0 + 0.03% sodium perborate (made with 1 phosphate citrate buffer with sodium perborate (PCSB) capsule (Sigma P4922) per 100ml distilled water), was added to each well. Plates were then incubated for 20-60 minutes at room temperature until the optical density value of the "total" control wells, measured at 405nm using a plate reading spectrophotometer, was approximately 1.0. "Blank" (no ATP) and "total" (no compound) control values were used to determine the dilution range of test compound which gave 50% inhibtion of enzyme activity.

(b) In Vitro HUVEC Proliferation Assay

This assay determines the ability of a test compound to inhibit the growth factor-stimulated proliferation of human umbilical vein endothelial cells (HUVEC).

HUVEC cells were isolated in MCDB 131 (Gibco BRL) + 7.5% v/v foetal calf serum (FCS) and were plated out (at passage 2 to 8), in MCDB 131 + 2% v/v FCS + 3µg/ml heparin + 1µg/ml hydrocortisone, at a concentration of 1000 cells/well in 96 well plates. After a minimum of 4 hours they were dosed with the appropriate growth factor (i.e. VEGF 3ng/ml, EGF 3ng/ml or b-FGF 0.3ng/ml) and compound. The cultures were then incubated for 4 days at 37°C with 7.5% CO_2. On day 4 the cultures were pulsed with 1µCi/well of tritiated-thymidine (Amersham product TRA 61) and incubated for 4 hours. The cells were harvested using a 96-well plate harvester (Tomtek) and then assayed for incorporation of

tritium with a Beta plate counter. Incorporation of radioactivity into cells, expressed as cpm, was used to measure inhibition of growth factor-stimulated cell proliferation by compounds.

(c) In Vivo Solid Tumour Disease Model

This test measures the capacity of compounds to inhibit solid tumour growth.

CaLu-6 tumour xenografts were established in the flank of female athymic Swiss *nu/nu* mice, by subcutaneous injection of $1x10^6$ CaLu-6 cells/mouse in 100µl of a 50% (v/v) solution of Matrigel in serum free culture medium. Ten days after cellular implant, mice were allocated to groups of 8-10, so as to achieve comparable group mean volumes. Tumours were measured using vernier calipers and volumes were calculated as: $(l \times w) \times \sqrt{(l \times w)} \times (\pi/6)$, where l is the longest diameter and w the diameter perpendicular to the longest. Test compounds were administered orally once daily for a minimum of 21 days, and control animals received compound diluent. Tumours were measured twice weekly. The level of growth inhibition was calculated by comparison of the mean tumour volume of the control group versus the treatment group using a Student T test and/or a Mann-Whitney Rank Sum Test. The inhibitory effect of compound treatment was considered significant when $p<0.05$.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula I as defined hereinbefore or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) for example as a sterile solution, suspension or emulsion, for topical administration for example as an ointment or cream or for rectal administration for example as a suppository. In general the above compositions may be prepared in a conventional manner using conventional excipients.

The compositions of the present invention are advantageously presented in unit dosage form. The compound will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000mg per square metre body area of the animal, i.e. approximately 0.1-100mg/kg. A unit dose in the range, for example, 1-100mg/kg, preferably 1-50mg/kg is envisaged and this normally provides a therapeutically-effective dose. A unit

dose form such as a tablet or capsule will usually contain, for example 1-250mg of active ingredient.

According to a further aspect of the present invention there is provided a compound of the formula I or a pharmaceutically acceptable salt thereof as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

We have found that compounds of the present invention inhibit VEGF receptor tyrosine kinase activity and are therefore of interest for their antiangiogenic effects and/or their ability to cause a reduction in vascular permeability.

A further feature of the present invention is a compound of formula I, or a pharmaceutically acceptable salt thereof, for use as a medicament, conveniently a compound of formula I, or a pharmaceutically acceptable salt thereof, for use as a medicament for producing an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human being.

According to a further feature of the invention there is provided a method for producing an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof as defined hereinbefore.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. Preferably a daily dose in the range of 1-50mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

The antiangiogenic and/or vascular permeability reducing treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may

be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment in addition to the antiangiogenic and/or vascular permeability reducing treatment defined hereinbefore may be: surgery, radiotherapy or chemotherapy. Such chemotherapy may cover three main categories of therapeutic agent:

(i) other antiangiogenic agents that work by different mechanisms from those defined hereinbefore (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function, angiostatin, razoxin, thalidomide), and including vascular targeting agents (for example combretastatin phosphate and the vascular damaging agents described in International Patent Application Publication No. WO 99/02166 the entire disclosure of which document is incorporated herein by reference, (for example N-acetylcolchinol-O-phosphate));

(ii) cytostatic agents such as antioestrogens (for example tamoxifen,toremifene, raloxifene, droloxifene, iodoxyfene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrazole, vorazole, exemestane), antiprogestogens, antiandrogens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), LHRH agonists and antagonists (for example goserelin acetate, luprolide), inhibitors of testosterone 5α-dihydroreductase (for example finasteride), anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors); and

(iii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as antimetabolites (for example antifolates like methotrexate, fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); antitumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa); antimitotic agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere);

topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan, and also irinotecan); also enzymes (for example asparaginase); and thymidylate synthase inhibitors (for example raltitrexed);

and additional types of chemotherapeutic agent include:

(iv) biological response modifiers (for example interferon); and

(v) antibodies (for example edrecolomab).

For example such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of a compound of formula I as defined hereinbefore, and a vascular targeting agent described in WO 99/02166 such as N-acetylcolchinol-O-phosphate (Exampe 1 of WO 99/02166).

As stated above the compounds defined in the present invention are of interest for their antiangiogenic and/or vascular permeability reducing effects. Such compounds of the invention are expected to be useful in a wide range of disease states including cancer, diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, excessive scar formation and adhesions, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation. In particular such compounds of the invention are expected to slow advantageously the growth of primary and recurrent solid tumours of, for example, the colon, breast, prostate, lungs and skin. More particularly such compounds of the invention are expected to inhibit the growth of those primary and recurrent solid tumours which are associated with VEGF, especially those tumours which are significantly dependent on VEGF for their growth and spread, including for example, certain tumours of the colon, breast, prostate, lung, vulva and skin.

In addition to their use in therapeutic medicine, the compounds of formula I and their pharmaceutically acceptable salts 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 VEGF receptor tyrosine kinase activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

It is to be understood that where the term "ether" is used anywhere in this specification it refers to diethyl ether.

The invention will now be illustrated in the following non-limiting Examples 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, that is in the range 18-25°C and 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) or Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck, Darmstadt, Germany;

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

(v) melting points are uncorrected and were determined using a Mettler SP62 automatic melting point apparatus, an oil-bath apparatus or a Koffler hot plate apparatus.

(vi) the structures of the end-products of the formula I were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet, quin, quintet;

(vii) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), infra-red (IR) or NMR analysis;

(viii) HPLC were run under 2 different conditions:

1) on a TSK Gel super ODS 2μM 4.6mm x 5cm column, eluting with a gradient of methanol in water (containing 1% acetic acid) 20 to 100% in 5 minutes. Flow rate 1.4 ml/minute. Detection: U.V. at 254 nm and light scattering detections;

2) on a TSK Gel super ODS 2μM 4.6mm x 5cm column, eluting with a gradient of methanol in water (containing 1% acetic acid) 0 to 100% in 7 minutes. Flow rate 1.4 ml/minute. Detection: U.V. at 254 nm and light scattering detections.

(ix) petroleum ether refers to that fraction boiling between 40-60°C

(x) the following abbreviations have been used:-

DMF N,N-dimethylformamide

DMSO dimethylsulphoxide

TFA trifluoroacetic acid

NMP 1-methyl-2-pyrrolidinone

THF tetrahydrofuran

HMDS 1,1,1,3,3,3-hexamethyldisilazane.

HPLC RT HPLC retention time

DEAD diethyl azodicarboxylate

DMA dimethylacetamide

DMAP 4-dimethylaminopyridine

Example 1

A mixture of 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (225mg, 0.67mmol), potassium carbonate (106mg, 0.77mmol) and 6-hydroxyquinoline (112mg, 0.77mmol) in DMF (7.5ml) was stirred at 100°C for 5 hours and allowed to cool to ambient temperature. The reaction mixture was treated with 1M aqueous sodium hydroxide solution (40ml) and stirred at ambient temperature for a few minutes. The crude solid was collected by filtration and washed with water. The resultant solid was dissolved in dichloromethane (2ml) and filtered through phase separating paper. The filtrate was evaporated under vacuum and the residue was triturated with ether, collected by filtration and dried to give **6-methoxy-7-(3-morpholinopropoxy)-4-(quinolin-6-yloxy)quinazoline** (163mg, 55%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.98(m, 2H); 2.40(m, 4H); 2.48(t, 2H); 3.59(m, 4H); 4.00(s, 3H); 4.25(t, 2H); 7.40(s, 1H); 7.58(m, 1H); 7.62(s, 1H); 7.74(dd, 1H); 7.92(d, 1H); 8.10(d, 1H); 8.38(d, 1H); 8.55(s, 1H); 8.92(m, 1H)

MS (ESI): 447 $(MH)^+$

Elemental analysis:	Found	C 65.9	H 5.7	N 12.4
$C_{25}H_{26}N_4O_4$ $0.5H_2O$	Requires	C 65.9	H 6.0	N 12.3%

The starting material was prepared as follows:

A mixture of 2-amino-4-benzyloxy-5-methoxybenzamide (10g, 0.04mol), (J. Med. Chem. 1977, vol 20, 146-149), and Gold's reagent (7.4g, 0.05mol) in dioxane (100ml) was

stirred and heated at reflux for 24 hours. Sodium acetate (3.02g, 0.037mol) and acetic acid (1.65ml, 0.029mol) were added to the reaction mixture and it was heated for a further 3 hours. The volatiles were removed by evaporation, water was added to the residue, the solid was collected by filtration, washed with water and dried. Recrystallisation from acetic acid gave 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (8.7g, 84%).

7-Benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (35g, 124mmol) was suspended in thionyl chloride (440ml) and DMF (1.75ml) and heated at reflux for 4 hours. The thionyl chloride was evaporated under vacuum and the residue azeotroped with toluene three times. The residue was dissolved in NMP (250ml) to give a solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline.

Phenol (29.05g, 309mmol) was dissolved in NMP (210ml), sodium hydride (11.025g, 60% dispersion in mineral oil) was added in portions with cooling and the mixture was stirred for 3 hours. The viscous suspension was diluted with NMP (180ml) and stirred overnight. The solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline was added and the suspension stirred at 100°C for 2.5 hours. The suspension was allowed to cool to ambient temperature and poured into water (1.5l) with vigorous stirring. The precipitate was collected by filtration, washed with water and dried under vacuum. The residue was dissolved in dichloromethane, washed with brine and filtered through phase separating paper. The filtrate was evaporated under vacuum then triturated with ether to give 7-benzyloxy-6-methoxy-4-phenoxyquinazoline (87.8g, 83%) as a pale cream solid.

^{1}H NMR Spectrum: ($CDCl_3$) 4.09(s, 3H); 5.34(s, 2H); 7.42(m, 12H); 7.68(s, 1H)

MS (ESI): 359 $(MH)^+$

7-Benzyloxy-6-methoxy-4-phenoxyquinazoline (36.95g, 105.5mmol) was suspended in TFA (420ml) and heated at reflux for 3 hours. The reaction mixture was allowed to cool and evaporated under vacuum. The residue was stirred mechanically in water then basified with saturated aqueous sodium hydrogen carbonate solution and stirred overnight. The water was decanted and the solid suspended in acetone. After stirring the white solid was collected by filtration, washed with acetone and dried to give 7-hydroxy-6-methoxy-4-phenoxyquinazoline (26.61g, 96%).

^{1}H NMR Spectrum: ($DMSOd_6$) 3.97(s, 3H); 7.22(s, 1H); 7.30(m, 3H); 7.47(t, 2H); 7.56(s, 1H); 8.47(s, 1H); 10.70(s, 1H)

MS (ESI): 269 $(MH)^+$

Morpholine (52.2ml, 600mmol) and 1-bromo-3-chloropropane (30ml, 300mmol) were dissolved in dry toluene (180ml) and heated to 70°C for 3 hours. The solid was removed by filtration and the filtrate evaporated under vacuum. The resulting oil was decanted from the additional solid residue and the oil was vacuum distilled to yield 1-chloro-3-morpholinopropane (37.91g, 77%) as an oil.

^{1}H NMR Spectrum: ($DMSOd_6$) 1.85(m, 2H); 2.30(t, 4H); 2.38(t, 2H); 3.53(t, 4H); 3.65(t, 2H)

MS (ESI): 164 $(MH)^+$

7-Hydroxy-6-methoxy-4-phenoxyquinazoline (25.27g, 0.1mol) and 1-chloro-3-morpholinopropane (18.48g, 0.11mol) were taken up in DMF (750ml) and potassium carbonate (39.1g, 0.33mol) was added. The suspension was heated at 90°C for 3 hours then allowed to cool. The suspension was filtered and the volatiles were removed by evaporation. The residue was triturated with ethyl acetate and 6-methoxy-7-(3-morpholinopropoxy)-4-phenoxyquinazoline (31.4g, 84%) was collected by filtration as a yellow crystalline solid.

^{1}H NMR Spectrum: ($DMSOd_6$) 1.97(m, 2H); 2.39(t, 4H); 2.47(t, 2H); 3.58(t, 4H); 3.95(s, 3H); 4.23(t, 2H); 7.31(m, 3H); 7.36(s, 1H); 7.49(t, 2H); 7.55(s, 1H); 8.52(s, 1H)

MS (ESI): 396 $(MH)^+$

6-Methoxy-7-(3-morpholinopropoxy)-4-phenoxyquinazoline (33.08g, 84mmol) was dissolved in 6M aqueous hydrochloric acid (800ml) and heated at reflux for 1.5 hours. The reaction mixture was decanted and concentrated to 250ml then basified (pH9) with saturated aqueous sodium hydrogen carbonate solution. The aqueous layer was extracted with dichloromethane (4x400ml), the organic layer was separated and filtered through phase separating paper. The solid was triturated with ethyl acetate to give 6-methoxy-7-(3-morpholinopropoxy)-3,4-dihydroquinazolin-4-one (23.9g, 89%) as a white solid.

^{1}H NMR Spectrum: ($DMSOd_6$) 1.91(m, 2H); 2.34(t, 4H); 2.42(t, 2H); 3.56(t, 4H); 3.85(s, 3H); 4.12(t, 2H); 7.11(s, 1H); 7.42(s, 1H); 7.96(s, 1H); 12.01(s, 1H)

MS (ESI): 320 $(MH)^+$

6-Methoxy-7-(3-morpholinopropoxy)-3,4-dihydroquinazolin-4-one (23.9g, 75mmol) was suspended in thionyl chloride (210ml) and DMF (1.8ml) then heated at reflux for 1.5 hours. The thionyl chloride was removed by evaporation under vacuum and the residue azeotroped with toluene three times. The residue was taken up in water and basified (pH8) with saturated aqueous sodium hydrogen carbonate solution. The aqueous layer was extracted with dichloromethane (4x400ml), the organic layer was washed with water and brine then

dried ($MgSO_4$). After filtration the organic layer was concentrated under vacuum to give a yellow solid which was triturated with ethyl acetate to give 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (17.39g, 52%) as a pale cream solid.

^{1}H NMR Spectrum: ($CDCl_3$) 2.10-2.16(m, 2H); 2.48(br s, 4H); 2.57(t, 2H); 3.73(t, 4H); 4.05(s, 3H); 4.29(t, 2H); 7.36(s, 1H); 7.39(s, 1H); 8.86(s, 1H)

MS-ESI: 337 [MH]+

Example 2

A mixture of 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (225mg, 0.67mmol), (prepared as described for the starting material in Example 1), potassium carbonate (106mg, 0.77mmol) and 7-hydroxyquinoline (112mg, 0.77mmol) in DMF (7.5ml) was stirred at 100°C for 5 hours and allowed to cool to ambient temperature. The reaction mixture was treated with 1M aqueous sodium hydroxide solution (40ml) and stirred at ambient temperature for a few minutes. The crude solid was collected by filtration washing with water. The resultant solid was dissolved in dichloromethane (2ml) and filtered through phase separating paper. The filtrate was evaporated under vacuum to give a solid residue which was triturated with ether, filtered and dried to give **6-methoxy-7-(3-morpholinopropoxy)-4-(quinolin-7-yloxy)quinazoline** (116mg, 39%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.98(m, 2H); 2.39(m, 4H); 2.48(t, 2H); 3.59(m, 4H); 4.00(s, 3H); 4.25(t, 2H); 7.40(s, 1H); 7.58(m, 2H); 7.62(s, 1H); 7.92(d, 1H); 8.10(d, 1H); 8.44(d, 1H); 8.55(s, 1H); 8.92(m, 1H)

MS (ESI): 447 $(MH)^+$

Elemental analysis:	Found	C 66.6	H 5.7	N 12.4	
$C_{25}H_{26}N_4O_4$ 0.25H_2O	Requires	C 66.6	H 5.9	N 12.4%	

Example 3

A mixture of 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (225mg, 0.67mmol), (prepared as described for the starting material in Example 1), potassium carbonate (106mg, 0.77mmol) and 1-naphthol (111mg, 0.77mmol) in DMF (7.5ml) was stirred at 100°C for 5 hours then allowed to cool to ambient temperature. The reaction mixture was treated with 1M aqueous sodium hydroxide solution (40ml) and stirred at ambient temperature for a few minutes. The reaction mixture was extracted with ethyl acetate

and the organic extracts were washed with water. The organic extracts were dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol (95/5) to give a solid which was triturated with ether, filtered and dried to give **6-methoxy-7-(3-morpholinopropoxy)-4-(1-naphthyloxy)quinazoline** (194mg, 65%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.98(m, 2H); 2.39(m, 4H); 2.48(t, 2H); 3.59(m, 4H); 4.00(s, 3H); 4.26(t, 2H); 7.40(s, 1H); 7.48(m, 2H); 7.58(m, 2H); 7.74(s, 1H); 7.75(d, 1H); 7.92(d, 1H); 8.03(d, 1H); 8.42(s, 1H)

MS (ESI): 446 $(MH)^+$

Elemental analysis:	Found	C 69.9	H 6.2	N 9.4
$C_{26}H_{27}N_3O_4$	Requires	C 70.1	H 6.1	N 9.4%

Example 4

A mixture of 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (225mg, 0.67mmol), (prepared as described for the starting material in Example 1), potassium carbonate (106mg, 0.77mmol) and 7-hydroxy-4-methylquinoline (122mg, 0.77mmol), (Chem. Berich. 1967, 100, 2077), in DMF (7.5ml) was stirred at 100°C for 5 hours then allowed to cool to ambient temperature. The reaction mixture was treated with 1M aqueous sodium hydroxide solution (40ml) and stirred at ambient temperature for a few minutes. The crude solid was collected by filtration washing with water. The resultant solid was dissolved in dichloromethane (2ml) and was filtered through phase separating paper. The filtrate was evaporated under vacuum to give a solid residue which was triturated with ether, filtered and dried to give **6-methoxy-4-(4-methylquinolin-7-yloxy)-7-(3-morpholinopropoxy)quinazoline** (175mg, 57%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.98(m, 2H); 2.39(m, 4H); 2.48(t, 2H); 2.71(s, 3H); 3.59(m, 4H); 4.00(s, 3H); 4.26(t, 2H); 7.40(s, 1H); 7.41(m, 1H); 7.61(dd, 1H); 7.62(s, 1H); 7.90(d, 1H); 8.20(d, 1H); 8.52(s, 1H); 8.78(d, 1H)

MS (ESI): 461 $(MH)^+$

Elemental analysis:	Found	C 67.1	H 5.9	N 12.1
$C_{26}H_{28}N_4O_4$ 0.2H_2O	Requires	C 67.3	H 6.2	N 12.1%

Example 5

A mixture of 4-chloro-7-(3-(1,1-dioxothiomorpholino)propoxy)-6-methoxyquinazoline (220mg, 0.57mmol), potassium carbonate (106mg, 0.77mmol) and 7-hydroxyquinoline (111mg, 0.76mmol) in DMF (7.5ml) was stirred at 100°C for 5 hours then allowed to cool to ambient temperature. The reaction mixture was treated with 1M aqueous sodium hydroxide solution (40ml) and stirred at ambient temperature for a few minutes. The crude solid was collected by filtration washing with water. The resultant solid was dissolved in dichloromethane (2ml) and was filtered through phase separating paper. The filtrate was evaporated under vacuum to give a solid residue which was triturated with ether, filtered and dried to give **7-(3-(1,1-dioxothiomorpholino)propoxy)-6-methoxy-4-(quinolin-7-yloxy)quinazoline** (205mg, 73%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.98(m, 2H); 2.65(t, 2H); 2.92(m, 4H); 3.10(m, 4H); 4.00(s, 3H); 4.28(t, 2H); 7.42(s, 1H); 7.58(m, 2H); 7.64(s, 1H); 7.92(d, 1H); 8.10(d, 1H); 8.44(d, 1H); 8.55(s, 1H); 8.92(m, 1H)

MS (ESI): 495 $(MH)^+$

Elemental analysis:	Found	C 60.0	H 5.0	N 11.1	
$C_{25}H_{26}N_4O_5S$ 0.25H_2O	Requires	C 60.2	H 5.4	N 11.2%	

The starting material was prepared as follows:

7-Benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (20.3g, 124mmol), (prepared as described for the starting material in Example 1), was taken up in thionyl chloride (440ml) and DMF (1.75ml) then heated at reflux for 4 hours. The thionyl chloride was evaporated under vacuum and the residue azeotroped with toluene three times to give 7-benzyloxy-4-chloro-6-methoxyquinazoline.

A mixture of the crude 7-benzyloxy-4-chloro-6-methoxyquinazoline, potassium carbonate (50g, 362mmol) and 4-chloro-2-fluorophenol (8.8ml, 83mmol) in DMF (500ml) was stirred at 100°C for 5 hours then allowed to cool to ambient temperature overnight. The reaction mixture was poured into water (2l) and was stirred at ambient temperature for a few minutes. The crude solid was collected by filtration washing with water. The resultant solid was dissolved in dichloromethane and filtered through diatomaceous earth. The filtrate was treated with decolourising charcoal, boiled for a few minutes then filtered through diatomaceous earth. The filtrate was filtered through phase separating paper and then evaporated under vacuum to give a solid residue which was triturated with ether, filtered and

dried to give 7-benzyloxy-4-(4-chloro-2-fluorophenoxy)-6-methoxyquinazoline (23.2g, 76%).

^{1}H NMR Spectrum: ($DMSOd_6$) 3.98(s, 3H); 5.34(s, 2H); 7.42(m, 9H); 7.69(dd, 1H); 8.55(s, 1H)

MS (ESI): 411 $(MH)^+$

7-Benzyloxy-4-(4-chloro-2-fluorophenoxy)-6-methoxyquinazoline (1.4g, 3.4mmol) was suspended in TFA (15ml) and heated at reflux for 3 hours. The reaction mixture was allowed to cool, toluene was added and the volatiles were removed by evaporation under vacuum. The residue was triturated with ether and then acetone. The precipitate was collected by filtration and dried to give 4-(4-chloro-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline (21.8g). This was used without further purification in the next step.

^{1}H NMR Spectrum: ($DMSOd_6$) 3.97(s, 3H); 7.22(s, 1H); 7.39(d, 1H); 7.53(m, 2H); 7.67(dd, 1H); 8.46(s, 1H)

MS (ESI): 321 $(MH)^+$

A mixture of 3-amino-1-propanol (650µl, 8.4mmol) and vinyl sulphone (1g, 8.4mmol) was heated at 110°C for 45 minutes. The mixture was allowed to cool and was purified by column chromatography eluting with methylene chloride/methanol (95/5) to give 3-(1,1-dioxothiomorpholino)-1-propanol (800mg, 90%).

^{1}H NMR Spectrum: ($CDCl_3$) 1.7-1.8(m, 2H); 2.73(t, 2H); 3.06(br s, 8H); 3.25(s, 1H); 3.78(t, 2H)

MS - ESI: 194 $[MH]^+$

4-(4-Chloro-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline (5.0g, 15.6mmol) was suspended in dichloromethane (150ml) and tributylphosphine (11.1ml, 44.6mmol) was added followed by stirring at ambient temperature for 30 minutes. To this mixture was added 3-(1,1-dioxothiomorpholino)-1-propanol (4.2g, 21.8mmol) followed by the addition of 1,1'-(azodicarbonyl)dipiperidine (11.7g, 46.4mmol) in portions. The mixture was stirred at ambient temperature overnight then diluted with ether (300ml) and the precipitate was removed by filtration. The residue was chromatographed on silica eluting with dichloromethane and methanol (95/5). The relevant fractions were combined and evaporated to give a solid which was triturated with ethyl acetate filtered and dried to give 4-(4-chloro-2-fluorophenoxy)-7-(3-(1,1-dioxothiomorpholino)propoxy)-6-methoxyquinazoline (5.4g, 70%). This was used without further purification in the next step.

^{1}H NMR Spectrum: ($DMSOd_6$) 1.86(m, 2H); 2.65(t, 2H); 2.92(m, 4H); 3.08(m, 4H); 3.97(s,

3H); 4.26(t, 2H); 7.40(m, 1H); 7.42(s, 1H); 7.56(m, 2H); 7.68(dd, 1H); 8.54(s, 1H)

MS (ESI): 496 $(MH)^+$

Elemental analysis:	Found	C 52.7	H 4.4	N 8.3	
$C_{22}H_{23}N_3ClFO_5S$ 0.25H_2O	Requires	C 52.8	H 4.7	N 8.4%	

4-(4-Chloro-2-fluorophenoxy)-7-(3-(1,1-dioxothiomorpholino)propoxy)-6-methoxyquinazoline (3.5g, 7mmol) was dissolved in 2M aqueous hydrochloric acid (56ml) and heated at 95°C for 2 hours. The cooled reaction mixture was treated with solid sodium hydrogen carbonate solution to give a thick paste which was diluted with water and filtered. The solid was transferred to a flask and azeotroped with toluene twice to give a dry solid. The solid was flash chromatographed on silica eluting with dichloromethane and methanol (95/5). The relevant fractions were combined and evaporated to give 7-(3-(1,1-dioxothiomorpholino)propoxy)-6-methoxy-3,4-dihydroquinazolin-4-one (2.26g, 87%) as a white solid.

MS (ESI): 368 $(MH)^+$

7-(3-(1,1-Dioxothiomorpholino)propoxy)-6-methoxy-3,4-dihydroquinazolin-4-one (4.2g, 11.4mmol) was suspended in thionyl chloride (45ml) and DMF (0.1ml) then heated at reflux for 2.5 hours. The residue was diluted with toluene, the thionyl chloride was evaporated under vacuum, the residue was then azeotroped with toluene three times. The residue was taken up in water and basified (pH8) with saturated aqueous sodium hydrogen carbonate solution. The aqueous layer was extracted with dichloromethane (x4), the organic layer was washed with water and brine then filtered through phase separating paper. The organic layer was concentrated under vacuum to give an orange solid. The solid was flash chromatographed on silica eluting with dichloromethane and methanol (95/5). The relevant fractions were combined and evaporated to give a solid which was triturated with ether then filtered and dried to give 4-chloro-7-(3-(1,1-dioxothiomorpholino)propoxy)-6-methoxyquinazoline (2.27g, 52%).

MS (ESI): 386 $(MH)^+$

Example 6

6,7-Dimethoxy-3,4-dihydroquinazolin-4-one (290mg, 1.4mmol) was suspended in thionyl chloride (5ml) and DMF (2 drops) and heated at reflux for 2 hours. The thionyl chloride was evaporated under vacuum and the residue azeotroped with toluene three times to

give 4-chloro-6,7-dimethoxyquinazoline. A mixture of the crude 4-chloro-6,7-dimethoxyquinazoline, potassium carbonate (970mg, 7mmol) and 7-hydroxyquinoline (235mg, 1.62mmol) in DMF (10ml) was stirred at 100°C for 5 hours and allowed to cool to ambient temperature overnight. The reaction mixture was treated with 1M aqueous sodium hydroxide solution and stirred at ambient temperature for a few minutes. The reaction mixture was extracted with ethyl acetate (x4) and the organic extracts washed with water and brine. The organic extracts were dried ($MgSO_4$), filtered and the solvent removed under vacuum. The residue was triturated with ethyl acetate and then recrystallised from hot ethyl acetate to give **6,7-dimethoxy-4-(quinolin-7-yloxy)quinazoline** (110mg, 24%) as a white solid.

^{1}H NMR Spectrum: ($DMSOd_6$) 4.00(s, 3H); 4.00(s, 3H); 7.40(s, 1H); 7.59(m, 3H); 7.92(d, 1H); 8.08(d, 1H); 8.42(d, 1H); 8.55(s, 1H); 8.92(dd, 1H)

MS (ESI): 334 $(MH)^+$

Elemental analysis:	Found	C 68.2	H 4.3	N 12.5	
$C_{19}H_{15}N_3O_3$	Requires	C 68.5	H 4.5	N 12.6%	

The starting material was prepared as follows:

A mixture of 4,5-dimethoxyanthranilic acid (19.7g) and formamide (10ml) was stirred and heated at 190°C for 5 hours. The mixture was allowed to cool to approximately 80°C and water (50ml) was added. The mixture was then allowed to stand at ambient temperature for 3 hours. The precipitate was collected by filtration, washed with water and dried to give 6,7-dimethoxy-3,4-dihydroquinazolin-4-one (3.65g).

Example 7

A mixture of (*R,S*)-4-chloro-6-methoxy-7-((1-methylpiperidin-3-yl)methoxy)quinazoline (183mg, 0.57mmol), potassium carbonate (106mg, 0.77mmol) and 7-hydroxyquinoline (111mg, 0.77mmol) in DMF (7ml) was stirred at 100°C for 5 hours and allowed to cool to ambient temperature. The reaction mixture was treated with 1M aqueous sodium hydroxide solution (30ml) and stirred for 10 minutes. The crude solid was collected by filtration washing with water. The resultant solid was dissolved in dichloromethane (2ml) and filtered through phase separating paper. The filtrate was evaporated under vacuum to give a solid residue which was triturated with ether, filtered and dried to give a scalemic

mixture of **6-methoxy-7-((1-methylpiperidin-3-yl)methoxy)-4-(quinolin-7-yloxy)quinazoline** (149mg, 61%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.10(m, 1H); 1.51(m, 1H); 1.64(m, 1H); 1.85(m, 3H); 2.09(m, 1H); 2.15(s, 3H); 2.62(m, 1H); 2.82(m, 1H); 3.99(s, 3H); 4.09(d, 2H); 7.38(s, 1H); 7.55(m, 2H); 7.63(s, 1H); 7.91(d, 1H); 8.10(d, 1H); 8.44(d, 1H); 8.54(s, 1H); 8.93(d, 1H)

MS (ESI): 431 $(MH)^+$

Elemental analysis:	Found	C 68.7	H 5.7	N 12.8	
$C_{25}H_{26}N_4O_3$ $0.3H_2O$	Requires	C 68.9	H 6.2	N 12.8%	

The starting material was prepared as follows:

(*R*)-Ethyl nipecotate (5.7g 365mmol), (prepared by resolution of ethyl nipecotate by treatment with L(+)-tartaric acid as described in J. Org. Chem. 1991, (56), 1168), was dissolved in 38.5% aqueous formaldehyde solution (45ml) and formic acid (90ml) and the mixture heated at reflux for 18 hours. The mixture was allowed to cool and added dropwise to cooled saturated aqueous sodium hydrogen carbonate solution. The mixture was adjusted to pH12 by addition of sodium hydroxide and the mixture was extracted with methylene chloride. The organic extract was washed with brine, dried ($MgSO_4$) and the solvent removed by evaporation to give (*R*)-ethyl 1-methylpiperidine-3-carboxylate (4.51g, 73%) as a colourless oil.

MS - ESI: 172 $[MH]^+$

A solution of (*R*)-ethyl 1-methylpiperidine-3-carboxylate (5.69g, 33mmol) in ether (20ml) was added dropwise to a stirred solution of lithium aluminium hydride (36.6ml of a 1M solution in THF, 36.6mmol) in ether (85ml) cooled to maintain a reaction temperature of 20°C. The mixture was stirred for 1.5 hours at ambient temperature and then water (1.4ml), 15% aqueous sodium hydroxide solution (1.4ml) and then water (4.3ml) were added. The insolubles were removed by filtration and the volatiles removed from the filtrate by evaporation to give (*R*)-(1-methylpiperidin-3-yl)methanol (4.02g, 94%) as a colourless oil.

^{1}H NMR Spectrum: ($DMSOd_6$) 1.06(q, 1H); 1.51-1.94(m, 5H); 2.04(s, 3H); 2.34(br s, 1H); 2.62(m, 1H); 2.78(d, 1H); 3.49(m, 1H); 3.59(m, 1H)

MS - ESI: 130 $[MH]^+$

4-(4-Chloro-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline (12.1g, 38mmol), (prepared as described for the starting material in Example 5), was suspended in dichloromethane

(375ml) and treated with triphenylphosphine (29.6g, 113mmol) then stirred at ambient temperature for 30 minutes. (1-Methylpiperidin-3-yl)methanol (8.25g, 63.8mmol) and (*R*)-(1-methylpiperidin-3-yl)methanol (1.46g, 11.3mmol), (CAS 205194-11-2), giving R:S (57.5:42.5 by chiral HPLC) (9.7g, 75mmol) were dissolved in dichloromethane (75ml) and added to the suspension. Diethyl azodicarboxylate (17.7ml, 75mmol) was added in portions using a syringe pump and the mixture was then allowed to warm to ambient temperature and stirred overnight. The residue was concentrated under vacuum then chromatographed on silica eluting with dichloromethane followed by dichloromethane/methanol /ammonia (93/6/1). The relevant fractions were combined and evaporated to give an oil. The residue was triturated with ether, filtered and dried to give (*R,S*)-4-(4-chloro-2-fluorophenoxy)-6-methoxy-7-((1-methylpiperidin-3-yl)methoxy)quinazoline (8.7g, 53%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.11(m, 1H); 1.50(m, 1H); 1.58-1.98(m, 4H); 2.09(m, 1H); 2.15(s, 3H); 2.62(d, 1H); 2.81(d, 1H); 3.95(s, 3H); 4.09(d, 2H); 7.39(m, 2H); 7.55(m, 2H); 7.67(d, 1H); 8.53(s, 1H)

MS (ESI): 432 $(MH)^+$

(*R,S*)-4-(4-Chloro-2-fluorophenoxy)-6-methoxy-7-((1-methylpiperidin-3-yl)methoxy)quinazoline (8.7g, 20mmol) was dissolved in 2M aqueous hydrochloric acid (150ml) and heated at reflux for 1.5 hours. The reaction mixture was concentrated then basified (pH9) with saturated aqueous ammonia solution (0.88). The aqueous layer was extracted with dichloromethane (4x400ml) and the organic extracts filtered through phase separating paper then evaporated under vacuum. The solid was triturated with ether to give (*R,S*)-6-methoxy-7-((1-methylpiperidin-3-yl)methoxy)-3,4-dihydroquinazolin-4-one (4.05g, 66%) as a white solid.

^{1}H NMR Spectrum: ($DMSOd_6$) 1.05(m, 1H); 1.40-1.95(m, 5H); 2.02(m, 1H); 2.14(s, 3H); 2.59(d, 1H); 2.78(d, 1H); 3.85(s, 3H); 3.95(d, 2H); 7.09(s, 1H); 7.42(s, 1H); 7.95(s, 1H); 12.00(s, 1H)

MS (ESI): 304 $(MH)^+$

(*R,S*)-6-methoxy-7-((1-methylpiperidin-3-yl)methoxy)-3,4-dihydroquinazolin-4-one (2.72g, 8.9mmol) was suspended in thionyl chloride (90ml) and DMF (0.5ml) and heated at reflux for 45 minutes. The thionyl chloride was evaporated under vacuum and the residue azeotroped with toluene three times. The residue was taken up in water and basified (pH8) with saturated aqueous sodium hydrogen carbonate solution. The aqueous layer was extracted

with ethyl acetate (4x400ml). The organic extracts were washed with saturated aqueous sodium hydrogen carbonate solution, water and brine then dried ($MgSO_4$). After filtration the organic extracts were concentrated under vacuum then dried overnight at 40°C under vacuum to give (*R,S*)-4-chloro-6-methoxy-7-((1-methylpiperidin-3-yl)methoxy)quinazoline (2.62g, 91%) as a solid.

^{1}H NMR Spectrum: ($DMSOd_6$) 1.10(m, 1H); 1.42-1.96(m, 5H); 2.09(m, 1H); 2.15(s, 3H); 2.60(d, 1H); 2.80(d, 1H); 3.98(s, 3H); 4.10(d, 2H); 7.35(s, 1H); 7.42(s, 1H); 8.84(s, 1H)
MS (ESI): 322 $(MH)^+$

Example 8

(*R,S*)-6-Methoxy-7-((1-methylpiperidin-3-yl)methoxy)-4-(quinolin-7-yloxy)quinazoline, (prepared as described in Example 7), was chromatographed on Chiral CEL OD (250mm x 4.6mm), (trade mark of Daicel Chemical Industries Ltd), in isohexane/ethanol/triethylamine/TFA (80/20/0.5/0.25). The relevant fractions for *S* (RT 12.55) and *R* (RT 15.88) enantiomers were each combined separately and worked up as follows.

The solution was evaporated under vacuum to give a liquid. This was treated with 5M aqueous sodium hydroxide solution (15ml) and extracted with ethyl acetate. The organic extracts were washed with water then brine and filtered through phase separating paper. The filtrate was evaporated to give **(*S*)-6-methoxy-7-((1-methylpiperidin-3-yl)methoxy)-4-(quinolin-7-yloxy)quinazoline** (50mg). The same method was used to give **(*R*)-6-methoxy-7-((1-methylpiperidin-3-yl)methoxy)-4-(quinolin-7-yloxy)quinazoline** (71mg).

Example 9

A suspension of 4-chloro-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline (0.13g, 0.4mmol), 5-hydroxy-2-methylindole (74mg, 0.5mmol) and potassium carbonate (83mg, 0.6mmol) in DMF (1.5ml) was stirred at 100°C for 2 hours. After cooling to ambient temperature, water (20ml) was added. The precipitate was collected by filtration, washed with water and dried under vacuum at 60°C to give **6-methoxy-4-(2-methylindol-5-yloxy)-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline** (80mg, 46%).

^{1}H NMR Spectrum: ($DMSOd_6$, CF_3CO_2D) 1.9-2.0(m, 2H); 2.05-2.2(m, 2H); 2.25-2.4(m, 2H); 2.43(s, 3H); 3.05-3.2(m, 2H); 3.35-3.5(m, 2H); 3.65-3.75(m, 2H); 4.12(s, 3H); 4.35-4.5(t,

2H); 7.0(dd, 1H); 7.35(d, 1H); 7.42(d, 1H); 7.6(s, 1H); 7.85(s, 1H); 9.15(s, 1H)
MS (ESI): 433 $(MH)^+$

The starting material was prepared as follows:

A mixture of 4-hydroxy-3-methoxybenzoic acid (8.4g, 50mmol), 3-(pyrrolidin-1-yl)propyl chloride (14.75g, 0.1mol), (J. Am. Chem. Soc. 1955, 77, 2272), potassium carbonate (13.8g, 0.1mol) and potassium iodide (1.66g, 10mmol) in DMF (150ml) was stirred and heated at 100°C for 3 hours. The mixture was allowed to cool and the insolubles were removed by filtration and the volatiles were removed from the filtrate by evaporation. The residue was dissolved in ethanol (75ml), 2M aqueous sodium hydroxide (75ml) was added and the mixture was heated at 90°C for 2 hours. The mixture was concentrated by evaporation, acidified with concentrated hydrochloric acid, washed with ether and then subjected to purification on a Diaion (trade mark of Mitsubishi) HP20SS resin column, eluting with water and then with a gradient of methanol (0 to 25%) in dilute hydrochloric acid (pH2.2). The methanol was removed by evaporation and the aqueous residue was freeze dried to give 3-methoxy-4-(3-(pyrrolidin-1-yl)propoxy)benzoic acid hydrochloride (12.2g, 77%).
^{1}H NMR Spectrum: ($DMSOd_6$, CF_3CO_2D) 2.2(m, 2H); 3.15(t, 2H); 3.3(t, 2H); 3.5(d, 2H); 3.7(t, 2H); 3.82(s, 3H); 4.05(d, 2H); 4.15(t, 2H); 7.07(d, 1H); 7.48(s, 1H); 7.59(d, 1H)
MS - EI: 279 $[M^{\cdot}]^+$

Fuming nitric acid (2.4ml, 57.9mmol) was added slowly at 0°C to a solution of 3-methoxy-4-(3-(pyrrolidin-1-yl)propoxy)benzoic acid hydrochloride (12.15g, 38.17mmol) in TFA (40ml). The cooling bath was removed and the reaction mixture stirred at ambient temperature for 1 hour. The TFA was removed by evaporation and ice/water was added to the residue and the solvent removed by evaporation. The solid residue was dissolved in dilute hydrochloric acid (pH2.2), poured onto a Diaion (trade mark of Mitsubishi) HP20SS resin column and eluted with methanol (gradient 0 to 50%) in water. Concentration of the fractions by evaporation gave a precipitate which was collected by filtration and dried under vacuum over phosphorus pentoxide to give 5-methoxy-2-nitro-4-(3-(pyrrolidin-1-yl)propoxy)benzoic acid hydrochloride (12.1g, 90%).

^{1}H NMR Spectrum: ($DMSOd_6$, TFA) 1.8-1.9 (m, 2H); 2.0-2.1(m, 2H); 2.1-2.2(m, 2H); 3.0-3.1(m, 2H); 3.3(t, 2H); 3.6-3.7(m, 2H); 3.95(s, 3H); 4.25(t, 2H); 7.35(s, 1H); 7.62(s, 1H)

A solution of 5-methoxy-2-nitro-4-(3-(pyrrolidin-1-yl)propoxy)benzoic acid

hydrochloride (9.63g, 24mmol) in thionyl chloride (20ml) and DMF (50µl) was heated at 45°C for 1.5 hours. The excess thionyl chloride was removed by evaporation and by azeotroping with toluene (x2). The resulting solid was suspended in THF (250ml) and methylene chloride (100ml) and ammonia was bubbled though the mixture for 30 minutes and the mixture stirred for a further 1.5 hours at ambient temperature. The volatiles were removed by evaporation, the residue was dissolved in water and applied to a Diaion (trade mark of Mitsubishi) HP20SS resin column and eluted with water/methanol (100/0 to 95/5). The solvent was removed by evaporation from the fractions containing product and the residue was dissolved in a minimum of methanol and the solution was diluted with ether. The resulting precipitate was collected by filtration, washed with ether and dried under vacuum to give 5-methoxy-2-nitro-4-(3-(pyrrolidin-1-yl)propoxy)benzamide (7.23g, 73%).

^{1}H NMR Spectrum: ($DMSOd_6$, CF_3CO_2D) 1.85-1.95(m, 2H); 2-2.1(m, 2H); 2.15-2.25(m, 2H); 3.0-3.1(m, 2H); 3.31(t, 2H); 3.62(t, 2H); 3.93(s, 3H); 4.2(t, 2H); 7.16(s, 1H); 7.60(s, 1H)

MS - EI: 323 $[M]^+$

Concentrated hydrochloric acid (5ml) was added to a suspension of 5-methoxy-2-nitro-4-(3-(pyrrolidin-1-yl)propoxy)benzamide (1.5g, 4.64mmol) in methanol (20ml) and the mixture was heated at 50°C to give a solution. Iron powder (1.3g, 23.2mmol) was added in portions and the reaction mixture was then heated at reflux for 1 hour. The mixture was allowed to cool, the insolubles were removed by filtration through diatomaceous earth and the volatiles were removed from the filtrate by evaporation. The residue was purified on a Diaion (trade mark of Mitsubishi) HP20SS resin column, eluting with water and then with dilute hydrochloric acid (pH2). The fractions containing product were concentrated by evaporation and the resulting precipitate was collected by filtration and dried under vacuum over phosphorus pentoxide to give 2-amino-5-methoxy-4-(3-(pyrrolidin-1-yl)propoxy)benzamide hydrochloride (1.44g, 85%).

^{1}H NMR Spectrum: ($DMSOd_6$, CF_3CO_2D) 1.9(br s, 2H); 2.05(br s, 2H); 2.2(br s, 2H); 3.05(br s, 2H); 3.3(t, 2H); 3.61(br s, 2H); 3.8(s, 3H); 4.11(t, 2H); 7.05(s, 1H); 7.53(s, 1H)

MS - EI: 293 $[M]^+$

A mixture of 2-amino-5-methoxy-4-(3-(pyrrolidin-1-yl)propoxy)benzamide hydrochloride (5.92g, 16.2mmol) and Gold's reagent (3.5g, 21.4mmol) in dioxane (50ml) was heated at reflux for 5 hours. Acetic acid (0.7ml) and sodium acetate (1.33g) were added to the reaction mixture which was heated at reflux for a further 5 hours. The mixture was allowed to

cool and the volatiles were removed by evaporation. The residue was dissolved in water, adjusted to pH8 with 2M aqueous sodium hydroxide solution and purified on a Diaion (trademark of Mitsubishi) HP20SS resin column eluting with methanol (gradient 0-50 %) in water. The fractions containing product were concentrated by evaporation and then freeze dried to give 4-hydroxy-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline (4.55g, 83%).

^{1}H NMR Spectrum: ($DMSOd_6$, CF_3CO_2D) 1.9(m, 2H); 2.0-2.1(m, 2H); 2.2-2.3(m, 2H); 3.05(m, 2H); 3.34(t, 2H); 3.6-3.7(br s, 2H); 3.94(s, 3H); 4.27(t, 2H); 7.31(s, 1H); 7.55(s, 1H); 9.02(s, 1H)

A mixture of 4-hydroxy-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline (1.7g, 5mmol) and thionyl chloride (25ml) containing DMF (0.2ml) was heated at reflux for 3 hours. Excess thionyl chloride was removed by evaporation and by azeotroping with toluene (x2). The residue was suspended in ether and 10% aqueous solution of sodium hydrogen carbonate was added to the mixture. The organic layer was separated, dried ($MgSO_4$) and the solvent removed by evaporation to give 4-chloro-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline (1.94g, quantitative).

^{1}H NMR Spectrum: ($CDCl_3$) 1.8(br s, 4H); 2.17(m, 2H); 2.6(br s, 4H); 2.7(t, 2H); 4.05(s, 3H); 4.3(t, 2H); 7.35(s, 1H); 7.38(s, 1H); 8.86(s, 1H)

MS - ESI: 322 $[MH]^+$

Example 10

A suspension of 4-chloro-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (74mg, 0.23mmol), potassium carbonate (48mg, 0.35mmol) and 7-hydroxyquinoline (40.6mg, 0.28mmol) in DMF (1.5ml) was heated at 100°C for 3 hours. After cooling, the mixture was stirred for 10 hours at ambient temperature and then overnight at 5°C. After dilution with methylene chloride (5ml), the mixture was poured onto a column of silica and was eluted with an increasing gradient of methanol/methylene chloride (10/90, 20/80) followed by ammonia/methanol (5%) in methylene chloride (25/75) to give, after removal of the volatiles by evaporation and drying under vacuum, **6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)-4-(quinolin-7-yloxy)quinazoline** (82mg, 88%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.3-1.5(m, 2H); 1.75-1.9(m, 3H); 1.9-2.05(m, 2H); 2.12(s, 3H); 2.8-2.9(d, 2H); 4.5(s, 3H); 4.1(d, 2H); 7.4(s, 1H); 7.6(dd, 1H); 7.62(dd, 1H)

MS (ESI): 431 $[MH]^+$

The starting material was prepared as follows:

To a solution of ethyl 4-piperidinecarboxylate (30g, 0.19mol) in ethyl acetate (150ml) cooled at 5°C was added dropwise a solution of di-tert-butyl dicarbonate (41.7g, 0.19mol) in ethyl acetate (75ml) while maintaining the temperature in the range 0-5°C. After stirring for 48 hours at ambient temperature, the mixture was poured onto water (300ml). The organic layer was separated, washed successively with water (200ml) , 0.1M aqueous hydrochloric acid (200ml) , saturated sodium hydrogen carbonate (200ml) and brine (200ml), dried ($MgSO_4$) and evaporated to give ethyl 4-(1-tert-butyloxycarbonylpiperidine)carboxylate (48g, 98%).

^{1}H NMR Spectrum: ($CDCl_3$) 1.25(t, 3H); 1.45(s, 9H); 1.55-1.70(m, 2H); 1.8-2.0(d, 2H); 2.35-2.5(m, 1H); 2.7-2.95(t, 2H); 3.9-4.1(br s, 2H); 4.15 (q, 2H)

To a solution of ethyl 4-(1-tert-butyloxycarbonylpiperidine)carboxylate (48g, 0.19mol) in dry THF (180ml) cooled at 0°C was added dropwise a solution of 1M lithium aluminium hydride in THF (133ml, 0.133mol). After stirring at 0°C for 2 hours, water (30ml) was added followed by 2M sodium hydroxide (10ml). The precipitate was filtered through diatomaceous earth and washed with ethyl acetate. The filtrate was washed with water, brine, dried ($MgSO_4$) and evaporated to give 4-hydroxymethyl-1-tert-butyloxycarbonylpiperidine (36.3g, 89%).

^{1}H NMR Spectrum: ($CDCl_3$) 1.05-1.2(m, 2H); 1.35-1.55(m, 10H); 1.6-1.8(m, 2H); 2.6-2.8(t, 2H); 3.4-3.6(t, 2H); 4.0-4.2(br s, 2H)

MS (EI): 215 [M.]+

To a solution of 4-hydroxymethyl-1-tert-butyloxycarbonylpiperidine (52.5g, 0.244mol) in tert-butyl methyl ether (525ml) was added 1,4-diazabicyclo[2.2.2]octane (42.4g, 0.378mol). After stirring for 15 minutes at ambient temperature, the mixture was cooled to 5°C and a solution of toluene sulphonyl chloride (62.8g, 0.33mmol) in tert-butyl methyl ether (525ml) was added dropwise over 2 hours while maintaining the temperature at 0°C. After stirring for 1 hour at ambient temperature, petroleum ether (1l) was added. The precipitate was removed by filtration. The filtrate was evaporated to give a solid. The solid was dissolved in ether and washed successively with 0.5M aqueous hydrochloric acid (2x500ml), water, saturated sodium hydrogen carbonate and brine, dried ($MgSO_4$) and evaporated to give 4-(4-methylphenylsulphonyloxymethyl)-1-tert-butyloxycarbonylpiperidine (76.7g, 85%).

^{1}H NMR Spectrum: ($CDCl_3$) 1.0-1.2(m, 2H); 1.45(s, 9H); 1.65(d, 2H); 1.75-1.9(m, 2H); 2.45(s, 3H); 2.55-2.75(m, 2H); 3.85(d, 1H); 4.0-4.2(br s, 2H); 7.35(d, 2H); 7.8(d, 2H)

MS (ESI): 392 $[MNa]^+$

To a suspension of ethyl 3-methoxy-4-hydroxybenzoate (19.6g, 0.1mol) and potassium carbonate (28g, 0.2mol) in dry DMF (200ml) was added 4-(4-methylphenylsulphonyloxymethyl)-1-tert-butyloxycarbonylpiperidine (40g, 0.11mol). After stirring at 95°C for 2.5 hours, the mixture was cooled to ambient temperature and partitioned between water and ethyl acetate/ether. The organic layer was washed with water, brine, dried ($MgSO_4$) and evaporated. The resulting oil was crystallised from petroleum ether and the suspension was stored overnight (at 5°C). The solid was collected by filtration, washed with petroleum ether and dried under vacuum to give ethyl 3-methoxy-4-(1-tert-butyloxycarbonylpiperidin-4-ylmethoxy)benzoate (35g, 89%).

m.p. 81-83°C

^{1}H NMR Spectrum: ($CDCl_3$) 1.2-1.35(m, 2H); 1.4(t, 3H); 1.48(s, 9H); 1.8-1.9(d, 2H); 2.0-2.15(m, 2H); 2.75(t, 2H); 3.9(d, 2H); 3.95(s, 3H); 4.05-4.25(br s, 2H); 4.35(q, 2H); 6.85(d, 1H); 7.55(s, 1H); 7.65(d, 1H)

MS (ESI): 416 $[MNa]^+$

Elemental analysis:	Found	C 63.4	H 8.0	N 3.5	
$C_{21}H_{31}NO_6$ $0.3H_2O$	Requires	C 63.2	H 8.0	N 3.5%	

To a solution of ethyl 3-methoxy-4-(1-tert-butyloxycarbonylpiperidin-4-ylmethoxy)benzoate (35g, 89mmol) in formic acid (35ml) was added formaldehyde (12M, 37% in water, 35ml, 420mmol). After stirring at 95°C for 3 hours, the volatiles were removed by evaporation. The residue was dissolved in methylene chloride and 3M hydrogen chloride in ether (40ml, 120mmol) was added. After dilution with ether, the mixture was triturated until a solid was formed. The solid was collected by filtration, washed with ether and dried under vacuum overnight at 50°C to give ethyl 3-methoxy-4-(1-methylpiperidin-4-ylmethoxy)benzoate (30.6g, quant.).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.29(t, 3H); 1.5-1.7(m, 2H); 1.95(d, 2H); 2.0-2.15(br s, 1H); 2.72(s, 3H); 2.9-3.1(m, 2H); 3.35-3.5(br s, 2H); 3.85(s, 3H); 3.9-4.05(br s, 2H); 4.3(q, 2H); 7.1(d, 1H); 7.48(s, 1H); 7.6(d, 1H)

MS (ESI): 308 $[MH]^+$

A solution of ethyl 3-methoxy-4-(1-methylpiperidin-4-ylmethoxy)benzoate (30.6g,

89mmol) in methylene chloride (75ml) was cooled to 0-5°C. TFA (37.5ml) was added followed by the dropwise addition over 15 minutes of a solution of fuming 24M nitric acid (7.42ml, 178mmol) in methylene chloride (15ml). After completion of the addition, the solution was allowed to warm up and stirred at ambient temperature for 2 hours. The volatiles were removed under vacuum and the residue was dissolved in methylene chloride (50ml). The solution was cooled to 0-5°C and ether was added. The precipitate was collected by filtration, and dried under vacuum at 50°C. The solid was dissolved in methylene chloride (500ml) and 3M hydrogen chloride in ether (30ml) was added followed by ether (500ml). The solid was collected by filtration and dried under vacuum at 50°C to give ethyl 3-methoxy-4-(1-methylpiperidin-4-ylmethoxy)-6-nitrobenzoate (28.4g, 82%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.3(t, 3H); 1.45-1.65(m, 2H); 1.75-2.1(m, 3H); 2.75(s, 3H); 2.9-3.05(m, 2H); 3.4-3.5(d, 2H); 3.95(s, 3H); 4.05(d, 2H); 4.3(q, 2H); 7.32(s, 1H); 7.66(s, 1H)
MS (ESI): 353 $[MH]^+$

A suspension of ethyl 3-methoxy-4-(1-methylpiperidin-4-ylmethoxy)-6-nitrobenzoate (3.89g, 10mmol) in methanol (80ml) containing 10% platinum on activated carbon (50% wet) (389mg) was hydrogenated at 1.8 atmospheres pressure until uptake of hydrogen ceased. The mixture was filtered and the filtrate was evaporated. The residue was dissolved in water (30ml) and adjusted to pH10 with a saturated solution of sodium hydrogen carbonate. The mixture was diluted with ethyl acetate/ether (1/1) and the organic layer was separated. The aqueous layer was further extracted with ethyl acetate/ether and the organic layers were combined. The organic layers were washed with water, brine, dried ($MgSO_4$), filtered and evaporated. The resulting solid was triturated in a mixture of ether/petroleum ether, filtered, washed with petroleum ether and dried under vacuum at 60°C to give ethyl 6-amino-3-methoxy-4-(1-methylpiperidin-4-ylmethoxy)benzoate (2.58g, 80%).

m.p. 111-112°C

^{1}H NMR Spectrum: ($CDCl_3$) 1.35(t, 3H); 1.4-1.5(m, 2H); 1.85(m, 3H); 1.95(t, 2H); 2.29(s, 3H); 2.9(d, 2H); 3.8(s, 3H); 3.85(d, 2H); 4.3(q, 2H); 5.55(br s, 2H); 6.13(s, 1H); 7.33(s, 1H)
MS (ESI): 323 $[MH]^+$

Elemental analysis:	Found	C 62.8	H 8.5	N 8.3	
$C_{17}H_{26}N_2O_4$ $0.2H_2O$	Requires	C 62.6	H 8.2	N 8.6%	

A solution of ethyl 6-amino-3-methoxy-4-(1-methylpiperidin-4-ylmethoxy)benzoate (16.1g, 50mmol) in 2-methoxyethanol (160ml) containing formamidine acetate (5.2g,

50mmol) was heated at 115°C for 2 hours. Formamidine acetate (10.4g, 100mmol) was added in portions every 30 minutes during 4 hours. Heating was prolonged for 30 minutes after the last addition. After cooling, the volatiles were removed under vacuum. The solid was dissolved in ethanol (100ml) and methylene chloride (50ml). The precipitate was removed by filtration and the filtrate was concentrated to a final volume of 100ml. The suspension was cooled to 5°C and the solid was collected by filtration, washed with cold ethanol followed by ether and dried under vacuum overnight at 60°C to give 6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)-3,4-dihydroquinazolin-4-one (12.7g, 70%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.25-1.4(m, 2H); 1.75(d, 2H); 1.9(t, 1H); 1.9(s, 3H); 2.16(s, 2H); 2.8(d, 2H); 3.9(s, 3H); 4.0(d, 2H); 7.11(s, 1H); 7.44(s, 1H); 7.97(s, 1H)

MS (ESI): 304 $[MH]^+$

A solution of 6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)-3,4-dihydroquinazolin-4-one (2.8g, 9.24mmol) in thionyl chloride (28ml) containing DMF (280µl) was refluxed at 85°C for 1 hour. After cooling, the volatiles were removed by evaporation. The precipitate was triturated with ether, filtered, washed with ether and dried under vacuum. The solid was dissolved in methylene chloride and saturated aqueous sodium hydrogen carbonate was added. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and evaporated to give 4-chloro-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (2.9g, 98%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.3-1.5(m, 2H); 1.75-1.9(m, 3H); 2.0(t, 1H); 2.25(s, 3H); 2.85(d, 2H); 4.02(s, 3H); 4.12(d, 2H); 7.41(s, 1H); 7.46(s, 1H); 8.9(s, 1H)

MS (ESI): 322 $[MH]^+$

Example 11

Using a procedure analogous to that described for Example 9, 4-chloro-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (0.13g, 0.4mmol), (prepared as described for the starting material in Example 10), was reacted with 5-hydroxy-2-methylindole (74mg, 0.5mol) to give **6-methoxy-4-(2-methylindol-5-yloxy)-7-((1-methylpiperidin-4-yl)methoxy)quinazoline** (137mg, 79%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.3-1.45(m, 2H); 1.7-1.95(m, 5H); 2.15(s, 3H); 2.4(s, 3H); 2.8(d, 2H); 3.98(s, 3H); 4.05(d, 2H); 6.14(s, 1H); 6.88(d, 1H); 7.29(s, 1H); 7.32(d, 1H); 7.35(s, 1H); 7.6(s, 1H); 8.45(s, 1H)