(54) Titre : DERIVES DE QUINAZOLINE UTILISES COMME INHIBITEURS DE L'ANGIOGENESE
(55) Title: QUINAZOLINE DERIVATIVES AS ANGIogenesis INHIBITORS

(57) Abrégé/Abstract:
The invention relates to the use of compounds of formula (I), wherein ring C is an 8, 9, 10, 12 or 13-membered bicyclic or tricyclic moiety which optionally may contain 1-3 heteroatoms selected independently from O, N and S; Z is -O-, -NH-, -S-, -CH₂- or a direct bond; n is 0-5; m is 0-3; R² represents hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₁₋₃ alkylsulphonyl, -NR³R⁴ (wherein R³ and R⁴, which may be the same or different, each represents hydrogen or C₁₋₃ alkyl), or R⁵ X₁⁻ (wherein X¹ and R⁵ are as defined herein; R¹ represents hydrogen, o xo, halogeno, hydroxy, C₁₋₃ alkoxy, C₁₋₃ alkyl, C₁₋₄ alkoxymethyl, C₁₋₄ alkanoyl, C₁₋₄ haloalkyl, cyano, amino, C₂₋₅ alkenyl, C₂₋₅ alkynyl, C₁₋₃ alkanoyloxy, nitro, C₁₋₄ alkanoylamino,
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(57) Abrégé(suite)/Abstract(continued):

C_{1,4}-alkoxycarbonyl, C_{1,4}-alkylsulphonyl, 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_{2,3}-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} and R^{56} are as defined 
herein); and salts thereof, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular 
permeability reducing effect in warm-blooded animals, processes for the preparation of such compounds, pharmaceutical 
compositions containing a compound of formula (I) or a pharmaceutically acceptable salt thereof as active ingredient and 
compounds of formula (I). The compounds of formula (I) and the pharmaceutically acceptable salts thereof inhibit the effects of 
VEGF, a property of value in the treatment of a number of disease states including cancer and rheumatoid arthritis.
The invention relates to the use of compounds of formula (I), wherein ring C is an 8, 9, 10, 11 or 13-membered bicyclic or tricyclic moiety which optionally may contain 1–3 heteroatoms selected independently from O, N and S; Z is –O–, –NH–, –S–, –CH2– or a direct bond; n is 0–5; m is 0–3; R² represents hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃alkylsulphonyl, –NR¹R² (wherein R¹ and R² are as defined herein); R¹ represents hydrogen, oxo, halogeno, hydroxy, C₁₋₃alkoxy, C₁₋₃alkyl, C₁₋₃alkoxymethyl, C₁₋₃alkanoyl, C₁₋₃haloalky, cyano, amino, C₂₋₃alkyl, C₂₋₃alkynyl, C₁₋₃alkanoyloxy, nitro, C₁₋₃alkanoylamino, C₁₋₃alkoxycarbonyl, C₁₋₃alkylsulphonyl, C₁₋₃alkylsulphonyl, carbamoyl, N-C₁₋₃alkylcarbamoyl, N-N-di(C₁₋₃alkyl)carbamoyl, aminosulphonyl, N-C₁₋₃alkylaminosulphonyl, N,N-di(C₁₋₃alkyl)aminosulphonyl, N-(C₁₋₃alkylsulphonyl)amino, N-(C₁₋₃alkylsulphonyl)amino, N,N-di(C₁₋₃alkylsulphonyl)amino, a C₁₋₃alkylene chain joined to two ring C carbon atoms, C₁₋₃alkanoylamino,C₁₋₃alkyl, carboxy or a group R³RX⁻¹⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻]}
DEMANDES OU BREVETS VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS COMPREND PLUS D'UN TOME.

CECI EST LE TOME _1_ DE _2_

NOTE: Pour les tomes additionnels, veillez contacter le Bureau Canadien des Brevets.

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JUMBO APPLICATIONS / PATENTS

THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE THAN ONE VOLUME.

THIS IS VOLUME _1_ OF _2_

NOTE: For additional volumes please contact the Canadian Patent Office.
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:

![Chemical Structure](image)

(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-, -CH2- or a direct bond;
- n is an integer from 0 to 5;
- m is an integer from 0 to 3;
- R2 represents hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, C13alkyl, C1.
- 3alkoxy, C13alkylsulphonyl, -NR3R4 (wherein R3 and R4, which may be the same or different, each represents hydrogen or C13alkyl), or R2X1- (wherein X1 represents a direct bond, -O-, -CH2-, -OC(O)-, -C(O)-, -S-, -SO-, -SO2-, -NR6C(O)-, -C(O)NR7-, -SO2NR8-, -NR8SO2- or -NR9- (wherein R6, R7, R8 and R10 each independently represents hydrogen, C13alkyl or C1.
- 3alkoxyC23alkyl), and R5 is selected from one of the following twenty-two groups:
- 1) hydrogen, oxiranylC14alkyl or C15alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, chloro, bromo and amino;
- 2) C15alkylX2C(O)R11 (wherein X2 represents -O- or -NR12- (in which R12 represents hydrogen, C13alkyl or C13alkoxyC23alkyl) and R11 represents C13alkyl, -NR13R14 or -OR15 (wherein R13, R14 and R15 which may be the same or different each represents hydrogen, C1.
- 3) C15alkylX3R16 (wherein X3 represents -O-, -S-, -SO-, -SO2-, -OC(O)-, -NR17C(O)-, -C(O)NR18-, -SO2NR19-, -NR20SO2- or -NR21- (wherein R17, R18, R19, R20 and R21 each
independently represents hydrogen, C<sub>1</sub>alkyl or C<sub>1</sub>alkoxyC<sub>2</sub>alkyl) and R<sup>16</sup> represents hydrogen, C<sub>1</sub>alkyl, cyclopentyl, cyclohexyl, azetidinyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C<sub>1</sub>alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C<sub>1</sub>alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C<sub>1</sub>, 4cyanoalkyl, C<sub>1</sub>alkyl, C<sub>1</sub>hydroxyalkyl, C<sub>1</sub>alkoxy, C<sub>1</sub>alkoxyC<sub>1</sub>alkyl, C<sub>1</sub>alkylamine, C<sub>1</sub>alkoxycarbonyl, C<sub>1</sub>aminoalkyl, C<sub>1</sub>alkylamino, di(C<sub>1</sub>alkylamino, C<sub>1</sub>alkylaminoC<sub>1</sub>alkyl, di(C<sub>1</sub>alkyl)aminoC<sub>1</sub>alkyl, C<sub>1</sub>alkylaminoC<sub>1</sub>alkoxy, di(C<sub>1</sub>alkyl)aminoC<sub>1</sub>alkoxy and a group -(O)-(C<sub>1</sub>alkyl)<sub>f</sub>ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is an azetidinyl or a 5-6-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<sub>1</sub>alkyl);

4) C<sub>1</sub>alkylX<sup>4</sup>C<sub>1</sub>alkylX<sup>5</sup>R<sup>22</sup> (wherein X<sup>4</sup> and X<sup>5</sup> which may be the same or different are each -O-, -S-, -SO-, -SO<sub>2</sub>-, -NR<sup>23</sup>C(O)-, -C(O)NR<sup>24</sup>-,-SO<sub>2</sub>NR<sup>25</sup>-,-NR<sup>26</sup>SO<sub>2</sub>- or -NR<sup>27</sup>- (wherein R<sup>23</sup>, R<sup>24</sup>, R<sup>25</sup>, R<sup>26</sup> and R<sup>27</sup> each independently represents hydrogen, C<sub>1</sub>alkyl or C<sub>1</sub>alkoxyC<sub>2</sub>alkyl) and R<sup>22</sup> represents hydrogen, C<sub>1</sub>alkyl or C<sub>1</sub>alkoxyC<sub>2</sub>alkyl);

5) R<sup>28</sup> (wherein R<sup>28</sup> is an azetidinyl or 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<sub>1</sub>, 4cyanoalkyl, C<sub>1</sub>alkyl, C<sub>1</sub>hydroxyalkyl, C<sub>1</sub>alkoxy, C<sub>1</sub>alkoxyC<sub>1</sub>alkyl, C<sub>1</sub>alkylamine, C<sub>1</sub>alkoxycarbonyl, C<sub>1</sub>aminoalkyl, C<sub>1</sub>alkylamino, di(C<sub>1</sub>alkylamino, C<sub>1</sub>alkylaminoC<sub>1</sub>alkyl, di(C<sub>1</sub>alkyl)aminoC<sub>1</sub>alkyl, C<sub>1</sub>alkylaminoC<sub>1</sub>alkoxy, di(C<sub>1</sub>alkyl)aminoC<sub>1</sub>alkoxy and a group -(O)-(C<sub>1</sub>alkyl)<sub>f</sub>ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is an azetidinyl or a 5-6-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<sub>1</sub>alkyl));

6) C<sub>1</sub>alkylR<sup>28</sup> (wherein R<sup>28</sup> is as defined hereinbefore);

7) C<sub>2</sub>alkenylR<sup>28</sup> (wherein R<sup>28</sup> is as defined hereinbefore);

8) C<sub>2</sub>alkynylR<sup>28</sup> (wherein R<sup>28</sup> is as defined hereinbefore);

9) R<sup>29</sup> (wherein R<sup>29</sup> 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 3 substituents
selected from hydroxy, halogeno, amino, C₁₄alkyl, C₁₄alkoxy, C₁₄hydroxyalkyl, C₁₄aminoalkyl, C₁₄alkylamino, C₁₄hydroxyalkoxy, carboxy, trifluoromethyl, cyano, -C(O)NR³⁶R³¹, -NR³²C(O)R³³ (wherein R³⁰, R³¹, R³² and R³³, which may be the same or different, each represents hydrogen, C₁₄alkyl or C₁₃alkoxyC₃₃alkyl) and a group -(C₅H₄)₉(C₁₄alkyl)ₕringD (wherein ℎ is 0 or 1, ₉ is 0 or 1 and ring D is an azetidinyl or a 5-6-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 C₁₄alkyl));

10) C₁₃alkylR²⁹ (wherein R²⁹ is as defined hereinbefore);

11) C₂₅alkenylR²⁹ (wherein R²⁹ is as defined hereinbefore);

12) C₂₅alkynylR²⁹ (wherein R²⁹ is as defined hereinbefore);

13) C₁₅alkylX⁶R²⁹ (wherein X⁶ represents -O-, -S-, -SO₂-, -SO₂-, -NR³⁴C(O)-, -C(O)NR³⁵-, -SO₂NR³⁶-, -NR³⁷SO₂- or -NR³⁸- (wherein R³⁴, R³⁵, R³⁶, R³⁷ and R³⁸ each independently represents hydrogen, C₁₃alkyl or C₁₃alkoxyC₂₅alkyl) and R²⁹ as as defined hereinbefore);

14) C₂₅alkenylX⁷R²⁹ (wherein X⁷ represents -O-, -S-, -SO₂-, -SO₂-, -NR³⁹C(O)-, -C(O)NR⁴₀-, -SO₂NR⁴¹-, -NR⁴₂SO₂- or -NR⁴₃- (wherein R³⁹, R⁴₀, R⁴¹, R⁴² and R⁴³ each independently represents hydrogen, C₁₃alkyl or C₁₃alkoxyC₂₅alkyl) and R²⁹ as as defined hereinbefore);

15) C₂₅alkynylX⁸R²⁹ (wherein X⁸ represents -O-, -S-, -SO₂-, -SO₂-, -NR⁴₄C(O)-, -C(O)NR⁴₅-, -SO₂NR⁴₆-, -NR⁴₇SO₂- or -NR⁴₈- (wherein R⁴⁴, R⁴₅, R⁴₆, R⁴₇ and R⁴₈ each independently represents hydrogen, C₁₃alkyl or C₁₃alkoxyC₂₅alkyl) and R²⁹ as as defined hereinbefore);

16) C₁₄alkylX⁹C₂₅alkylR²⁹ (wherein X⁹ represents -O-, -S-, -SO₂-, -SO₂-, -NR⁴₉C(O)-, -C(O)NR⁵₀-, -SO₂NR⁵₁-, -NR⁵₂SO₂- or -NR⁵₃- (wherein R⁴⁹, R⁵₀, R⁵₁, R⁵₂ and R⁵₃ each independently represents hydrogen, C₁₃alkyl or C₁₃alkoxyC₂₅alkyl) and R²⁹ as as defined hereinbefore);

17) C₁₄alkylX⁹C₁₄alkylR²₈ (wherein X⁹ and R²₈ are as defined hereinbefore);

18) C₂₅alkenyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C₁₄alkylamino, N,N-di(C₁₄alkyl)amino, aminosulphonyl, N-C₁₄alkylaminosulphonyl and N,N-di(C₁₄alkyl)aminosulphonyl;

19) C₂₅alkynyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C₁₄alkylamino, N,N-di(C₁₄alkyl)amino, aminosulphonyl, N-C₁₄alkylaminosulphonyl and N,N-di(C₁₄alkyl)aminosulphonyl;

20) C₂₅alkenylX⁹C₁₄alkylR²₈ (wherein X⁹ and R²₈ are as defined hereinbefore);

21) C₂₅alkynylX⁹C₁₄alkylR²₈ (wherein X⁹ and R²₈ are as defined hereinbefore); and
22) \( C_{1-4}alkylR^{54}(C_{1-4}alkyl)_4(X^9),R^{55} \) (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, cycloheptyl, azetidinyl and 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, cyano, \( C_{1-4}cyanoalkyl \), \( C_{1-4}alkyl \), \( C_{1-4}hydroxyalkyl \), \( C_{1-4}alkoxy \), \( C_{1-4}alkoxyC_{1-4}alkyl \), \( C_{1-4}alkylsulphonylC_{1-4}alkyl \), \( C_{1-4}alkoxycarbonyl \), \( C_{1-4}aminoalkyl \), \( C_{1-4}alkylamino \), \( di(C_{1-4}alkyl)amino \) and \( C_{1-4}alkylaminoC_{1-4}alkyl \), \( C_{1-4}alkyl \), \( di(C_{1-4}alkyl)aminoC_{1-4}alkyl \), \( C_{1-4}alkylaminoC_{1-4}alkoxy \), \( di(C_{1-4}alkyl)aminoC_{1-4}alkoxy \) 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 an azetidinyl or a 5-6-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 \( C_{1-3}alkyl \), \( C_{2-5}alkenyl \) or \( C_{2-5}alkynyl \) group in \( R^{54}X^9 \) 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, \( C_{2-5}alkenyl \), \( C_{2-5}alkynyl \), \( C_{3-9}alkanoyloxy \), nitro, \( C_{1-4}alkanoylamino \), \( C_{1-4}alkoxycarbonyl \), \( C_{1-4}alkylsulphonyl \), \( C_{1-4}alkylsulphinyl \), \( C_{1-4}alkylsulphonyl \), 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, \( N-(C_{1-4}alkyl)sulphonyl \), \( N-(C_{1-4}alkyl)sulphonyl \)-aminosulphonyl, \( N,N\)-di(\( C_{1-4}alkyl \))aminosulphonyl, \( N\)-amino-, \( N\)-(\( C_{1-4}alkyl \))aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-amino- and \( N\)-(\( C_{1-4}alkyl \))aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-amino- and \( N\)-(\( C_{1-4}alkyl \))aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-amino- and \( N\)-(\( C_{1-4}alkyl \))aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-amino- and \( N\)-(\( C_{1-4}alkyl \))aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-amino- and \( N\)-(\( C_{1-4}alkyl \))aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-amino- and \( N\)-(\( C_{1-4}alkyl \))aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-amino- and \( N\)-(\( C_{1-4}alkyl \))aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-amino- and \( N\)-(\( C_{1-4}alkyl \))aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-amino- and \( N\)-(\( C_{1-4}alkyl \))aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-amino- and \( N\)-(\( C_{1-4}alkyl \))aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-amino- and \( N\)-(\( C_{1-4}alkyl \))aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-amino- and \( N\)-(\( C_{1-4}alkyl \))aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-amino- and \( N\)-(\( C_{1-4}alkyl \))aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-amino- and \( N\)-(\( C_{1-4}alkyl \))aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-amino- and \( N\)-(\( C_{1-4}alkyl \))aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-amino- and \( N\)-(\( C_{1-4}alkyl \))aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-amino- and \( N\)-(\( C_{1-4}alkyl \))aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-amino- and \( N\)-(\( C_{1-4}alkyl \))aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-amino- and \( N\)-(\( C_{1-4}alkyl \))aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-amino- and \( N\)-(\( C_{1-4}alkyl \))aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-amino- and \( N\)-(\( C_{1-4}alkyl \))aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-amino- and \( N\)-(\( C_{1-4}alkyl \))aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-amino- and \( N\)-(\( C_{1-4}alkyl \))aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-amino- and \( N\)-(\( C_{1-4}alkyl \))aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-amino- and \( N\)-(\( C_{1-4}alkyl \))aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-amino- and \( N\)-(\( C_{1-4}alkyl \))aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-amino- and \( N\)-(\( C_{1-4}alkyl \))aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-amino- and \( N\)-(\( C_{1-4}alkyl \))aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-amino- and \( N\)-(\( C_{1-4}alkyl \))aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-aminosulphonyl, \( N\)-amino- and \( N\)-(\( C_{1-4}alkyl \))}
3) \( \text{C}_1\text{-alkylX}^{12}\text{R}^{67} \) (wherein \( \text{X}^{12} \) represents \(-\text{O}^-, -\text{S}^-, -\text{SO}^-, -\text{SO}_2^-, -\text{OC}(\text{O})^-, -\text{NR}^{68}\text{C}(\text{O})^-, -\text{C}(\text{O})\text{NR}^{69}, -\text{SO}_2\text{NR}^{70}, -\text{NR}^{71}\text{SO}_2^- \) or \(-\text{NR}^{72}^- \) (wherein \( \text{R}^{68}, \text{R}^{69}, \text{R}^{70}, \text{R}^{71} \) and \( \text{R}^{72} \) each independently represents hydrogen, \( \text{C}_1\text{-alkyl} \) or \( \text{C}_1\text{-alkoxyC}_2\text{-alkyl} \) and \( \text{R}^{67} \) represents hydrogen, \( \text{C}_1\text{-alkyl} \), cyclopentyl, cyclohexyl, azetidinyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which \( \text{C}_1\text{-alkyl} \) group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and \( \text{C}_1\text{-alkoxy} \) and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, \( \text{C}_1\text{-alkyl} \), \( \text{C}_1\text{-alkoxyC}_2\text{-alkyl} \), \( \text{C}_1\text{-aminoalkyl} \), \( \text{C}_1\text{-alkylamino} \), di(\( \text{C}_1\text{-alkyl} \));

4) \( \text{C}_1\text{-alkylX}^{13}\text{C}_1\text{-alkylX}^{14}\text{R}^{73} \) (wherein \( \text{X}^{13} \) and \( \text{X}^{14} \) which may be the same or different are each \(-\text{O}^-, -\text{S}^-, -\text{SO}^-, -\text{SO}_2^-, -\text{NR}^{74}\text{C}(\text{O})^-, -\text{C}(\text{O})\text{NR}^{75}^-, -\text{SO}_2\text{NR}^{76}^-, -\text{NR}^{77}\text{SO}_2^- \) or \(-\text{NR}^{78}^- \) (wherein \( \text{R}^{74}, \text{R}^{75}, \text{R}^{76}, \text{R}^{77} \) and \( \text{R}^{78} \) each independently represents hydrogen, \( \text{C}_1\text{-alkyl} \) or \( \text{C}_1\text{-alkoxyC}_2\text{-alkyl} \) and \( \text{R}^{73} \) represents hydrogen, \( \text{C}_1\text{-alkyl} \) or \( \text{C}_1\text{-alkoxyC}_2\text{-alkyl} \));

5) \( \text{R}^{79} \) (wherein \( \text{R}^{79} \) is an azetidinyl or 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, \( \text{C}_1\text{-alkyl} \), \( \text{C}_1\text{-alkoxyC}_2\text{-alkyl} \), \( \text{C}_1\text{-aminoalkyl} \), \( \text{C}_1\text{-alkylamino} \), di(\( \text{C}_1\text{-alkyl} \));

6) \( \text{C}_1\text{-alkylR}^{79} \) (wherein \( \text{R}^{79} \) is as defined hereinbefore);

7) \( \text{C}_2\text{-alkenylR}^{79} \) (wherein \( \text{R}^{79} \) is as defined hereinbefore);

8) \( \text{C}_2\text{-alkynylR}^{79} \) (wherein \( \text{R}^{79} \) is as defined hereinbefore);
9) R_{80}^{0} (wherein R_{80}^{0} 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}^{0}, -NR_{82}^{0}C(O)R_{84}^{0} (wherein R_{81}^{0}, R_{82}^{0}, R_{83}^{0} and R_{84}^{0} 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-)(C_{1,4}alkyl)_{f}ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is an azetidinyl or a 5-6-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_{1,4}alkylR_{80}^{0} (wherein R_{80}^{0} is as defined hereinbefore);
11) C_{2,5}alkenylR_{80}^{0} (wherein R_{80}^{0} is as defined hereinbefore);
12) C_{2,5}alkynylR_{80}^{0} (wherein R_{80}^{0} is as defined hereinbefore);
13) C_{1,4}alkylX_{15}R_{80}^{0} (wherein X_{15} represents -O, -S, -SO_{2}, -SO_{2}^{2}, -NR_{85}^{0}C(O), -C(O)NR_{86}^{0}, -SO_{2}NR_{87}^{0}, -NR_{88}^{0}SO_{2}, -NR_{89}^{0} (wherein R_{85}^{0}, R_{86}^{0}, R_{87}^{0}, R_{88}^{0} and R_{89}^{0} each independently represents hydrogen, C_{1,3}alkyl or C_{1,3}alkoxyC_{2,3}alkyl) and R_{80}^{0} is as defined hereinbefore);
14) C_{2,5}alkenylX_{16}R_{80}^{0} (wherein X_{16} represents -O, -S, -SO_{2}, -SO_{2}^{2}, -NR_{85}^{0}C(O), -C(O)NR_{86}^{0}, -SO_{2}NR_{87}^{0}, -NR_{88}^{0}SO_{2}, -NR_{89}^{0} (wherein R_{85}^{0}, R_{86}^{0}, R_{87}^{0}, R_{88}^{0} and R_{89}^{0} each independently represents hydrogen, C_{1,3}alkyl or C_{1,3}alkoxyC_{2,3}alkyl) and R_{80}^{0} is as defined hereinbefore);
15) C_{2,5}alkynylX_{17}R_{80}^{0} (wherein X_{17} represents -O, -S, -SO_{2}, -SO_{2}^{2}, -NR_{85}^{0}C(O), -C(O)NR_{86}^{0}, -SO_{2}NR_{87}^{0}, -NR_{88}^{0}SO_{2}, -NR_{89}^{0} (wherein R_{85}^{0}, R_{86}^{0}, R_{87}^{0}, R_{88}^{0} and R_{89}^{0} each independently represents hydrogen, C_{1,3}alkyl or C_{1,3}alkoxyC_{2,3}alkyl) and R_{80}^{0} is as defined hereinbefore);
16) C_{1,4}alkylX_{18}C_{1,4}alkylR_{80}^{0} (wherein X_{18} represents -O, -S, -SO_{2}^{2}, -NR_{100}^{0}C(O), -C(O)NR_{101}^{0}, -SO_{2}NR_{102}^{0}, -NR_{103}^{0}SO_{2}^{2}, -NR_{104}^{0} (wherein R_{100}^{0}, R_{101}^{0}, R_{102}^{0}, R_{103}^{0} and R_{104}^{0} each independently represents hydrogen, C_{1,3}alkyl or C_{1,3}alkoxyC_{2,3}alkyl) and R_{80}^{0} is as defined hereinbefore);
17) C_{1,4}alkylX_{18}C_{1,4}alkylR_{79}^{0} (wherein X_{18} and R_{79}^{0} 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) C₂₅alkynyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C₁₄alkylamino, N,N-di(C₁₄alkyl)amino, aminosulphonyl, N-C₁₄alkylaminosulphonyl and N,N-di(C₁₄alkyl)aminosulphonyl;

20) C₂₅alkenylX¹⁸C₁₄alkylR⁷⁹ (wherein X¹⁸ and R⁷⁹ are as defined hereinbefore);

21) C₂₅alkynylX¹⁸C₁₄alkylR⁷⁹ (wherein X¹⁸ and R⁷⁹ are as defined hereinbefore); and

22) C₁₄alkyl(R¹⁰⁵(C₁₄alkyl)ₙ(X¹⁸),R¹⁰⁶ (wherein X¹⁸ is as defined hereinbefore, x is 0 or 1, y is 0 or 1, and R¹⁰⁵ and R¹⁰⁶ are each independently selected from hydrogen, C₁₃alkyl, cyclopentyl, cyclohexyl, azetidinyl and a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C₁₃alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C₁₄alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₄cyanoalkyl, C₁₄alkyl, C₁₄hydroxyalkyl, C₁₄alkoxy, C₁₄alkoxyC₁₄alkyl, C₁₄alkylsulphonylC₁₄alkyl, C₁₄alkoxycarbonyl, C₁₄aminoalkyl, C₁₄alkylamino, di(C₁₄alkyl)amino, C₁₄alkylaminoC₁₄alkyl, di(C₁₄alkyl)aminoC₁₄alkyl, C₁₄alkylaminoC₁₄alkoxy, di(C₁₄alkyl)aminoC₁₄alkoxy and a group --(O)--(C₁₄alkyl)ₙringD (wherein f is 0 or 1, g is 0 or 1 and ring D is an azetidinyl or a 5-6-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 C₁₄alkyl) with the proviso that R¹⁰⁵ cannot be hydrogen); and additionally wherein any C₁₃alkyl, C₁₅alkenyl or C₂₅alkynyl group in R⁵₆X¹⁰⁻ 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:
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-, -CH₂- or a direct bond;
- R¹ represents hydrogen, oxo, halogeno, hydroxy, C₁₋₄ alkoxy, C₁₋₄ alkyl, C₁₋₄ alkoxy methyl, C₁₋₄ alkanoyl, C₁₋₄ haloalkyl, cyano, amino, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₃ alkanoyloxy, nitro, C₁₋₄ alkanoylamino, C₁₋₄ alkoxy carbonyl, C₁₋₄ alkylsulphonyl, C₁₋₄ alkyl sulphanyl, C₁₋₄ alkyl sulphynyl, C₁₋₄ alkysulphonyl, carboxamido, N-C₁₋₄ alkylcarboxamido, N,N-di(C₁₋₄ alkyl)carboxamido, aminosulphonyl, N-C₁₋₄ alkylaminosulphonyl, N,N-di(C₁₋₄ alkyl)aminosulphonyl, N-(C₁₋₄ alkylsulphonyl) amino, N-(C₁₋₄ alkylsulphonyl)-N-(C₁₋₄ alkyl) amino, N,N-di(C₁₋₄ alkylsulphonyl) amino or a C₃₋₄ alkyne chain joined to two ring C carbon atoms;
- n is an integer from 0 to 5;
- m is an integer from 0 to 3;
- R² represents hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, C₁₋₃ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkyl sulphanyl, -NR³R⁴ (wherein R³ and R⁴, which may be the same or different, each represents hydrogen or C₁₋₃ alkyl), or R³X¹⁻ (wherein X¹ represents a direct bond, -O-, -CH₂-, -OC(O) -, -C(O) -, -S-, -SO -, -SO₂-, -NR³C(O) -, -C(O)NR³-, -SO₂NR³-, -NR³SO₂-, or -NR¹⁰⁻ (wherein R⁵, R⁷, R⁸, R⁹ and R¹⁰ each independently represents hydrogen, C₁₋₃ alkyl or C₁₋₃ alkoxyC₂₋₃ alkyl), and R³ is selected from one of the following twenty-one groups:
  1) hydrogen or C₁₋₃ alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro and amino;
  2) C₁₋₃ alkylX²C(O)R¹¹ (wherein X² represents -O- or -NR¹²⁻ (in which R¹² represents hydrogen, C₁₋₃ alkyl or C₁₋₃ alkoxyC₂₋₃ alkyl) and R¹¹ represents C₁₋₃ alkyl, -NR¹³R¹⁴⁻ or -OR¹⁵⁻.
(wherein $R^{13}$, $R^{14}$ and $R^{15}$ which may be the same or different each represents hydrogen, $\text{C}_{1-3}\text{alkyl or C}_{1-3}\text{alkoxyC}_{2-3}\text{alkyl}$); 3) $\text{C}_{1-3}\text{alkylX}^{3}R^{16}$ (wherein $X^{3}$ represents $-\text{O}-$, $-\text{S}-$, $-\text{SO}_{2}$, $-\text{OC(O)}$, $-\text{NR}^{17}\text{C(O)}$, $-\text{C(O)}\text{NR}^{18}$, $-\text{SO}_{2}\text{NR}^{19}$, $-\text{NR}^{20}\text{SO}_{2}$ or $-\text{NR}^{21}$ (wherein $R^{17}$, $R^{18}$, $R^{19}$, $R^{20}$ and $R^{21}$ each independently represents hydrogen, $\text{C}_{1-3}\text{alkyl or C}_{1-3}\text{alkoxyC}_{2-3}\text{alkyl}$) and $R^{16}$ represents hydrogen, $\text{C}_{1-3}\text{alkyl}$, cyclopentyl, cyclohexyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which $\text{C}_{1-3}\text{alkyl}$ group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and $\text{C}_{1-4}\text{alkoxy}$ and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, $\text{C}_{1-4}\text{alkyl}$, 4) $\text{C}_{1-4}\text{hydroxyalkyl and C}_{1-4}\text{alkoxy}$); 5) $\text{C}_{1-3}\text{alkylX}^{4}\text{C}_{1-3}\text{alkylX}^{5}R^{22}$ (wherein $X^{4}$ and $X^{5}$ which may be the same or different are each $-\text{O}-$, $-\text{S}$, $-\text{SO}_{2}$, $-\text{OC(O)}$, $-\text{C(O)}\text{NR}^{23}$, $-\text{SO}_{2}\text{NR}^{25}$, $-\text{NR}^{26}\text{SO}_{2}$ or $-\text{NR}^{27}$ (wherein $R^{23}$, $R^{24}$, $R^{25}$, $R^{26}$ and $R^{27}$ each independently represents hydrogen, $\text{C}_{1-3}\text{alkyl or C}_{1-3}\text{alkoxyC}_{2-3}\text{alkyl}$) and $R^{22}$ represents hydrogen or $\text{C}_{1-3}\text{alkyl}$); 6) $\text{C}_{1-3}\text{alkylR}^{28}$ (wherein $R^{28}$ is as defined hereinbefore); 7) $\text{C}_{2-5}\text{alkenylR}^{28}$ (wherein $R^{28}$ is as defined hereinbefore); 8) $\text{C}_{2-5}\text{alkynylR}^{28}$ (wherein $R^{28}$ is as defined hereinbefore); 9) $\text{R}^{29}$ (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, $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{alkoxy}$, $\text{C}_{1-4}\text{hydroxyalkyl}$, $\text{C}_{1-4}\text{aminoalkyl}$, $\text{C}_{1-4}\text{alkylamino}$, $\text{C}_{1-4}\text{hydroxyalkoxy}$, carboxy, trifluoromethyl, cyano, $-\text{C(O)}\text{NR}^{30}\text{R}^{31}$ and $-\text{NR}^{32}\text{C(O)}\text{R}^{33}$ (wherein $R^{30}$, $R^{31}$, $R^{32}$ and $R^{33}$, which may be the same or different, each represents hydrogen, $\text{C}_{1-4}\text{alkyl or C}_{1-3}\text{alkoxyC}_{2-3}\text{alkyl}$)); 10) $\text{C}_{1-3}\text{alkylR}^{29}$ (wherein $R^{29}$ is as defined hereinbefore); 11) $\text{C}_{2-5}\text{alkenylR}^{29}$ (wherein $R^{29}$ is as defined hereinbefore); 12) $\text{C}_{2-5}\text{alkynylR}^{29}$ (wherein $R^{29}$ is as defined hereinbefore);
13) C₁₅alkylX⁶R₂⁹ (wherein X⁶ represents -O-, -S-, -SO₂-, -NR³⁴C(O)-, -C(O)NR³⁵-, -
SO₂NR³⁶-, -NR²⁷SO₂- or -NR²⁸- (wherein R³⁴, R³⁵, R³⁶, R³⁷ and R³⁸ each independently represents hydrogen, C₁₅alkyl or C₁₅alkoxyC₂₃alkyl) and R²⁹ is as defined hereinbefore);
14) C₂₅alkenylX⁷R²⁹ (wherein X⁷ represents -O-, -S-, -SO₂-, -SO₃-, -NR³⁹C(O)-, -C(O)NR⁴⁰-, -
SO₂NR⁴¹-, -NR⁴²SO₂- or -NR⁴³- (wherein R³⁹, R⁴⁰, R⁴¹, R⁴² and R⁴³ each independently represents hydrogen, C₁₅alkyl or C₁₅alkoxyC₂₃alkyl) and R²⁹ is as defined hereinbefore);
15) C₂₅alkynylX⁸R²⁹ (wherein X⁸ represents -O-, -S-, -SO₂-, -SO₃-, -NR⁴⁴C(O)-, -C(O)NR⁴⁵-, -
SO₂NR⁴⁶-, -NR⁴⁷SO₂- or -NR⁴⁸- (wherein R⁴⁴, R⁴⁵, R⁴⁶, R⁴⁷ and R⁴⁸ each independently represents hydrogen, C₁₅alkyl or C₁₅alkoxyC₂₃alkyl) and R²⁹ is as defined hereinbefore);
16) C₁₅alkylX⁹C₉alkylR²⁹ (wherein X⁹ represents -O-, -S-, -SO₂-, -NR⁴⁹C(O)-, -
C(O)NR⁵⁰-, -SO₂NR⁵¹-, -NR⁵²SO₂- or -NR⁵₃- (wherein R⁴⁹, R⁵₀, R⁵¹, R⁵₂ and R⁵₃ each independently represents hydrogen, C₁₅alkyl or C₁₅alkoxyC₂₃alkyl) and R²⁹ is as defined hereinbefore);
17) C₁₅alkylX⁹C₉alkylR²⁸ (wherein X⁹ and R²⁸ are as defined hereinbefore);
18) C₂₅alkenyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C₃₋₅alkylamino, aminosulphonyl, N,N-di(C₃₋₅alkyl)amino, aminosulphonyl, N-C₃₋₅alkylaminosulphonyl and N,N-di(C₃₋₅alkyl)aminosulphonyl;
19) C₂₅alkynyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C₃₋₅alkylamino, aminosulphonyl, N-C₃₋₅alkylaminosulphonyl and N,N-di(C₃₋₅alkyl)aminosulphonyl;
20) C₂₅alkenylX⁹C₉alkylR²⁸ (wherein X⁹ and R²⁸ are as defined hereinbefore); and
21) C₂₅alkynylX⁹C₉alkylR²⁸ (wherein X⁹ and R²⁸ 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_1,2alkoxyethyl).

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_2-, -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_1,2alkoxyethyl).

Preferably X^{12} represents -O-, -S-, -SO_2-, -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).
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Preferably $\chi^{18}$ represents -O- or -NR$^{104}$- (wherein R$^{104}$ represents hydrogen or C$_1$-alkyl).

According to another aspect of the present invention $\chi^{18}$ 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 an azetidinyl or a 5-6-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$_{1,3}$-alkylsulphonylC$_{1,3}$-alkyl, C$_{1,3}$-alkylsulphonylethyl, C$_{1,3}$-haloalkyl, C$_{1,3}$-alkylamino, di(C$_{1,3}$-alkyl)amino, C$_{1,3}$-alkylaminoC$_{1,3}$-alkyl, di(C$_{1,3}$-alkyl)aminoC$_{1,3}$-alkylaminoC$_{1,3}$-alkyl, a group -(-O-)$(C_{1,3}$-alkyl)$_f$ringD (wherein $f$ is 0 or 1, g is 0 or 1 and ring D is an azetidinyl or a 5-6-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$_{1,3}$-alkylsulphonylC$_{1,3}$-alkyl, C$_{1,3}$-alkylsulphonylethyl, C$_{1,3}$-haloalkyl, C$_{1,3}$-alkylamino, di(C$_{1,3}$-alkyl)amino, C$_{1,3}$-alkylaminoC$_{1,3}$-alkyl, di(C$_{1,3}$-alkyl)aminoC$_{1,3}$-alkylaminoC$_{1,3}$-alkyl, a group -(-O-)$(C_{1,3}$-alkyl)$_f$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$_{1,3}$-alkylsulphonylC$_{1,3}$-alkyl, C$_{1,3}$-alkylsulphonylethyl, C$_{1,3}$-haloalkyl, C$_{1,3}$-alkylamino, di(C$_{1,3}$-alkyl)amino, C$_{1,3}$-alkylaminoC$_{1,3}$-alkyl, di(C$_{1,3}$-alkyl)aminoC$_{1,3}$-alkylaminoC$_{1,3}$-alkyl, a group -(-O-)$(C_{1,3}$-alkyl)$_f$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-)$(C_{1,3}$-alkyl)$_f$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).
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\( \text{alkyl}_{f} \text{ring}_D \) (wherein \( f \) is 0 or 1, \( g \) is 0 or 1 and \( D \) 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, \( C_{1,3} \text{cyanoalkyl} \), \( C_{1,3} \text{alkyl} \), \( C_{1,3} \text{hydroxyalkyl} \), \( C_{1,2} \text{alkoxy} \), \( C_{1,3} \text{alkylsulphonylC}_{1,3} \text{alkyl} \), \( C_{1,3} \text{alkoxycarbonyl} \), \( C_{1,3} \text{alkylamino} \), di\( (C_{1,3} \text{alkyl}) \text{amino} \), \( C_{1,3} \text{alkylaminoC}_{1,3} \text{alkyl} \), di\( (C_{1,3} \text{alkyl}) \text{aminoC}_{1,3} \text{alkyl} \), \( C_{1,3} \text{alkylaminoC}_{1,3} \text{alkoxy} \), di\( (C_{1,3} \text{alkyl}) \text{aminoC}_{1,3} \text{alkoxy} \) and a group \( -(O-)(C_{1,3} \text{alkyl})_g \text{ring}_D \) (wherein \( f \) is 0 or 1, \( g \) is 0 or 1 and \( D \) 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 \( C_{1,3} \text{alkyl} \)).

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, \( C_{1,3} \text{cyanoalkyl} \), \( C_{1,3} \text{alkyl} \), \( C_{1,3} \text{hydroxyalkyl} \), \( C_{1,3} \text{alkoxy} \), \( C_{1,2} \text{alkoxyC}_{1,3} \text{alkyl} \), \( C_{1,3} \text{alkylsulphonylC}_{1,3} \text{alkyl} \), \( C_{1,3} \text{alkoxycarbonyl} \), \( C_{1,3} \text{alkylamino} \), di\( (C_{1,3} \text{alkyl}) \text{amino} \), \( C_{1,3} \text{alkylaminoC}_{1,3} \text{alkyl} \), di\( (C_{1,3} \text{alkyl}) \text{aminoC}_{1,3} \text{alkyl} \), \( C_{1,3} \text{alkylaminoC}_{1,3} \text{alkoxy} \), di\( (C_{1,3} \text{alkyl}) \text{aminoC}_{1,3} \text{alkoxy} \) and a group \( -(O-)(C_{1,3} \text{alkyl})_g \text{ring}_D \) (wherein \( f \) is 0 or 1, \( g \) is 0 or 1 and \( D \) 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 \( -(O-)(C_{1,3} \text{alkyl})_g \text{ring}_D \) (wherein \( f \) is 0 or 1, \( g \) is 0 or 1 and \( D \) is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino).

Advantageously \( R^{105} \) and \( R^{106} \) are each independently an azetidinyl or a 5-6-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, \( C_{1,3} \text{cyanoalkyl} \), \( C_{1,3} \text{alkyl} \), \( C_{1,3} \text{hydroxyalkyl} \), \( C_{1,3} \text{alkoxy} \), \( C_{1,2} \text{alkoxyC}_{1,3} \text{alkyl} \), \( C_{1,3} \text{alkylsulphonylC}_{1,3} \text{alkyl} \), \( C_{1,3} \text{alkoxycarbonyl} \), \( C_{1,3} \text{alkylamino} \), di\( (C_{1,3} \text{alkyl}) \text{amino} \), \( C_{1,3} \text{alkylaminoC}_{1,3} \text{alkyl} \), di\( (C_{1,3} \text{alkyl}) \text{aminoC}_{1,3} \text{alkyl} \), \( C_{1,3} \text{alkylaminoC}_{1,3} \text{alkoxy} \), di\( (C_{1,3} \text{alkyl}) \text{aminoC}_{1,3} \text{alkoxy} \) and a group \( -(O-)(C_{1,3} \text{alkyl})_g \text{ring}_D \) (wherein \( f \) is 0 or 1, \( g \) is 0 or 1 and \( D \) is an azetidinyl or a 5-6-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 \( C_{1,3} \text{alkyl} \)).
Preferably R<sup>105</sup> and R<sup>106</sup> 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<sub>1</sub>-cyanoalkyl, C<sub>1</sub>-alkyl, C<sub>1</sub>-hydroxyalkyl, C<sub>1</sub>-alkoxy, C<sub>1</sub>-alkoxyC<sub>1</sub>alkyl, C<sub>1</sub>-alkylsulphonylC<sub>1</sub>alkyl, C<sub>1</sub>-alkoxycarbonyl, C<sub>1</sub>alkylamino, di(C<sub>1</sub>alkyl)amino, C<sub>1</sub>alkylaminoC<sub>1</sub>alkyl, di(C<sub>1</sub>alkyl)aminoC<sub>1</sub>alkyl, C<sub>1</sub>alkylaminoC<sub>1</sub>alkyl, C<sub>1</sub>alkylaminoC<sub>1</sub>alkoxy, di(C<sub>1</sub>alkyl)aminoC<sub>1</sub>alkoxy and a group (-O-)(C<sub>1</sub>alkyl)<sub>f</sub>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<sub>1</sub>-alkyl).

More preferably R<sup>105</sup> and R<sup>106</sup> 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<sub>1</sub>-cyanoalkyl, C<sub>1</sub>-alkyl, C<sub>1</sub>-hydroxyalkyl, C<sub>1</sub>-alkoxy, C<sub>1</sub>-alkoxyC<sub>1</sub>alkyl, C<sub>1</sub>-alkylsulphonylC<sub>1</sub>alkyl, C<sub>1</sub>-alkoxycarbonyl, C<sub>1</sub>alkylamino, di(C<sub>1</sub>alkyl)amino, C<sub>1</sub>alkylaminoC<sub>1</sub>alkyl, di(C<sub>1</sub>alkyl)aminoC<sub>1</sub>alkyl, C<sub>1</sub>alkylaminoC<sub>1</sub>alkyl, C<sub>1</sub>alkylaminoC<sub>1</sub>alkoxy, di(C<sub>1</sub>alkyl)aminoC<sub>1</sub>alkoxy and a group (-O-)(C<sub>1</sub>alkyl)<sub>f</sub>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<sup>105</sup> and R<sup>106</sup> 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-)(C<sub>1</sub>alkyl)<sub>f</sub>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<sup>1</sup> represents oxo, halogeno, hydroxy, C<sub>1</sub>-alkoxy, C<sub>1</sub>-alkyl, C<sub>1</sub>-alkoxymethyl, C<sub>1</sub>-alkanoyl, C<sub>1</sub>-haloalkyl, cyano, amino, C<sub>2</sub>-alkenyl, C<sub>2</sub>-alkynyl, C<sub>1</sub>-alkanoyloxy, nitro, C<sub>1</sub>-alkanoylamino, C<sub>1</sub>-alkoxycarbonyl, C<sub>1</sub>-alkylsulphinyl, C<sub>1</sub>-alkylsulphonyl, C<sub>1</sub>-alkylcarbamoyl, N-C<sub>1</sub>-alkylcarbamoyl, N<sub>1</sub>N-di(C<sub>1</sub>-alkyl), C<sub>1</sub>-alkylcarbamoyl, aminosulphonyl, N-C<sub>1</sub>-alkylaminosulphonyl, N<sub>1</sub>N-di(C<sub>1</sub>-alkyl).
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_{1,8}alkylX^{12}R^{57} (wherein X^{12} and R^{57} are as defined hereinbefore);
2) R^{79} (wherein R^{79} is as defined hereinbefore);
3) C_{1,8}alkylR^{79} (wherein R^{79} is as defined hereinbefore);
4) C_{2,8}alkenylR^{79} (wherein R^{79} is as defined hereinbefore);
5) C_{2,8}alkynylR^{79} (wherein R^{79} is as defined hereinbefore);
6) C_{1,8}alkylX^{18}C_{1,3}alkylR^{79} (wherein X^{18} and R^{79} are as defined hereinbefore);
7) C_{2,8}alkenylX^{18}C_{1,4}alkylR^{79} (wherein X^{18} and R^{79} are as defined hereinbefore);
8) C_{2,8}alkynylX^{18}C_{1,4}alkylR^{79} (wherein X^{18} and R^{79} are as defined hereinbefore); and
9) C_{1,3}alkylR^{105}(C_{1,3}alkyl)_{4}(X^{18})_{2}R^{106} (wherein X^{18}, x, y, R^{105} and R^{106} are as defined hereinbefore;

and additionally wherein any C_{1,8}alkyl, C_{2,8}alkenyl or C_{2,8}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}alkoxyethyl, C_{2,3}alkanoyl, C_{1,3}haloalkyl, cyano, amino, C_{2,4}alkenyl, C_{2,4}alkynyl, C_{2,5}alkanoyloxy, nitro, C_{2,3}alkanoylamino, C_{1,2}alkoxycarbonyl, C_{1,2}alkylsulphonyl, C_{1,2}alkylsulphinyl, C_{1,2}alkylsulphonyl, carbamoyl, N-C_{1,2}alkylcarbamoyl, N,N-di(C_{1,2})

Preferably C_{2,8}alkenyl, C_{2,8}alkynyl, C_{2,5}alkoxyethyl, C_{2,5}alkanoyl, N-N-di(C_{1,2})

More preferably R^{1} represents oxo, hydroxy, C_{1,2}alkoxymethyl, amino, halogeno, C_{1,2}alkenyl, 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^{8}C(O)-, -NR^{8}SO_{2} or -NR^{10} (wherein R^{8}, 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, \(-O-, -S-, -NR^6C(O) -, -NR^6SO_2-\) (wherein \( R^6 \) and \( R^2 \) each independently represents hydrogen or \( C_{1,2} \text{alkyl} \) or NH.

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

Particularly \( X^1 \) represents \(-O-\) or \(-NR^6C(O)-\) (wherein \( R^6 \) represents hydrogen or \( C_{1,2} \text{alkyl} \)), 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, \( C_{1,3} \text{alkyl} \) or \( C_{1,2} \text{alkoxyethyl} \)).

Advantageously \( X^2 \) represents \(-O-, -S-, -SO_2-, -SO_{2\cdot} \), \(-NR^{13}C(O)-, -NR^{20}SO_2-\) or \(-NR^{21}-\) (wherein \( R^{17}, R^{20} \) and \( R^{21} \) each independently represents hydrogen, \( C_{1,2} \text{alkyl} \) or \( C_{1,2} \text{alkoxyethyl} \)).

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

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

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, \( C_{1,3} \text{alkyl} \) or \( C_{1,2} \text{alkoxyethyl} \)).

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

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, \( C_{1,2} \text{alkyl} \) or \( C_{1,2} \text{alkoxyethyl} \)).

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, \( C_{1,2} \text{alkyl} \) or \( C_{1,3} \text{alkoxyethyl} \)).

Preferably \( X^6 \) represents \(-O-\) or \(-NR^{18}-\) (wherein \( R^{38} \) represents hydrogen or \( C_{1,2} \text{alkyl} \)).

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

Preferably \( X^7 \) represents \(-O-\) or \(-NR^{13}-\) (wherein \( R^{43} \) represents hydrogen or \( C_{1,2} \text{alkyl} \)).
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Advantageously X⁸ represents -O-, -S- or -NR⁴⁸ (wherein R⁴⁸ represents hydrogen, C₁-alkyl or C₁₋₂-alkoxyethyl).

Preferably X⁸ represents -O- or -NR⁴⁸ (wherein R⁴⁸ represents hydrogen or C₁₋₂-alkyl).

Advantageously X⁹ represents -O-, -S- or -NR⁵³ (wherein R⁵³ represents hydrogen, C₁-alkyl or C₁₋₂-alkoxyethyl).

Preferably X⁹ represents -O- or -NR⁵³ (wherein R⁵³ represents hydrogen or C₁₋₂-alkyl).

According to another aspect of the present invention X⁹ represents -O-, -CONR⁵⁰- or -NR⁵³ (wherein R⁵⁰ and R⁵³ each independently represents hydrogen or C₁₋₂-alkyl).

Conveniently R²⁸ is pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino or thiomorpholino which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₃-cyanoalkyl, C₁₋₃-alkyl, C₁₋₃-hydroxyalkyl, C₁₋₂-alkoxy, C₁₋₃-alkoxyC₁₋₃-alkyl, C₁₋₃-alkylsulphonylC₁₋₃-alkyl, C₁₋₃-alkoxycarbonyl, C₁₋₃-alkylamino, di(C₁₋₃-alkyl)amino, C₁₋₃-alkylaminoC₁₋₃-alkyl, di(C₁₋₃-alkyl)aminoC₁₋₃-alkyl, C₁₋₃-alkylaminoC₁₋₃-alkoxy, di(C₁₋₃-alkyl)aminoC₁₋₃-alkoxy and a group -(-O-)ₙ(C₁₋₃-alkyl)ₙ 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 C₁₋₂-alkyl).

Advantageously R²⁸ is pyrrolidinyl, piperazinyl, piperidinyl, azetidinyl, morpholino or thiomorpholino which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₃-cyanoalkyl, C₁₋₃-alkyl, C₁₋₃-hydroxyalkyl, C₁₋₂-alkoxy, C₁₋₃-alkoxyC₁₋₃-alkyl, C₁₋₃-alkylsulphonylC₁₋₃-alkyl, C₁₋₃-alkoxycarbonyl, C₁₋₃-alkylamino, di(C₁₋₃-alkyl)amino, C₁₋₃-alkylaminoC₁₋₃-alkyl, di(C₁₋₃-alkyl)aminoC₁₋₃-alkyl, C₁₋₃-alkylaminoC₁₋₃-alkoxy, di(C₁₋₃-alkyl)aminoC₁₋₃-alkoxy and a group -(-O-)ₙ(C₁₋₃-alkyl)ₙ 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 R²⁸ is pyrrolidinyl, piperazinyl, piperidinyl, azetidinyl, morpholino or thiomorpholino which group may bear 1 or 2 substituents selected from a group -(-O-)ₙ(C₁₋₃-alkyl)ₙ 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 R²⁸ is pyrrolidinyl, piperazinyl, piperidinyl, azetidinyl, morpholino or thiomorpholino which group may bear 1 or 2 substituents selected from oxo, hydroxy,
halogeno, cyano, C₁₃cyanoalkyl, C₁₃alkyl, C₁₃hydroxyalkyl, C₁₃alkoxy, C₁₂alkoxyC₁₃alkyl and C₁₃alkylsulphonylC₁₃alkyl.

According to another aspect of the present invention, preferably R²⁸ is pyrrolidinyl, piperazinyl, piperidinyl, morpholino or thiomorpholino which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₃cyanoalkyl, C₁₃alkyl, C₁₃hydroxyalkyl, C₁₃alkoxy, C₁₂alkoxyC₁₃alkyl and C₁₂alkylsulphonylC₁₃alkyl.

Where R²⁹ 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.

R²⁹ is particularly a pyridone, phenyl, pyridyl, imidazolyl, thiazolyl, thienyl, triazolyl or pyrazazinyl 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 R²⁹ 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 R²⁹, conveniently substituents are selected from halogeno, C₁₃alkyl, C₁₃alkoxy, cyano and a group -(O-)f(C₁₃alkyl)ᵣringD (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 C₁₃alkyl).

In the definition of R²⁹, more conveniently substituents are selected from chloro, fluoro, methyl, ethyl and a group -(O-)g(C₁₃alkyl)ᵣringD (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 embodiment of the present invention in the definition of R²⁹, conveniently substituents are selected from halogeno, C₁₃alkyl, C₁₃alkoxy and cyano, more conveniently substituents are selected from chloro, fluoro, methyl and ethyl.

Advantageously R⁵⁴ and R⁵⁵ are each independently an azetidinyl or a 5-6-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, C₁₃.
3cyanoalkyl, C1,3alkyl, C1,3hydroxyalkyl, C1,3alkoxy, C1,3alkoxyC1,3alkyl, C1.
2alkylsulphonylC1,3alkyl, C1,3alkoxycarbonyl and a group -(O)-{(C1,3alkyl)g}ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is an azetidinyl or a 5-6-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 C1,3alkyl).

Preferably R54 and R55 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, C1,3cyanoalkyl, C1,3alkyl, C1.
3hydroxyalkyl, C1,3alkoxy, C1,2alkoxyC1,3alkyl, C1,2alkylsulphonylC1,3alkyl, C1.

2alkoxycarbonyl and a group -(O)-{(C1,3alkyl)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 C1,3alkyl).

More preferably R54 and R55 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, C1,3cyanoalkyl, C1,3alkyl, C1.

3hydroxyalkyl, C1,3alkoxy, C1,2alkoxyC1,3alkyl, C1,2alkylsulphonylC1,3alkyl, C1.
2alkoxycarbonyl and a group -(O)-{(C1,3alkyl)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 R54 and R55 are each selected from pyrrolidinyl, piperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino which group may bear 1 or 2 substituents selected from a group -(O)-{(C1,3alkyl)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 R54 and R55 are each selected from pyrrolidinyl, piperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino which group is unsubstituted.

Conveniently R2 represents hydroxy, halogeno, cyano, nitro, trifluoromethyl, C1,3alkyl, amino or R3X1- [wherein X1 is as hereinbefore defined and R3 is selected from one of the following twenty-two groups:}
1) oxiranylC<sub>1</sub>alkyl or C<sub>1</sub>alkyl which may be unsubstituted or which may be substituted with one or more groups selected from fluoro, chloro and bromo, or C<sub>2</sub>alkyl which may be unsubstituted or substituted with one or more groups selected from hydroxy and amino;
2) C<sub>2</sub>alkylX<sup>2</sup>C(O)R<sup>11</sup> (wherein X<sup>2</sup> is as hereinbefore defined and R<sup>11</sup> represents C<sub>1</sub>alkyl, -NR<sup>13</sup>R<sup>14</sup> or -OR<sup>15</sup> (wherein R<sup>13</sup>, R<sup>14</sup> and R<sup>15</sup> which may be the same or different are each C<sub>1</sub>alkyl or C<sub>1</sub>alkoxyethyl));
3) C<sub>2</sub>alkylX<sup>3</sup>R<sup>16</sup> (wherein X<sup>3</sup> is as hereinbefore defined and R<sup>16</sup> represents hydrogen, C<sub>1</sub>alkyl, cyclopentyl, cyclohexyl, azetidinyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C<sub>1</sub>alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C<sub>1</sub>alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C<sub>1</sub>cyanoalkyl, C<sub>1</sub>alkyl, C<sub>1</sub>hydroxyalkyl, C<sub>1</sub>alkoxyC<sub>1</sub>alkyl, C<sub>1</sub>alkylsulphonylC<sub>1</sub>alkyl, C<sub>1</sub>alkoxycarbonyl, C<sub>1</sub>alkylamino, di(C<sub>1</sub>alkyl)amino, C<sub>1</sub>alkylaminoC<sub>1</sub>alkyl, di(C<sub>1</sub>alkyl)aminoC<sub>1</sub>alkyl, and a group -(O)-(C<sub>1</sub>alkyl) ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is an azetidinyl or a 5-6-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<sub>1</sub>alkyl));
4) C<sub>2</sub>alkylX<sup>4</sup>C<sub>2</sub>alkylX<sup>5</sup>R<sup>22</sup> (wherein X<sup>4</sup> and X<sup>5</sup> are as hereinbefore defined and R<sup>22</sup> represents hydrogen or C<sub>1</sub>alkyl);
5) R<sup>28</sup> (wherein R<sup>28</sup> is as defined hereinbefore);
6) C<sub>1</sub>alkylR<sup>107</sup> (wherein R<sup>107</sup> is an azetidinyl or 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<sub>1</sub>alkyl through a carbon atom and which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C<sub>1</sub>cyanoalkyl, C<sub>1</sub>alkyl, C<sub>1</sub>hydroxyalkyl, C<sub>1</sub>alkoxy, C<sub>1</sub>alkoxyC<sub>1</sub>alkyl, C<sub>1</sub>alkylsulphonylC<sub>1</sub>alkyl, C<sub>1</sub>alkoxycarbonyl, C<sub>1</sub>alkylamino, di(C<sub>1</sub>alkyl)amino, C<sub>1</sub>alkylaminoC<sub>1</sub>alkyl, di(C<sub>1</sub>alkyl)aminoC<sub>1</sub>alkyl, C<sub>1</sub>alkylaminoC<sub>1</sub>alkyl, di(C<sub>1</sub>alkyl)aminoC<sub>1</sub>alkyl and a group -(O)-(C<sub>1</sub>alkyl) ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is an azetidinyl or a 5-6-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<sub>1</sub>alkyl) or C<sub>2</sub>alkylR<sup>108</sup> (wherein R<sup>108</sup> is an azetidinyl or a 5-6-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<sub>2</sub>alkyl).
through a nitrogen atom and which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₄₋₅alkyl, C₁₋₉hydroxyalkyl, C₁₋₉alkoxy, C₁₋₉alkoxyC₁₋₉alkyl, C₁₋₉alkylsulphonylC₁₋₉alkyl, C₁₋₉alkoxy carbonyl, C₁₋₉alkylamino, di(C₁₋₉alkyl)amino, C₁₋₉alkylaminoC₁₋₉alkyl, di(C₁₋₉alkyl)aminoC₁₋₉alkoxy and a group -(O-)(C₁₋₉alkyl)₈ ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is an azetidinyl or a 5-6-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 C₁₋₉alkyl));
7) C₃₋₅alkenylR¹⁰⁹ (wherein R¹⁰⁹ represents R¹⁰⁷ or R¹⁰⁸ as defined hereinbefore);
8) C₃₋₅alkynylR¹⁰⁹ (wherein R¹⁰⁹ represents R¹⁰⁷ or R¹⁰⁸ as defined hereinbefore);
9) R²⁹ (wherein R²⁹ is as defined hereinbefore);
10) C₁₋₅alkylR²⁹ (wherein R²⁹ is as defined hereinbefore);
11) C₃₋₅alkenylR²⁹ (wherein R²⁹ is as defined hereinbefore);
12) C₃₋₅alkynylR²⁹ (wherein R²⁹ is as defined hereinbefore);
13) C₁₋₅alkylX⁶R²⁹ (wherein X⁶ and R²⁹ are as defined hereinbefore);
14) C₄₋₅alkenylX⁷R²⁹ (wherein X⁷ and R²⁹ are as defined hereinbefore);
15) C₄₋₅alkynylX⁸R²⁹ (wherein X⁸ and R²⁹ are as defined hereinbefore);
16) C₂₋₅alkylX⁹C₁₋₅alkylR²⁹ (wherein X⁹ and R²⁹ are as defined hereinbefore);
17) C₂₋₅alkylX⁹C₁₋₅alkylR²⁸ (wherein X⁹ and R²⁸ are as defined hereinbefore);
18) C₂₋₅alkenyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C₁₋₅alkylamino, N,N-di(C₁₋₅alkyl)amino, aminosulphonyl, N-C₁₋₅alkylaminosulphonyl and N,N-di(C₁₋₅alkyl)aminosulphonyl;
19) C₂₋₅alkynyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C₁₋₅alkylamino, N,N-di(C₁₋₅alkyl)amino, aminosulphonyl, N-C₁₋₅alkylaminosulphonyl and N,N-di(C₁₋₅alkyl)aminosulphonyl;
20) C₂₋₅alkenylX⁹C₁₋₅alkylR²⁸ (wherein X⁹ and R²⁸ are as defined hereinbefore);
21) C₂₋₅alkynylX⁹C₁₋₅alkylR²⁸ (wherein X⁹ and R²⁸ are as defined hereinbefore); and
22) C₁₋₅alkylX⁵⁴(C₁₋₅alkyl)₈(X⁹),R⁵⁵ (wherein X⁹, q, r, R⁵⁴ and R⁵⁵ are as defined hereinbefore);
and additionally wherein any C₁₋₅alkyl, C₂₋₅alkenyl or C₂₋₅alkynyl group in R²X¹ - may bear one or more substituents selected from hydroxy, halogeno and amino].
Advantageously $\text{R}^2$ represents hydroxy, halogeno, cyano, nitro, trifluoromethyl, C$_1$.  
$\text{alkyl}$, amino or R$^3$X$^1$ - [wherein X$^1$ is as hereinbefore defined and R$^3$ 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$^2$C(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$_1$.  
$\text{alkoxyethyl}$);

3) C$_{2-6}$alkylX$^3$R$^{16}$ (wherein X$^3$ is as hereinbefore defined and R$^{16}$ is a group selected from C$_1$.  
$\text{alkyl}$, 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$_1$.  
$\text{alkoxy}$ 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$_1$.  
$\text{hydroxyalkyl}$, C$_{1-3}$alkoxy, C$_{1-3}$alkoxyC$_{1-3}$alkyl, C$_{1-2}$alkylsulphonylC$_{1-3}$alkyl, C$_1$.  
$\text{alkoxy carbonyl}$, C$_{1-3}$alkylamino, di(C$_{1-3}$alkyl)amino, C$_{1-3}$alkylaminoC$_{1-3}$alkyl, di(C$_1$.  
$\text{alkyl}$)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$^1$ingD (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$_1$.  
$\text{alkyl}$);

4) C$_{2-3}$alkylX$^4$C$_{2-5}$alkylX$^5$R$^{22}$ (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$_1$.  
$\text{alkyl}$, C$_{1-3}$hydroxyalkyl, C$_{1-3}$alkoxy, C$_{1-3}$alkoxyC$_{1-3}$alkyl, C$_{1-3}$alkylsulphonylC$_{1-3}$alkyl, C$_1$.  
$\text{alkoxy carbonyl}$, C$_{1-3}$alkylamino, di(C$_{1-3}$alkyl)amino, C$_{1-3}$alkylaminoC$_{1-3}$alkyl, di(C$_1$.  
$\text{alkyl}$)aminoC$_{1-3}$alkyl, C$_{1-3}$alkylaminoC$_{1-3}$alkoxy, di(C$_{1-3}$alkyl)aminoC$_{1-3}$alkoxy and a group -(O-).
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,alkyl}R^{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,alkoxy}, C_{1,2,alkoxyC_{1,3,alkyl}}, C_{1,2,alkylsulphonylC_{1,3,alkyl}}, C_{1,3,hydroxyalkyl}, C_{1,3,alkoxyC_{1,3,alkyl}}, C_{1,3,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}), 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,alkeny}lR^{112} (wherein R^{112} represents R^{110} or R^{111} as defined hereinbefore);

8) C_{3,4,alkynyl}lR^{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,alkyl}R^{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,alkyl}X^9 R^{29} (wherein X^6 and R^{29} are as defined hereinbefore);

14) 1-(R^{29}X^5)but-2-en-4-yl (wherein X^5 and R^{29} are as defined hereinbefore);

15) 1-(R^{29}X^5)but-2-yn-4-yl (wherein X^5 and R^{29} are as defined hereinbefore);

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

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

18) C_{2,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_{1,3,alkylamino}, N,N-di(C_{1,3,alkyl})amino, aminosulphonyl, N-C_{1,4,alkylamino}sulphonyl and N,N-di(C_{1,4,alkyl})aminosulphonyl;
19) C₉₂,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, C₁₄,alkylamino, N,N-di(C₁₄,alkyl)amino, aminosulphonyl, N-C₁₄,alkylaminosulphonyl and N,N-di(C₁₄,alkyl)aminosulphonyl;

20) C₂₉,alkenylX⁹Cᵢ₁,alkylR²⁸ (wherein X⁹ and R²⁸ are as defined hereinbefore);

21) C₂₉,alkenylX⁹Cᵢ₁,alkylR²⁸ (wherein X⁹ and R²⁸ are as defined hereinbefore); and

22) C₁₃,alkylR²⁴(C₁₃,alkyl)₄(X⁹)₂R⁵⁵ (wherein X⁹, q, r, R³⁴ and R⁵⁵ are as defined hereinbefore); and additionally wherein any C₁₃,alkyl, C₂₅,alkenyl or C₂₅,alkynyl group in R⁸X¹⁺ may bear one or more substituents selected from hydroxy, halogeno and amino.

Preferably R² represents hydroxy, halogeno, nitro, trifluoromethyl, C₁₃,alkyl, cyano, amino or R²X¹⁺ [wherein X¹ is as hereinbefore defined and R¹ is selected from one of the following twenty groups:

1) C₁₃,alkyl which may be unsubstituted or which may be substituted with one or more groups selected from fluoro, chloro and bromo, or C₂₅,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) C₂₅,alkylX³R¹⁶ (wherein X³ is as hereinbefore defined and R¹⁶ is a group selected from C₁₃,alkyl, cyclopentyl, cyclohexyl, pyrrolidinyl, piperidinyl, piperazinyl, azetidinyl, imidazolidinyl and tetrahydropyranyl which group is linked to X³ through a carbon atom and which C₁₃,alkyl group may bear 1 or 2 substituents selected from hydroxy, halogeno and C₁₃,alkoxy and which cyclopentyl, cyclohexyl, pyrrolidinyl, piperidinyl, piperazinyl, azetidinyl, imidazolidinyl or tetrahydropyranyl group may bear one substituent selected from oxo, hydroxy, halogeno, cyano, C₁₃,cyanoalkyl, C₁₃,alkyl, C₁₃,hydroxyalkyl, C₁₃,alkoxy, C₁₃,alkoxyC₁₃,alkyl, C₁₃,alkylsulphonylC₁₃,alkyl, C₁₃,alkoxycarbonyl, C₁₃,alkylamino, di(C₁₃,alkyl)amino, C₁₃,alkylaminoC₁₃,alkyl, di(C₁₃,alkyl)aminoC₁₃,alkyl, C₁₃,alkylaminoC₁₃,alkoxy, di(C₁₃,alkyl)aminoC₁₃,alkoxy and a group -(O)⁻(C₁₃,alkyl)ᵢ⁺ 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_{1,2}alkylIR^{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_{1,2}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_{1,2})alkylaminoC_{1,3}alkyl, C_{1,3}alkylaminoC_{1,3}alkoxy, di(C_{1,3}alkyl)aminoC_{1,3}alkoxy and a group (-O-)_h(C_{1,3}alkyl)_g\text{ringD (wherein } f \text{ is 0 or 1, } g \text{ is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, methylpiperazinyl, piperidinyl, azetidinyl, morpholino and thiomorpholino)) or C_{2,3}alkylIR^{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_{1,2})alkylaminoC_{1,3}alkyl, C_{1,3}alkylaminoC_{1,3}alkoxy, di(C_{1,3}alkyl)aminoC_{1,3}alkoxy and a group (-O-)_h(C_{1,3}alkyl)_g\text{ringD (wherein } f \text{ is 0 or 1, } g \text{ 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_{1,2}alkylIR^{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}alkylIR^{29} (wherein X^9 and R^{29} are as defined hereinbefore);
15) C_{2,3}alkylX^9C_{1,3}alkylIR^{28} (wherein X^9 and R^{28} are as defined hereinbefore);
16) C_{2,3}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}.
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) \(C_2\)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\(_1\).

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) \(C_2\)alkenyI\(X^6\)C\(_{1-3}\)alkyl\(R^{28}\) (wherein \(X^6\) and \(R^{28}\) are as defined hereinbefore);

19) \(C_2\)alkynyl\(X^9\)C\(_{1-3}\)alkyl\(R^{28}\) (wherein \(X^9\) and \(R^{28}\) are as defined hereinbefore); and

20) \(C_1\)\(alkylR^{54}\)(C\(_{1-3}\)alkyl)\(q_(X^{54})R^{55}\) (wherein \(X^{54}\), \(q\), \(r\), \(R^{54}\), and \(R^{55}\) are as defined hereinbefore);

and additionally wherein any C\(_{1-5}\)alkyl, \(C_2\)alkenyl or \(C_2\)alkynyl group in \(R^9X^1\) may bear one or more substituents selected from hydroxy, halogeno and amino].

More preferably \(R^2\) represents hydroxy, C\(_{1-5}\)alkyl, amino or \(R^9X^1\) - [wherein \(X^1\) is as hereinbefore defined and \(R^2\) represents methyl, ethyl, benzyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, 2-(methylsulphonyl)ethyl, 2-(methylsulphonyl)ethyl, 2-(ethylsulphonyl)ethyl, 2-(ethylsulphonyl)ethyl, 2-(N,N-dimethylsulphamoyl)ethyl, 2-(N-methylsulphamoyl)ethyl, 2-sulphamoyl, 2-(methylamino)ethyl, 3-(methylamino)propyl, 2-(ethylamino)ethyl, 3-(aminopropyl, 2-(N,N-dimethylaminopropyl, 2-(N,N-diethylamino)ethyl, 3-(N,N-diethylamino)propyl, 2-(N-methyl-N-methylsulphonlamino)ethyl, 3-(N,N-meN-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)ethyl)piperidino)ethyl, 3-((2-methylsulphonyl)ethyl)piperidino)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-(1-cyanomethyl)piperidin-3-yl)methyl, 1-(1-cyanomethyl)piperidin-4-yl)methyl, 2-(methylpiperidin-3-yl)ethyl, 2-(methylpiperidin-4-yl)ethyl, 2-(1-cyanomethyl)piperidin-3-yl)ethyl, 2-(1-cyanomethyl)piperidin-4-yl)ethyl, 3-(methylpiperidin-3-yl)propyl, 3-(methylpiperidin-4-yl)propyl, 3-(1-cyanomethyl)piperidin-3-yl)propyl, 3-(1-cyanomethyl)piperidin-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-methylsulphonyl)ethyl)piperidin-3-yl)methyl, (1-(2-methylsulphonyl)ethyl)piperidin-4-yl)methyl, 2-((2-methylsulphonyl)ethyl)piperidin-3-yl)ethyl, 2-((2-methylsulphonyl)ethyl)piperidin-4-yl)ethyl, 3-((2-methylsulphonyl)ethyl)piperidin-3-yl)propyl, 3-((2-methylsulphonyl)ethyl)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-cyanomethyl)piperidin-4-yloxy)propyl, 2-((1-cyanomethyl)piperidin-4-yloxy)propyl, 2-((1-cyanomethyl)piperidin-4-yloxy)propyl, (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, 5(R)-(2-oxo-tetrahydro-2H-pyrrolidin-5-yl)methyl, (5S)-(2-oxo-tetrahydro-2H-pyrrolidin-5-yl)methyl, (1,3-dioxolan-2-yl)methyl, 2-(1,3-dioxolan-2-yl)ethyl, 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-(4-oxo-imidazolidin-1-yl)ethyl, 3-(2-oxo-imidazolidin-1-yl)propyl, 2-thiomorpholinooethyl, 3-thiomorpholinopropyl, 2-(1,1-dioxothiomorpholinoo)ethyl, 3-(1,1-dioxothiomorpholinoo)propyl, 2-(2-methoxyethoxy)ethyl, 2-(4-methylpiperazin-1-yl)ethyl, 3-(4-methylpiperazin-1-yl)propyl, 3-(methylsulphonyl)propyl, 3-(ethylsulphonyl)propyl, 3-(ethylsulphonyl)propyl, 2-(5-methyl-1,2,4-triazol-1-yl)ethyl, morpholino, 2-((N-(1-methylimidazol-4-ylsulphonyl)-N-methylamino)ethyl, 2-((N-(3-
- 30 -
morpholinopropyl(sulphonyl)-N-methyl)amino)ethyl, 2-((N-methyl-N-4-pyridyl)amino)ethyl, 3-(4-oxidomorpholino)propyl, 2-(2-(4-methyl(piperazin-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-ylmethy1, 1-(3-pyrrolidinylethyl)piperidin-4-ylmethyl, 1-(2-piperidinylethyl)piperidin-4-ylmethy1, 1-(3-piperidinylethyl)piperidin-4-ylmethyl, 1-(2-morpholinoethyl)piperidin-4-ylmethy1, 1-(3-morpholinoethyl)piperidin-4-ylmethy1, 1-(2-thiomorpholinoethyl)piperidin-4-ylmethy1, 1-(3-thiomorpholinoethyl)piperidin-4-ylmethy1, 1-(2-azetidinylethyl)piperidin-4-ylmethy1, 1-(3-azetidinylethyl)piperidin-4-ylmethy1, 3-morpholino-2-hydroxypropyl, (2R)-3-morpholino-2-hydroxypropyl, (2S)-3-morpholino-2-hydroxypropyl, 3-piperidino-2-hydroxypropyl, (2R)-3-piperidino-2-hydroxypropyl, (2S)-3-piperidino-2-hydroxypropyl, 3-pyrrolidin-1-yl-2-hydroxypropyl, (2R)-3-pyrrolidin-1-yl-2-hydroxypropyl, (2S)-3-pyrrolidin-1-yl-2-hydroxypropyl, 3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, (2R)-3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, (2S)-3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, 3-(N,N-diethylamino)-2-hydroxypropyl, (2R)-3-(N,N-diethylamino)-2-hydroxypropyl, (2S)-3-(N,N-diethylamino)-2-hydroxypropyl, 3-(isopropylamino)-2-hydroxypropyl, (2S)-3-(isopropylamino)-2-hydroxypropyl, 3-(N,N-diisopropylamino)-2-hydroxypropyl, (2R)-3-(N,N-diisopropylamino)-2-hydroxypropyl or (2S)-3-(N,N-diisopropylamino)-2-hydroxypropyl.

Particularly R² represents C₁₃-alkyl, amino or R⁵X¹ - [wherein X¹ is as hereinbefore defined and R⁵ 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,N-dimethylsulphamoyl)ethyl, 2-sulphamoyl-ethyl, 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)ethyl)piperidino)ethyl, 3-((2-methylsulphonyl)ethyl)piperidino)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, 5 (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-yl)methyl, 1-isopropylpiperidin-4-yl)methyl, 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-yl)ethyl, 3-(1-(cyanomethyl)piperidin-4-yl)oxy)propyl, 2-(1-cyanoethyl)piperidin-4-yl)ethyl, 3-(1-(cyanoethyl)piperidin-4-yl)oxy)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, 5(R)-(2-oxo-tetrahydro-2H-pyrrolidin-5-yl)methyl, (5S)-(2-oxo-tetrahydro-2H-pyrrolidin-5-yl)methyl, (1,3-dioxolan-2-yl)methyl, 2-(1,3-dioxolan-2-yl)ethy, 2-(2-methoxyethylamino)ethyl, 2-(N-(2-methoxyethyl)-N-methylamino)ethyl, 2-(2-hydroxyethylamino)ethyl, 3-(2-hydroxyethylamino)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-pyridyl)methyl, 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-(methoxyethoxy)ethyl, 2-(4-methylpiperazin-1-yl)ethyl, 3-(4-methylpiperazin-1-yl)propyl, 2-(3-methylsulphonyl)propyl, 3-(ethylsulphynyl)propyl, 3-(ethyloxysulphynyl)propyl, 2-(5-methyl-1,2,4-triazol-1-yl)ethyl, morpholino, 2-((N-(1-methylimidazol-4-yl)sulphonyl)-N-methyl)amino)ethyl, 2-((N-(3-morpholinopropyl)sulphonyl)-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-(tetrahydropropyl-4-yloxy)ethyl, 3-(tetrahydropropyl-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-pyrrolidinylethyl)piperidin-4-ylmethyl, 1-(3-pyrrolidinylpropyl)piperidin-4-ylmethyl, 1-(2-pyrrolidinylethyl)piperidin-4-ylmethyl, 1-(3-pyrrolidinylpropyl)piperidin-4-ylmethyl, 1-(2-morpholinoethyl)piperidin-4-ylmethyl, 1-(3-morpholinoethyl)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, (2R)-3-morpholino-2-hydroxypropyl, (2S)-3-morpholino-2-hydroxypropyl, 3-piperidino-2-hydroxypropyl, (2R)-3-piperidino-2-hydroxypropyl, (2S)-3-piperidino-2-hydroxypropyl, 3-pyrrolidin-1-yl-2-hydroxypropyl, (2R)-3-pyrrolidin-1-yl-2-hydroxypropyl, (2S)-3-pyrrolidin-1-yl-2-hydroxypropyl, 3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, (2R)-3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, (2S)-3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, 3-(N,N-diethylamino)-2-hydroxypropyl, (2R)-3-(N,N-diethylamino)-2-hydroxypropyl, (2S)-3-(N,N-diethylamino)-2-hydroxypropyl, 3-(isopropylamino)-2-hydroxypropyl, (2R)-3-(isopropylamino)-2-hydroxypropyl, (2S)-3-(isopropylamino)-2-hydroxypropyl, 3-(N,N-diisopropylamino)-2-hydroxypropyl, (2R)-3-(N,N-diisopropylamino)-2-hydroxypropyl or (2S)-3-(N,N-diisopropylamino)-2-hydroxypropyl.

More particularly R² represents C₁₃alkyl, amino or R⁵X¹ - [wherein X¹ is as hereinbefore defined and R⁵ represents ethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2-
hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, 2-(methylsulphinyl)ethyl, 2-(methylsulphonyl)ethyl, 2-(ethyIsulphinyl)ethyl, 2-(ethyIsulphonyl)ethyl, 2-(N,N-dimethylsulphamoyl)ethyl, 2-(N-methylsulphamoyl)ethyl, 2-sulphamoyylethyl, 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-methylsulphphonylaminio)ethyl, 3-(N-methyl-N-methylsulphphonylaminio)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-methoxysethyl)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-methylsulphonylethethyl)piperidin-3-yl)methyl, (1-(2-methylsulphonylethethyl)piperidin-4-yl)methyl, 2-((2-methylsulphonylethethyl)piperidin-3-yl)ethyl, 2-((2-methylsulphonylethethyl)piperidin-4-yl)ethyl, 3-((2-methylsulphonylethethyl)piperidin-3-yl)propyl, 3-((2-methylsulphonylethethyl)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-cyanomethylpiperidin-4-yloxy)ethyl, 3-(1-cyanomethylpiperidin-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-2H-pyrrolidin-5-yl)methyl, 5(R)-(2-oxo-tetrahydro-2H-pyrrolidin-5-yl)methyl, (5S)-(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-(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-di hydro-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-methylamino)ethyl, 2-((N-methyl-N-4-pyridyl)amino)ethyl, 3-(4-oxidomorpholinopropyl)propyl, 2-(2-(4-methylpiperazin-1-yl)ethoxy)ethyl, 2-(2-(4-methylpiperazin-1-yl)ethoxy)propyl, 2-(2-morpholinoethoxy)ethyl, 3-(2-morpholinoethoxy)propyl, 2-(tetrahydropryan-4-yloxy)ethyl, 3-(tetrahydropryan-4-yloxy)propyl, 2-((2-pyrrolidin-1-yl)ethyl)carbamoylvinyl, 3-((2-pyrrolidin-1-yl)ethyl)carbamoylprop-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, (2R)-3-morpholino-2-hydroxypropyl, (2S)-3-morpholino-2-hydroxypropyl, 3-piperidino-2-hydroxypropyl, (2R)-3-piperidino-2-hydroxypropyl, (2S)-3-piperidino-2-hydroxypropyl, 3-pyrrolidin-1-yl-2-hydroxypropyl, (2R)-3-pyrrolidin-1-yl-2-hydroxypropyl, (2S)-3-pyrrolidin-1-yl-2-hydroxypropyl, 3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, (2R)-3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, (2S)-3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, (2R)-3-(N,N-diethylamino)-2-hydroxypropyl, (2R)-3-(N,N-diethylamino)-2-hydroxypropyl, (2S)-3-(N,N-diethylamino)-2-hydroxypropyl, (2R)-3-(isopropylamino)-2-hydroxypropyl, (2R)-3-
(isopropylamino)-2-hydroxypropyl, (2S)-3-(isopropylamino)-2-hydroxypropyl, 3-(N,N-diisopropylamino)-2-hydroxypropyl, (2R)-3-(N,N-diisopropylamino)-2-hydroxypropyl or (2S)-3-(N,N-diisopropylamino)-2-hydroxypropyl).

In another aspect R₂ 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-morpholinooethoxy, 3-morpholinopropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-(methylpiperidino)ethoxy, 3-(methylpiperidino)propoxy, 2-(ethylvpiperidino)ethoxy, 3-(ethylpiperidino)propoxy, 2-((2-methoxyethyl)piperidino)ethoxy, 3-((2-methoxyethyl)piperidino)propoxy, 2-((2-methylsulphonyl)ethyl)piperidino)ethoxy, 3-((2-methylsulphonyl)ethyl)piperidino)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-ylmethoxy, (2-methoxyethyl)piperidin-4-ylmethoxy, 2-(2-methoxyethyl)piperidin-3-ylmethoxy, 2-(2-methoxyethyl)piperidin-4-ylmethoxy, 3-(2-methoxyethyl)piperidin-3-ylpropoxy, 3-(2-methoxyethyl)piperidin-4-ylpropoxy, (1-(2-methylsulphonylethyl)piperidin-3-yl)methoxy, (1-(2-methylsulphonylethyl)piperidin-4-yl)methoxy, 2-(2-methylsulphonylethyl)piperidin-3-ylmethoxy, 2-(2-methylsulphonylethyl)piperidin-4-ylmethoxy, 3-(2-methylsulphonylethyl)piperidin-3-ylpropoxy, 3-(2-methylsulphonylethyl)piperidin-4-ylpropoxy, 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-(pyrrolidin-4-yloxy)ethoxy, 3-(pyrrolidin-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-2H-pyrrolidin-5-yloxy)methoxy, 5(R)-(2-oxo-tetrahydro-2H-pyrrolidin-5-yl)methoxy, (5S)-(2-oxo-tetrahydro-2H-pyrrolidin-5-yl)methoxy, (1,3-dioxolan-2-yl)ethoxy, 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-pyridyl)oxy)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-dioxothiomorpholin)ethoxy, 3-(1,1-dioxothiomorpholin)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-oxidomorpholin)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-(tetrahydropran-4-yloxy)ethoxy, 3-(tetrahydropran-4-yloxy)propoxy, 2-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)vinyl, 3-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)prop-2-en-1-yl)oxy, 1-(2-pyrrolidinylethyl)piperidin-4-ylmethoxy, 1-(3-pyrrolidinylethyl)piperidin-4-ylmethoxy, 1-(2-piperidinylethyl)piperidin-4-ylmethoxy, 1-(3-piperidinylethyl)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-azetidinylethyl)piperidin-4-ylmethoxy, 3-morpholino-2-hydroxypropoxy,
(2R)-3-morpholino-2-hydroxypropoxy, (2S)-3-morpholino-2-hydroxypropoxy, 3-piperidino-2-hydroxypropoxy, (2R)-3-piperidino-2-hydroxypropoxy, (2S)-3-piperidino-2-hydroxypropoxy, 3-pyrrolidin-1-yl-2-hydroxypropoxy, (2R)-3-pyrrolidin-1-yl-2-hydroxypropoxy, (2S)-3-pyrrolidin-1-yl-2-hydroxypropoxy, 3-(1-methylpiperazin-4-yl)-2-hydroxypropoxy, (2R)-3-(1-methylpiperazin-4-yl)-2-hydroxypropoxy, (2S)-3-(1-methylpiperazin-4-yl)-2-hydroxypropoxy, 3-(N,N-diethylamino)-2-hydroxypropoxy, (2R)-3-(N,N-diethylamino)-2-hydroxypropoxy, (2S)-3-(N,N-diethylamino)-2-hydroxypropoxy, 3-(isopropylamino)-2-hydroxypropoxy, (2R)-3-(isopropylamino)-2-hydroxypropoxy, (2S)-3-(isopropylamino)-2-hydroxypropoxy, 3-(N,N-diisopropylamino)-2-hydroxypropoxy, (2R)-3-(N,N-diisopropylamino)-2-hydroxypropoxy or (2S)-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^2X^1 - [wherein X^1 is as hereinbefore defined and R^3 is selected from one of the following twenty-one groups:

1) C_{1-6}alkyl which may be unsubstituted or substituted with one or more fluorine atoms, or C_{2-6}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} may be the same or different are each C_{1-3}alkyl or C_{1-3}alkoxyethy)));

3) C_{2-4}alkylX^3R^{16} (wherein X^3 is as hereinbefore defined and R^{16} represents hydrogen, C_{1-6}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.}
alkoxy, C\textsubscript{1-4}alkoxyC\textsubscript{1-4}alkyl and C\textsubscript{1-4}alkylsulphonylC\textsubscript{1-4}alkyl) or C\textsubscript{2-3}alkylR\textsuperscript{130} (wherein R\textsuperscript{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\textsubscript{2-3}alkyl through a nitrogen atom and which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C\textsubscript{1-4}cyanoalkyl, C\textsubscript{1-4}alkyl, C\textsubscript{1-4}hydroxyalkyl, C\textsubscript{1-4}alkoxy, C\textsubscript{1-4}alkoxyC\textsubscript{1-4}alkyl and C\textsubscript{1-4}alkylsulphonylC\textsubscript{1-4}alkyl);  
6) C\textsubscript{3-4}alkenylR\textsuperscript{131} (wherein R\textsuperscript{131} represents R\textsuperscript{129} or R\textsuperscript{130} as defined hereinbefore);  
7) C\textsubscript{3-4}alkynylR\textsuperscript{131} (wherein R\textsuperscript{131} represents R\textsuperscript{129} or R\textsuperscript{130} as defined hereinbefore);  
8) R\textsuperscript{29} (wherein R\textsuperscript{29} is as defined hereinbefore);  
9) C\textsubscript{1-5}alkylR\textsuperscript{29} (wherein R\textsuperscript{29} is as defined hereinbefore);  
10) C\textsubscript{3-5}alkenylR\textsuperscript{29} (wherein R\textsuperscript{29} is as defined hereinbefore);  
11) C\textsubscript{3-5}alkynylR\textsuperscript{29} (wherein R\textsuperscript{29} is as defined hereinbefore);  
12) C\textsubscript{1-5}alkylX\textsuperscript{6}R\textsuperscript{29} (wherein X\textsuperscript{6} and R\textsuperscript{29} are as defined hereinbefore);  
13) C\textsubscript{4-5}alkenylX\textsuperscript{7}R\textsuperscript{29} (wherein X\textsuperscript{7} and R\textsuperscript{29} are as defined hereinbefore);  
14) C\textsubscript{4-5}alkynylX\textsuperscript{8}R\textsuperscript{29} (wherein X\textsuperscript{8} and R\textsuperscript{29} are as defined hereinbefore);  
15) C\textsubscript{2-3}alkylX\textsuperscript{9}C\textsubscript{1-2}alkylR\textsuperscript{29} (wherein X\textsuperscript{9} and R\textsuperscript{29} are as defined hereinbefore);  
16) R\textsuperscript{28} (wherein R\textsuperscript{28} is as defined hereinbefore);  
17) C\textsubscript{2-3}alkylX\textsuperscript{9}C\textsubscript{1-2}alkylR\textsuperscript{28} (wherein X\textsuperscript{9} and R\textsuperscript{28} are as defined hereinbefore);  
18) C\textsubscript{2-5}alkenyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C\textsubscript{1-4}alkylamino, N,N-di(C\textsubscript{1-4}alkyl)amino, aminosulphonyl, N-C\textsubscript{1-4}alkylaminosulphonyl and N,N-di(C\textsubscript{1-4}alkyl)aminosulphonyl;  
19) C\textsubscript{2-5}alkynyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C\textsubscript{1-4}alkylamino, N,N-di(C\textsubscript{1-4}alkyl)amino, aminosulphonyl, N-C\textsubscript{1-4}alkylaminosulphonyl and N,N-di(C\textsubscript{1-4}alkyl)aminosulphonyl;  
20) C\textsubscript{2-5}alkenylX\textsuperscript{9}C\textsubscript{1-3}alkylR\textsuperscript{28} (wherein X\textsuperscript{9} and R\textsuperscript{28} are as defined hereinbefore); and  
21) C\textsubscript{2-5}alkynylX\textsuperscript{9}C\textsubscript{1-3}alkylR\textsuperscript{28} (wherein X\textsuperscript{9} and R\textsuperscript{28} are as defined hereinbefore)].

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

1) C\textsubscript{1-4}alkyl which may be unsubstituted or substituted with one or more fluorine atoms, or C\textsubscript{2-4}alkyl which may be unsubstituted or substituted with 1 or 2 groups selected from hydroxy and amino;
2) C₃₋₉ alkyl X² C(O)R¹¹ (wherein X² is as hereinbefore defined and R¹¹ represents -NR¹³ R¹⁴ or -OR¹⁵ (wherein R¹³, R¹⁴ and R¹⁵ which may be the same or different are each C₁₋₉ alkyl or C₁₋₉ alkoxyethyl));
3) C₄₋₉ alkyl X³ R¹⁶ (wherein X³ is as hereinbefore defined and R¹⁶ is a group selected from C₁₋₉ alkyl, cyclopentyl, cyclohexyl, pyrrolidinyl, piperidinyl and tetrahydropyranyl which group is linked to X³ through a carbon atom and which C₁₋₉ alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C₁₋₉ alkoxy and which cyclopentyl, cyclohexyl, pyrrolidinyl or piperidinyl group may carry one substituent selected from oxo, hydroxy, halogeno, C₁₋₉ alkyl, C₁₋₉ hydroxyalkyl and C₁₋₉ alkoxy);
4) C₃₋₉ alkyl X⁴ C₃₋₉ alkyl X⁵ R²² (wherein X⁴ and X⁵ are as hereinbefore defined and R²² represents hydrogen or C₁₋₉ alkyl);
5) C₄₋₉ alkyl R¹³² (wherein R¹³² 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 C₄₋₉ alkyl through a carbon atom and which group may carry 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C₁₋₉ cyanoalkyl, C₁₋₉ alkyl, C₁₋₉ hydroxyalkyl, C₁₋₉ alkoxy, C₁₋₉ alkoxy alkyl and C₂₋₉ alkylsulphonyl(C₁₋₉ alkyl) or C₂₋₉ alkyl R¹³³ (wherein R¹³³ 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, C₁₋₉ cyanoalkyl, C₁₋₉ alkyl, C₁₋₉ hydroxyalkyl, C₁₋₉ alkoxy, C₁₋₉ alkoxy alkyl and C₁₋₉ alkyl sulphonyl(C₁₋₉ alkyl);
6) C₄₋₉ alkenyl R¹³⁴ (wherein R¹³⁴ represents R¹³² or R¹³³ as defined hereinbefore);
7) C₄₋₉ alkynyl R¹³⁴ (wherein R¹³⁴ represents R¹³² or R¹³³ as defined hereinbefore);
8) R²⁹ (wherein R²⁹ is as defined hereinbefore);
9) C₄₋₉ alkyl R²⁹ (wherein R²⁹ is as defined hereinbefore);
10) 1-R²⁹ prop-1-en-3-yl or 1-R²⁹ but-2-en-4-yl (wherein R²⁹ is as defined hereinbefore with the proviso that when R⁵ is 1-R²⁹ prop-1-en-3-yl, R²⁹ is linked to the alkenyl group via a carbon atom);
11) 1-R²⁹ prop-1-yn-3-yl or 1-R²⁹ but-2-yn-4-yl (wherein R²⁹ is as defined hereinbefore with the proviso that when R⁵ is 1-R²⁹ prop-1-yn-3-yl, R²⁹ is linked to the alkenyl group via a carbon atom);
12) C₁₋₉ alkyl X⁶ R²⁹ (wherein X⁶ and R²⁹ are as defined hereinbefore);
13) 1-(R²⁹ X⁷) but-2-en-4-yl (wherein X⁷ and R²⁹ are as defined hereinbefore);
14) 1-(R²⁹X⁸)but-2-yn-4-yl (wherein X⁸ and R²⁹ are as defined hereinbefore);
15) C₃₅ alkylX⁶C₁₃ alkylR²⁹ (wherein X⁹ and R²⁹ are as defined hereinbefore);
16) R²⁸ (wherein R²⁸ is as defined hereinbefore);
17) C₃₅ alkylX⁶C₁₃ alkylR²⁸ (wherein X⁹ and R²⁸ are as defined hereinbefore);
18) C₃₅ 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, C₁₃ alkylamino, N,N-di(C₁₃ alkyl)amino, aminosulphonyl, N-C₁₃ alkylaminosulphonyl and N,N-di(C₁₃ alkyl)aminosulphonyl;
19) C₃₅ 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, C₁₃ alkylamino, N,N-di(C₁₃ alkyl)amino, aminosulphonyl, N-C₁₃ alkylaminosulphonyl and N,N-di(C₁₃ alkyl)aminosulphonyl;
20) C₃₅ alkenylX⁹C₁₃ alkylR²⁸ (wherein X⁹ and R²⁸ are as defined hereinbefore); and
21) C₃₅ alkynylX⁹C₁₃ alkylR²⁸ (wherein X⁹ and R²⁸ are as defined hereinbefore]).

According to another aspect of the present invention preferably R² represents hydroxy, halogeno, nitro, trifluoromethyl, C₁₃ alkyl, cyano, amino or R²X¹ - [wherein X¹ is as hereinbefore defined and R² is selected from one of the following nineteen groups:

1) C₁₃ alkyl which may be unsubstituted or substituted with one or more fluorine atoms, or C₂₅ 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) C₂₅ alkylX¹R¹⁶ (wherein X¹ is as defined hereinbefore and R¹⁶ is a group selected from C₁₃ alky1, cyclopentyl, cyclohexyl, pyrrolidinyl, piperidinyl and tetrahydropyranyl which group is linked to X¹ through a carbon atom and which C₁₃ alkyl group may bear 1 or 2 substituents selected from hydroxy, halogeno and C₁₃ alkoxy and which cyclopentyl, cyclohexyl, pyrrolidinyl or piperidinyl group may carry one substituent selected from oxo, hydroxy, halogeno, C₁₃ alkyl, C₁₃ hydroxyalkyl and C₁₃ alkoxy);

4) C₂₅ alkylX¹⁴C₂₅ alkylX¹'R²² (wherein X¹ and X¹ are as hereinbefore defined and R²² represents hydrogen or C₁₃ alkyl);
5) C_{12}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_{12}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_{1,3}alkoxyC_{1,3}alkyl and C_{1,3}alkyloxycarbonyl) 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_{1,3}alkoxyC_{1,3}alkyl and C_{1,3}alkyloxycarbonyl;)

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_{1,4}alkylX^{6}R^{29} (wherein X^{6} and R^{29} are as defined hereinbefore;)
11) 1-(R^{6}X^{7})but-2-en-4-yl (wherein X^{7} and R^{29} are as defined hereinbefore;)
12) 1-(R^{7}X^{9})but-2-yn-4-yl (wherein X^{9} and R^{29} are as defined hereinbefore;)
13) ethylX^{7}methylR^{29} (wherein X^{9} and R^{29} are as defined hereinbefore;)
14) R^{28} (wherein R^{28} is as defined hereinbefore;)
15) ethylX^{6}C_{1,4}alkylR^{28} (wherein X^{9} and R^{28} are as defined hereinbefore;)
16) C_{2,3}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_{2,3}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}alkenyloxycarbonylX^{9}C_{1,3}alkylR^{28} (wherein X^{9} and R^{28} are as defined hereinbefore; and
19) C_{2,3}alkenyloxycarbonylX^{6}C_{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^{6}X^{7} - [wherein X^{7} is as hereinbefore defined and R^{6} represents methyl, ethyl, benzyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2-hydroxyethyl, 3-hydroxypropyl,
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2-methoxyethyl, 3-methoxypropyl, 2-(methylsulphonyl)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)ethyl)piperidino)ethyl, 3-((2-methylsulphonyl)ethyl)piperidino)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, (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-methylsulphonyl)ethyl)piperidin-3-yl)methyl, (1-(2-methylsulphonyl)ethyl)piperidin-4-yl)methyl, 2-((2-methylsulphonyl)ethyl)piperidin-3-yl)ethyl, 2-((2-methylsulphonyl)ethyl)piperidin-4-yl)ethyl, 3-((2-methylsulphonyl)ethyl)piperidin-3-yl)propyl, 3-((2-methylsulphonyl)ethyl)piperidin-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-pyridyl)oxy)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-yl)sulphonyl)-N-methyl)amino)ethyl, 2-((N-(3-thiomorpholinopropyl)sulphonyl)-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-yl)oxy)ethyl, 3-(tetrahydropyran-4-yl)oxy)propyl, 2-((2-pyrrolicin-1-yl)ethyl)carbamoyl)vinyl or 3-((2-(pyrrolicin-1-yl)ethyl)carbamoyl)prop-2-en-1-yl].

According to another aspect of the present invention particularly R² represents C₁₃:

alkyl, amino or R²X₁- [wherein X₁ is as hereinbefore defined and R² 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)ethyl)piperidino)ethyl, 3-((2-methylsulphonyl)ethyl)piperidino)propyl, 2-(piperidin-3-yl)methyl, piperidin-4-yl)methyl, 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, 2-(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, 2-(ethylpiperidin-3-yl)ethyl, 2-(ethylpiperidin-4-yl)ethyl, 3-(ethylpiperidin-3-yl)propyl, 3-(ethylpiperidin-4-yl)propyl, (2-methoxyethyl)piperidin-3-
(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-dioxaethorpholin)oxime, 3-(1,1-dioxaethorpholin)oxime, 2-(methoxyethoxy)ethyl, 2-(4-methylpiperazin-1-yl)ethyl, 3-(4-methylpiperazin-1-yl)propyl, 3-(methylsulphonyl)propyl, 3-(methylsulphonyl)propyl, 2-(5-methyl-1,2,4-triazol-1-yl)ethyl, morpholino, 2-((N-(1-methylimidazol-4-yl)sulphonyl)-N-methylamino)ethyl, 2-((N-(3-morpholinopropyl)sulphonyl)-N-methylamino)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 R² represents C₁₃alkyl, amino or R⁵X¹ - [wherein X¹ is as hereinbefore defined and R³ represents ethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, 2-(methylsulphonyl)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-morpholinooethyl, 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-(methylsulphonyl)ethylpiperidino)ethyl, 3-((2-methoxysulphonyl)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-ylmethyl, (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-methylsulphonyl)ethyl)piperidin-3-yl)methyl, (1-((2-methylsulphonyl)ethyl)piperidin-4-yl)methyl, 2-((2-methylsulphonyl)ethyl)piperidin-3-yl)ethyl, 2-((2-methylsulphonyl)ethyl)piperidin-4-yl)ethyl, 3-((2-methylsulphonyl)ethyl)piperidin-3-yl)propyl, 3-((2-methylsulphonyl)ethyl)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-(methylsulphiny1)propyl, 3-(methylsulphony1)propyl, morpholino, 2-((N-(3-morpholinopropyl)sulphony1)-N-methylamino)ethyl, 2-((N-methyl-N-4-pyridyl)amino)ethyl, 3-(4-oxomorpholino)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-yl)oxy)ethyl, 3-(tetrahydropyran-4-yl)oxy)propyl, 2-((2-pyrroloidin-1-yl)ethyl)carbamoyl)vinyl or 3-((2-pyrroloidin-1-yl)ethyl)carbamoyl)prop-2-en-1-yl].

According to another embodiment of the present invention in another aspect R² represents methoxy, 2-methoxyethoxy, 2-(2-methoxyethoxy)ethoxy, 3-methoxypropoxy, 2-methylsulphonyl ethoxy, 3-methylsulphonyl propoxy, benzyl oxy, 2-(tetrahydropyran-4-yl)oxy)ethoxy, 3-(tetrahydropyran-4-yl)oxy)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-ylmethoxy, 1-cyanomethylpiperidin-4-ylmethoxy, 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-ylmethoxy, (2-methoxyethyl)piperidin-4-ylmethoxy, 2-(N-(2-methoxyethyl)-N-methylamino)ethoxy, 4-(pyrroloidin-1-yl)but-2-en-1-yloxy, 2-(2-oxopyrroloidin-1-yl)ethoxy, 3-(2-oxopyrroloidin-1-yl)propoxy, (pyrroloidin-2-yl)methoxy, 2-(pyrroloidin-1-yl)ethoxy, 3-(pyrroloidin-1-yl)propoxy, 2-(2-(pyrroloidin-1-yl)ethoxy)ethoxy, 2-oxo-tetrahydro-2H-pyrroloidin-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-methylsulphonyl)ethyl)piperidin-3-ylmethoxy, 1-(2-
methylsulphonylethyl)piperidin-4-ylmethoxy, 2-((2-methylsulphonyl)ethyl)piperidino)ethoxy, 3-((2-methylsulphonyl)ethyl)piperidino)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-(methyl)piperidin-3-yl)ethoxy, 2-(methyl)piperidin-4-yl)ethoxy, 3-(methyl)piperidin-3-yl)propoxy, 3-(methyl)piperidin-4-yl)propoxy, 2-(ethyl)piperidin-3-yl)ethoxy, 2-(ethyl)piperidin-4-yl)ethoxy, 3-(ethyl)piperidin-3-yl)propoxy, 3-(ethyl)piperidin-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-methylsulphonyl)ethyl)piperidin-3-yl)ethoxy, 2-((2-methylsulphonyl)ethyl)piperidin-4-yl)ethoxy, 3-((2-methylsulphonyl)ethyl)piperidin-3-yl)propoxy, 3-((2-methylsulphonyl)ethyl)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-methylpiperaizin-1-yl)ethoxy)ethoxy, 3-(2-(4-methylpiperaizin-1-yl)ethoxy)ethoxy, 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 R² substituents is R²X⁻¹ the substituent R²X⁻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 R² substituents is at the 6-position of the quinazoline ring it is preferably hydrogen, halogeno, C₁₃alkyl, trifluoromethyl, C₁₃alkoxy, C₁₃alkylsulphanyl or -NR³R⁴ (wherein R³ and R⁴ are as defined hereinbefore).

When one of the R² substituents is at the 6-position of the quinazoline ring it is more preferably C₁₃alkoxy, especially methoxy.

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

ring C, R¹, R², n and Z are as defined hereinbefore with the provisos that R² is not hydrogen and that Z is not CH₂ or a direct bond; and

R²a represents hydrogen, halogeno, C₁₃alkyl, trifluoromethyl, C₁₃alkoxy, C₁₃alkylsulphanyi,
-NR³aR⁴a (wherein R³a and R⁴a, which may be the same or different, each represents hydrogen or C₁₃alkyl), or R⁴a(CH₂)₂aX¹a (wherein R⁴a is an azetidinyl or 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, cyano, C₁, a cyanoalkyl, C₁₄alkyl, C₁₄hydroxyalkyl, C₁₄alkoxy, C₁₄alkoxyC₁₄alkyl, C₁₄alkylsulphonylC₁₄alkyl, C₁₄alkoxycarbonyl, C₁₄aminoalkyl, C₁₄alkylamino, di(C₁₄alkyl)amino, C₁₄alkylaminoC₁₄alkyl, di(C₁₄alkyl)aminoC₁₄alkyl, C₁₄alkylaminoC₁₄alkoxy, di(C₁₄alkyl)aminoC₁₄alkoxy and a group -(O)-(C₁₄alkyl)₄ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is an azetidinyl or a 5-6-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 C₁₄alkyl)], za is an integer from 0 to 4 and X¹a represents a direct bond, -O-, -CH₂-, -S-, -SO₂-, -SO₂-, -NR³a(C)O-, -C(O)NR⁷a-, -SO₂NR³a-, -NR³aSO₂- or -NR³aSO₂- (wherein R⁶a, R⁷a, R⁸a, R⁹a, R¹₀a each independently represents hydrogen, C₁₃alkyl or C₁₃alkoxyC₂,3alkyl));

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:
[wherein:

ring C, R¹, R², n and Z are as defined hereinbefore with the provisos that R² is not hydrogen and that Z is not CH₂ or a direct bond; and

R²ⁿ represents hydrogen, halogeno, C₁₋₃ alkyl, trifluoromethyl, C₁₋₃ alkoxy, C₁₋₃ alkylsulphonyl, -NR²ⁿR⁴ⁿ (wherein R³ⁿ and R⁴ⁿ, which may be the same or different, each represents hydrogen or C₁₋₃ alkyl), or R⁵ⁿ(CH₂)ₓXⁿ (wherein R⁵ⁿ 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, C₁₋₃ alkyl, C₁₋₃ hydroxyalkyl and C₁₋₃ alkoxy, za is an integer from 0 to 4 and Xⁿ represents a direct bond, -O-, -CH₂-, -S-, -SO₂-, -NR⁶ⁿC(O)-, -C(O)NR⁷ⁿ-, -SO₂NR⁸ⁿ-, -NR⁹ⁿSO₂⁻ or -NR¹⁰ⁿ⁻ (wherein R⁶ⁿ, R⁷ⁿ, R⁸ⁿ, R⁹ⁿ and R¹⁰ⁿ each independently represents hydrogen, C₁₋₃ alkyl or C₁₋₃ alkoxyC₂₋₃ 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 Xⁿ represents -O-, -S-, -NR⁶ⁿC(O)-, -NR⁹ⁿSO₂⁻ or -NR¹⁰ⁿ⁻ (wherein R⁶ⁿ, R⁹ⁿ and R¹⁰ⁿ each independently represents hydrogen, C₁₋₃ alkyl or C₁₋₃ alkoxyethyl).

Preferably Xⁿ represents -O-, -S-, -NR⁶ⁿCO-, -NR⁹ⁿSO₂⁻ (wherein R⁶ⁿ and R⁹ⁿ each independently represents hydrogen or C₁₋₃ alkyl) or NH.

More preferably Xⁿ represents -O-, -S-, -NR⁶ⁿCO⁻ (wherein R⁶ⁿ represents hydrogen or C₁₋₃ alkyl) or NH.

Particularly Xⁿ represents -O- or -NR⁶ⁿCO⁻ (wherein R⁶ⁿ represents hydrogen or C₁₋₃ alkyl), more particularly -O- or -NHCO-, especially -O-.

Preferably za is an integer from 1 to 3.
Preferably $R^{3a}$ 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, $C_{1-3}$alkyl$C_{1-3}$alkoxy$C_{1-3}$alkyl, $C_{1-3}$alkyl$sulphonyl$C_{1-3}$alkyl, $C_{1-3}$alkyloxycarbonyl, $C_{1-3}$alkylamino, di($C_{1-3}$alkyl)$amino$, $C_{1-3}$alkyl$aminoC_{1-3}$alkyl, di($C_{1-3}$alkyl)$aminoC_{1-3}$alkyl, $C_{1-3}$alkyl$aminoC_{1-3}$alkoxy, $C_{1-3}$alkyl$aminoC_{1-3}$alkoxy and a group $\text{(-O-)}_{f}(C_{1-3}$alkyl)$_g$, ring$D$ (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 $R^{3a}$ 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, $C_{1-3}$alkyloxycarbonyl, $C_{1-3}$alkylamino, di($C_{1-3}$alkyl)$amino$, $C_{1-3}$alkyl$aminoC_{1-3}$alkyl, $C_{1-3}$alkyl$aminoC_{1-3}$alkoxy, $C_{1-3}$alkyl$aminoC_{1-3}$alkoxy and a group $\text{(-O-)}_{f}(C_{1-3}$alkyl)$_g$, ring$D$ (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 $R^{3a}$ is pyrrolidinyl, piperazinyl, piperidinyl, azetidinyl, morpholino or thiomorpholino which group may bear 1 or 2 substituents selected from a group $\text{(-O-)}_{f}(C_{1-3}$alkyl)$_g$, ring$D$ (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 $R^{3a}$ is a group selected from pyrrolidinyl, piperazinyl, piperidinyl, morpholino and thiomorpholino which group may carry 1 or 2 substituents selected from oxo, hydroxy, halogeno, $C_{1-3}$alkyl, $C_{1-3}$hydroxyalkyl and $C_{1-3}$alkoxy.

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

More preferably $R^{2a}$ is methyl, ethyl, methoxy, ethoxy or $R^{3a}(CH_{2})_{za}X^{1a}$ (wherein $R^{3a}$ is a group selected from pyrrolidinyl, piperazinyl, piperidinyl, morpholino and thiomorpholino
which group may carry 1 or 2 substituents selected from oxo, hydroxy, halogeno, C₁-alkyl, C₁₂-hydroxyalkyl and C₁₂-alkoxy, X₁a is -O-, -S-, -NR₆C(O)-, -NR₆SO₂- (wherein R₆ and R₆a each independently represents hydrogen or C₁₂-alkyl) or NH, and za is an integer from 1 to 3).

Particularly R₂a represents methyl, methoxy or R₅(CH₂)₉aX₁a (wherein R₅, X₁a and za are as defined hereinbefore).

More particularly R₂a represents methoxy.

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

![Chemical Structure Image]

(Ib)

[wherein:

ring C, R¹, R², R₆a and n are as defined hereinbefore with the proviso that R² 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:
[wherein:
ring C, R₁, R², R²a, Zb and n are as defined hereinbefore with the proviso that R² is not hydrogen and excluding the compounds:
6,7-dimethoxy-4-(1-naphthylsulphanil)quinazoline, 6,7-dimethoxy-4-(2-naphthylsulphanil)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:
[wherein:
ring C, R¹, R², R²a, Zb and n are as defined hereinbefore with the proviso that R² does not have any of the following values:
hydrogen, substituted or unsubstituted C₁₋₅ alkyl, halogeno or phenoxy and excluding the compounds:
6,7-dimethoxy-4-(1-naphthylsulphonyl)quinazoline, 6,7-dimethoxy-4-(2-naphthylsulphonyl)quinazoline, 6,7-dimethoxy-4-(1-naphthoxy)quinazoline and 6,7-dimethoxy-4-(2-naphthoxy)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:

![Chemical Structure](image)

(IIb)

[wherein:
ring C, R¹, R², R²a, Zb and n are as defined hereinbefore with the proviso that R² does not have any of the following values:
hydrogen, substituted or unsubstituted C₁₋₅ alkyl, halogeno, C₁₋₅ alkoxy, C₂₋₅ alkenyl, phenoxy or phenylC₁₋₅ 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-naphthoxy)quinazoline,
6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)-4-(quinolin-7-ylmethoxy)quinazoline,
7-(3-(1,1-dioxothiomorpholino)propoxy)-6-methoxy-4-(quinolin-7-ylmethoxy)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-morpholinoproxy)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-(methoxythoxy)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-y1)methoxy)quinazoline,
4-(indol-5-yloxy)-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline,
7-(3-N,N-dimethylaminoproxy)-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-piperidinoproxy)-4-(quinolin-7-yloxy)quinazoline,
4-(2-methylindol-5-yloxy)-7-(3-morpholinoproxy)quinazoline,
4-(2-methylindol-5-yloxy)-7-(2-(piperidin-1-yl)ethoxy)quinazoline,
4-(2-methylindol-5-yloxy)-7-(2-(1H-1,2,4-triazol-1-yl)ethoxy)quinazoline,
6-methoxy-7-(3-piperidinoproxy)-4-(6-trifluoromethylindol-5-yloxy)quinazoline,
7-(3-(methylsulphonylpropoxy)-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,
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-(1H-1,2,4-triazol-1-yl)ethoxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(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-yethyl)carbamoyl)vinyl)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(3-(4-methylpiperazin-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-ylmethoxy)ethoxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(N,N-methylsulphonylamino)ethoxy)quinazoline,
7-(2-(1-(2-cyanoethyl)piperidin-4-ylmethoxy)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-pyridyl)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-pyridyl)ethoxy)quinazoline,
4-(indol-5-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
(2R)-6-methoxy-(2-methyl-1H-indol-5-yloxy)-7-(2-hydroxy-3-piperidinopropoxy)quinazoline,
(5R)-6-methoxy-(2-methyl-1H-indol-5-yloxy)-7-(2-oxopyrrolidin-5-ylmethoxy)quinazoline,
4-(4-bromoindol-5-yl)oxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(1-(2-(pyrrolidin-1-yl)ethyl)piperidin-4-ylmethoxy)quinazoline,
(2R)-7-(2-hydroxy-3-(pyrrolidin-1-yl)propoxy)-4-(indol-5-yl)oxy)-6-methoxyquinazoline,
(2R)-7-(2-hydroxy-3-morpholinopropoxy)-4-(indol-5-yl)oxy)-6-methoxyquinazoline,
(2R)-7-(2-hydroxy-3-piperidinopropoxy)-4-(indol-5-yl)oxy)-6-methoxyquinazoline,
(2S)-7-(2-hydroxy-3-((N,N-diisopropyl)amino)propoxy)-4-(indol-5-yl)oxy)-6-
methoxyquinazoline,
(2R)-7-(2-hydroxy-3-piperidinopropoxy)-4-(indol-5-yl)oxy)-6-methoxyquinazoline,
(2R)-7-(2-hydroxy-3-piperidinopropoxy)-6-methoxy-4-(3-methylindol-5-yl)oxy)quinazoline,
(2R)-7-(2-hydroxy-3-(pyrrolidin-1-yl)propoxy)-6-methoxy-4-(3-methylindol-5-
yl)oxy)quinazoline,
(2R)-7-(2-hydroxy-3-(4-methylpiperazin-1-yl)propoxy)-6-methoxy-4-(2-methylindol-5-
yl)oxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yl)oxy)-7-(1-(2-morpholinoethyl)piperidin-4-
yl)methoxy)quinazoline,
4-(3-fluoro-quinolin-7-yl)oxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,
4-(3-fluoro-quinolin-7-yl)oxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline,
6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)-4-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)quinazoline,
(2S)-6-methoxy-(2-methyl-1H-indol-5-yl)oxy)-7-(2-hydroxy-3-piperidinopropoxy)quinazoline,
and
4-(6-fluoro-2-methylindol-5-yl)oxy)-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-yl)oxy)-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline,
4-(4-fluorooindol-5-yl)oxy)-6-methoxy-7-(1-methylpiperidin-4-yl)ethoxy)quinazoline,
4-(4-fluorooindol-5-yl)oxy)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline,
4-(6-fluorooindol-5-yl)oxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline,
4-(4-fluorooindol-5-yl)oxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline,
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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,
5
4-(4-fluoroindol-5-yloxy)-6-methoxy-7-(2-(1-methylpiperidin-4-yl)ethoxy)quinazoline,
(2R)-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-naphthyl)quinazoline,
4-(1H-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-1H-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-(1H-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-2H-4H-1,4-benzoazin-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-3H-indazol-1-yl)quinazoline,
4-(2,3-dihydro-1H-indan-5-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
6-methoxy-4-(2-methyl-4-oxo-4H-chromen-7-yloxy)-7-((1-methylpiperidin-4-yl)methoxy)quinazoline,
6-methoxy-4-(4-methyl-4H-1,4-benzoazin-6-yloxy)-7-((1-methylpiperidin-4-yl)methoxy)quinazoline,
6-methoxy-4-(2-methyl-4-oxo-4H-chromen-7-yloxy)-7-((3-pyrrolidin-1-yl)propoxy)quinazoline,
6-methoxy-4-(4-methyl-3,4-dihydro-2H-1,4-benzoazin-6-yloxy)-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,
7-benzylolxy-6-methoxy-4-(quinolin-7-yloxy)quinazoline,
4-(2,4-dimethylquinolin-7-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,
5 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-2H-4H-1,4-benzoazin-6-yloxy)quinazoline,
10 7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,
6,7-dimethoxy-4-(2-methyl-1H-benzimidazol-5-yloxy)quinazoline,
and salts thereof especially hydrochloride salts thereof and prodrugs thereof for example esters, amides and sulphones, 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-naphthyl)oxy)-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,
30 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-2H-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-methylsulphonyl)propoxy)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-methylsulphonyl)propoxy)-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-naphthoxy)quinazoline,
7-(3-(1,1-dioxothiomorpholin-1-yl)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-yl)oxy)-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-(((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-dioxothiomorpholin)propoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(1-(methylpiperazin-4-y1)ethoxy)ethoxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(2-(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-1H-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-ylxy)-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$_2$alkanoyl is ethanoyl and refers to CH$_2$C=O, C$_i$alkanoyl 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-butylnyl 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 R² has a value of substituted or unsubstituted C₁₅ alkyl, R² has been selected from C₁₃ alkyl or from a group R³X¹ wherein X¹ is a direct bond or -CH₂- and R³ is C₁₅ 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 X¹ is, for example, a group of formula -NR⁶C(O)-, it is the nitrogen atom bearing the R⁶ group which is attached to the quinazoline ring and the carbonyl (C(O)) group is attached to R³, whereas when X¹ is, for example, a group of formula -C(O)NR⁷-, it is the carbonyl group which is attached to the quinazoline ring and the nitrogen atom bearing the R⁷ group is attached to R⁵. A similar convention applies to the other two atom X¹ linking groups such as -NR³SO₂- and -SO₂NR⁶-. When X¹ is -NR¹⁰- it is the nitrogen atom bearing the R¹⁰ group which is linked to the quinazoline ring and to R⁵. An analogous convention applies to other groups. It is further to be understood that when X¹ represents -NR¹⁰- and R¹⁰ is C₁₃alkoxyC₂₃alkyl it is the C₂₃alkyl moiety which is linked to the nitrogen atom of X¹ 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 R² is, for example, a group of formula C₁₃alkylX⁹C₁₃alkylR²⁹, it is the terminal C₁₃alkyl moiety which is linked to X¹, similarly when R² is, for example, a group of formula C₂₃alkenylR²⁸ it is the C₂₃alkenyl moiety which is linked to X¹ and an analogous convention applies to other groups. When R⁵ is a group 1-R²⁸prop-1-en-3-yl it is the first carbon to which the group R²⁹ is attached and it is the third carbon which is linked to X¹ 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 R² is, for example, R²⁸ and R²⁸ is a pyrrolidinyl ring which bears a group -(O-)(C₁₃alkyl)ₖringD, it is the -O- or C₁₃alkyl 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 R²⁹ carries a C₁₃aminoalkyl substituent it is the C₁₃alkyl moiety which is attached to R²⁹ whereas when R²⁹ carries a C₁₃alkylamino substituent it is the amino moiety which is attached to R²⁹ and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that when R²⁸ carries a C₁₃alkoxyC₁₃alkyl substituent it is the C₁₃alkyl moiety which is attached to R²⁸ 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:
(wherein $R^2$ and $m$ are as defined hereinbefore and $L^1$ is a displaceable moiety), with a compound of the formula IV:

$$
(\text{III})
$$

(wherewith $n$ 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), arylx, 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)amidate, potassium amide or potassium bis(trimethylsilyl)amidate. 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 sulphonylic 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 R² is R⁵X¹ wherein R⁵ is as defined hereinbefore and X¹ is -O-, -S-, -OC(O)- or -NR⁹-

(therein R⁹ independently represents hydrogen, C₃,₅alkyl or C₃,₅alkoxyC₂,₃alkyl) 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:

![Chemical Structure Diagram]

(V)

(therein ring C, Z, R¹, R² and n are as hereinbefore defined and X¹ is as hereinbefore defined in this section and s is an integer from 0 to 2) with a compound of formula VI:

![Chemical Structure Diagram]

(VI)

(therein R⁵ and L¹ are as hereinbefore defined), L¹ is a displaceable moiety for example a halogeno or sulphonyloxy group such as a bromo, methanesulphonyloxy or toluene-4-sulphonyloxy group, or L¹ 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 \( R^5 X^1 \) wherein \( R^3 \) 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:

![Chemical Structure Diagram]

(VII)

with a compound of the formula VIII:

\[
R^5 X^1 - H
\]

(VIII)

(wherein \( L^1, R^1, R^2, R^3, Z, n \) 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 \( R^5 X^1 \) wherein \( X^1 \) is as defined hereinbefore and \( R^3 \) is \( C_{1,3}\)alkyl\( R^{113} \), 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) \(X^{20}C_{1,3}\text{-alkyl}X^{3}R^{22}\) (wherein \(X^{20}\) represents -O-, -S-, -SO₂-, -NR\(^{118}\)C(O)-, -NR\(^{119}\)SO₂- or -NR\(^{120}\) (wherein \(R^{118}, R^{119}, \) and \(R^{120}\) which may be the same or different are each hydrogen, \(C_{1,3}\text{-alkyl}\) or \(C_{1,3}\text{-alkoxyC}_{2,3}\text{-alkyl}\) and \(X^{3}\) 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-, -SO₂-, -NR\(^{121}\)C(O)-, -NR\(^{122}\)SO₂- or -NR\(^{123}\) (wherein \(R^{121}, R^{122}, \) and \(R^{123}\) which may be the same or different are each hydrogen, \(C_{1,3}\text{-alkyl}\) or \(C_{1,3}\text{-alkoxyC}_{2,3}\text{-alkyl}\) and \(R^{29}\) is as defined hereinbefore); and

6) \(X^{22}C_{1,3}\text{-alkyl}R^{29}\) (wherein \(X^{22}\) represents -O-, -S-, -SO₂-, -NR\(^{124}\)C(O)-, -NR\(^{125}\)SO₂- or -NR\(^{126}\) (wherein \(R^{124}, R^{125}, \) and \(R^{126}\) each independently represents hydrogen, \(C_{1,3}\text{-alkyl}\) or \(C_{1,3}\text{-alkoxyC}_{2,3}\text{-alkyl}\) 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) \(X^{22}C_{1,4}\text{-alkyl}R^{28}\) (wherein \(X^{22}\) and \(R^{28}\) are as defined hereinbefore); and

9) \(R^{54}(C_{1,4}\text{-alkyl})_{q}(X^{9})_{r}R^{55}\) (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:

\[
\begin{align*}
\text{IX} & \\
& \\
& \\
& \\
& \\
& \\
& \\
& \\
& \\
& \\
& \\
\end{align*}
\]

(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:

\[
R^{113}\text{-H} \quad \text{(X)}
\]

(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 \((R^3)_n\) 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:
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:

(II)

(III)

(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 $-O$, $-S$, $-SO_2$, $-SO_3$, $-C(O)$, $-C(O)NR^7$, $-SO_2NR^8$- or $NR^{10}$- (wherein $R^2$, $R^8$
and R¹⁰ each independently represents hydrogen, C₁₃₃-alkyl or C₁₃₃-alkoxyC₂₃₃-alkyl), may for example also be prepared by the reaction of a compound of the formula XIII:

![Chemical structure](image)

(XIII)

(therein R² and s are as hereinbefore defined and X¹ 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:

![Chemical structure](image)

(XIV)

(therein R² and m, are as hereinbefore defined, and A¹ is an hydroxy, alkoxy (preferably C₁₃₃-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 A¹ 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 A¹ 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-C₁₄₄alkoxymethane, 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:

```
(R²)m -N²⁺

O

O

A¹
```

(XV)

(wherein R², m and A¹ 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:

\[
\begin{align*}
\text{(XVI)} \\
\end{align*}
\]

(therein \(R^2, s, L^1\) 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 \(R^2X^1\) and wherein \(X^1\) is \(-\text{O}-, -\text{S}-, -\text{SO}_2-, -\text{C(O)}-, -\text{C(O)}\text{NR}^7-, -\text{SO}_2\text{NR}^8-\) or \(-\text{NR}^{10}-\) (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:

\[
\begin{align*}
\text{(XVII)} \\
\end{align*}
\]
(wherein R², s and A¹ are as hereinbefore defined and X¹ 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 R² is R²X¹ and wherein X¹ is -CH₂- may be prepared for example as described above from a compound of the formula XV (in which R² is -CH₃) or XIII (in which HX¹ is -CH₃), by radical bromination or chlorination to give a -CH₂Br or -CH₂Cl group which may then be reacted with a compound of the formula R⁵-H under standard conditions for such substitution reactions.

The compounds of formula III and salts thereof wherein at least one R² is R²X¹ and wherein X¹ is a direct bond may be prepared for example as described above from a compound of the formula XI, wherein the R² 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 R² is R²X¹ and wherein X¹ is -NR⁶C(O)- or -NR⁶SO₂- may be prepared for example from a compound of the formula XIII in which HX¹ is an -NHR⁶- or -NHR²- 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 R⁵COCl or R⁵SO₂Cl.

The compounds of formula III and salts thereof wherein at least one R² is R²X¹ and wherein X¹ is -O-, -S-, -SO₂-, -OC(O)-, -C(O)NR²-, -SO₂NR⁸- or -NR¹⁰- (wherein R², R⁸ and R¹⁰ each independently represents hydrogen, C₁₅alkyl or C₁₅alkoxyC₂₃alkyl), may also be prepared for example by reacting a compound of the formula XVIII:

![Diagram of compound XVIII](image)

(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:

\[
\begin{align*}
& \text{L}^2 \\
& \text{P}^1 \text{X}^1 \\
& (\text{R}^2)^s \\
& \text{H}
\end{align*}
\]

(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:
(wherein ring C, Z, R, R, P, n and s are as hereinbefore defined and X 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:

![Chemical structure](image)

(XXI)

(wherein R, s and each L are as hereinbefore defined and the L in the 4-position and the other L 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:

\[ L^1-C_1-alkyl-L^1 \]  

(XXII)

(wherein L 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 is -SO- or -SO- may be prepared by oxidation from the corresponding compound in which X is -S- or -SO- (when X is -SO- 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/PMFS (20mM Hepes pH7.5, 150mM sodium chloride, 10% v/v glycerol, 1% v/v Triton X100, 1.5mM magnesium chloride, 1mM ethylene glycol-bis(β-aminoethyl 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/PMFS 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 (PCS) 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% inhibition 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% CO₂. 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 nm/nm 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: \( V = l \times w \times \sqrt{l \times w} \times (\pi/6) \), 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 αvβ3 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 (for example N-acetylcolchinel-O-phosphate));

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene, iodoxifene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrozole, voroxole, 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-fluourouracil, 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, thiopeta); 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-acetylcolchinel-O-phosphate (Example 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.
The invention also relates to the use of the compounds, salts or compositions of the invention for the production of an antiangiogenic and/or vascular permeability reducing effect or an anticancer effect in a warm-blooded animal such as a human.

The invention also relates to a commercial package comprising a compound, salt or composition of the invention and associated therewith instructions for the use thereof as defined above.

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 standardization 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,

(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-morpholinopropanoxy)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-morpholinopropanyl)-4-(quinolin-6-yloxy)quinazoline** (163mg, 55%).

1H NMR Spectrum: (DMSO-d₆) 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:

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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-Benzylloxy-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); 7.63(s, 1H)
MS (ESI): 359 (MH$^+$)

7-Benzylloxy-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: (DMSO$_d_6$) 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-morpholinopropionate (37.91g, 77%) as an oil.

$^1$H NMR Spectrum: (DMSO$_d_6$) 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-phenoxiquinazoline (25.27g, 0.1mol) and 1-chloro-3-morpholinopropionate (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-phenoxiquinazoline (31.4g, 84%) was collected by filtration as a yellow crystalline solid.

$^1$H NMR Spectrum: (DMSO$_d_6$) 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-phenoxiquinazoline (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: (DMSO$_d_6$) 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 azetroped 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 (MgSO₄). 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.

¹H NMR Spectrum: (CDCl₃) 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%).

¹H NMR Spectrum: (DMSO-d₆) 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

C₂₃H₂₀N₄O₄ 0.25H₂O 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 (MgSO₄) 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-naphthylcloxy)quinazoline (194mg, 65%).

¹H NMR Spectrum: (DMSO) δ 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:

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</table>

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-ylxylo)-7-(3-morpholinopropoxy)quinazoline (175mg, 57%).

¹H NMR Spectrum: (DMSO) δ 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:

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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%).

\[ \text{C}_25\text{H}_26\text{N}_4\text{O}_5\text{S} \cdot 0.25\text{H}_2\text{O} \]

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<td>N</td>
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The starting material was prepared as follows:

7-Benzyl-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-benzyl-6-methoxyquinazoline.

A mixture of the crude 7-benzyl-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-fluorophenoxo)-6-methoxyquinazoline (23.2g, 76%).

1H NMR Spectrum: (DMSO_d6) 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-Benzylloxy-4-(4-chloro-2-fluorophenoxo)-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-fluorophenoxo)-7-hydroxy-6-methoxyquinazoline (21.8g). This was used without further purification in the next step.

1H NMR Spectrum: (DMSO_d6) 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%).

1H 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-fluorophenoxo)-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-fluorophenoxo)-7-(3-(1,1-dioxothiomorpholino)propoxy)-6-methoxyquinazoline (5.4g, 70%). This was used without further purification in the next step.

1H NMR Spectrum: (DMSO_d6) 1.86(m, 2H); 2.65(t, 2H); 2.92(m, 4H); 3.08(m, 4H); 3.97(s,
- 95 -

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:

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C_{22}H_{23}N_7ClF_2O_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 (MgSO₄), 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.

¹H NMR Spectrum: (DMSO-d₆) 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:

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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-methylpiperdin-3-yl)methoxy)-4-(quinolin-7-yloxy)quinazoline (149mg, 61%).

\(^1\)H NMR Spectrum: (DMSO\(_d_6\)) 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\(_{29}\)N\(_3\)O\(_3\) 0.3H\(_2\)O Requires C 68.9 H 6.2 N 12.8%

10 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 drop wise 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 (Mg\(_2\)CO\(_3\)) and the solvent removed by evaporation to give (\(R\))-ethyl 1-methylpiperidine-3-carboxylate (4.51g, 73%) as a colourless oil.

15 MS - ESI: 172 [MH\(^+\)]

A solution of (\(R\))-ethyl 1-methylpiperidine-3-carboxylate (5.69g, 33mmol) in ether (20ml) was added drop wise 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\(^\circ\)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-methylpiperdin-3-yl)methanol (4.02g, 94%) as a colourless oil.

\(^1\)H NMR Spectrum: (DMSO\(_d_6\)) 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)

20 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%).

^1H NMR Spectrum: (DMSO_d6) 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.

^1H NMR Spectrum: (DMSO_d6) 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 (MgSO₄). 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.

¹H NMR Spectrum: (DMSO₆₆) 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%).

¹H NMR Spectrum: (DMSO₆₆, CF₃CO₂D) 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%).

^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]^+

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%).

^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: (DMSO\(_d_6\), CF\(_3\)CO\(_2\)D) 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: (DMSO\(_d_6\), CF\(_3\)CO\(_2\)D) 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 pH 8 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: (DMSO$_d_6$, CF$_3$CO$_2$D) 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-yl)oxy)quinazoline (82mg, 88%).

$^1$H NMR Spectrum: (DMSO$_d_6$) 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 (MgSO₄) and evaporated to give ethyl 4-(1-tert-butyloxycarboxyloxyethyl)piperidinecarboxylate (48g, 98%).

¹H NMR Spectrum: (CDCl₃) 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-butyloxycarboxyloxyethyl)piperidinecarboxylate (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 (MgSO₄) and evaporated to give 4-hydroxymethyl-1-tert-butyloxycarbonylpiperidine (36.3g, 89%).

¹H NMR Spectrum: (CDCl₃) 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 (11) 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 (MgSO₄) and evaporated to give 4-(4-methylphenylsulphonyloxyethyl)-1-tert-butyloxycarbonylpiperidine (76.7g, 85%).
- 104 -

1H NMR Spectrum: (CDCl₃) 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-butoxycarbonylpiperidine (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 (MgSO₄) 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-butoxycarbonylpiperidin-4-ylmethoxy)benzoate (35g, 89%).

m.p. 81-83°C

1H NMR Spectrum: (CDCl₃) 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:

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<td>C 63.2 H 8.0 N 3.5%</td>
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To a solution of ethyl 3-methoxy-4-(1-tert-butoxycarbonylpiperidin-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.).

1H NMR Spectrum: (DMSO-d₆) 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%).

1H NMR Spectrum: (DMSO-d₆) 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 (MgSO₄), 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

1H NMR Spectrum: (CDCl₃) 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

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,
- 106 -

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%).

1H NMR Spectrum: (DMSO, ) 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 (MgSO₄) and evaporated to give 4-chloro-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (2.9g, 98%).

1H NMR Spectrum: (DMSO, ) 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-yl)oxy)-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (137mg, 79%).

1H NMR Spectrum: (DMSO, ) 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)
Example 12

To a solution of 4-chloro-6-methoxy-7-((1-(2-methylsulphonylethyl)piperidin-4-yl)methoxy)quinazoline (115mg, 0.28mmol) and 7-hydroxyquinoline (50mg, 0.33mmol) in DMF (1.5ml) was added potassium carbonate (60mg, 0.42mmol). The mixture was stirred for 2 hours at 100°C. After cooling, and removal of the volatiles by evaporation, the residue was partitioned between ethyl acetate and water. The organic layer was washed with water, brine, dried (MgSO₄) and evaporated. The residue was purified by column chromatography eluting with ethylacetate/methylene chloride/methanol (1/1/0 followed by 40/50/10 and 0/9/1). After removal of the volatiles by evaporation, the residue was triturated with pentane, filtered and dried under vacuum to give 6-methoxy-7-((1-(2-methylsulphonylethyl)piperidin-4-yl)methoxy)-4-(quinolin-7-yl oxy)quinazoline (110mg, 76%).

1H NMR Spectrum: (DMSO-d₆) 1.3-1.45(m, 2H); 1.75-1.9(m, 3H); 2.05(t, 2H); 2.72(t, 2H);
2.95(d, 2H); 3.05(s, 3H); 3.35-3.45(m, 2H); 4.00(s, 3H); 4.1(d, 2H); 7.41(s, 1H); 7.57(dd,
1H); 7.62(dd, 1H); 7.65(s, 1H); 7.93(s, 1H); 8.12(d, 1H); 8.45(d, 1H); 8.55(s, 1H); 8.95(d,
1H)

MS (ESI): 523 [MH]^+

Elemental analysis:

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| C 61.3 | H 6.0 | N 10.6
| C 61.2 | H 5.9 | N 10.6%

The starting material was prepared as follows:

Sodium hydride (1.44g of a 60% suspension in mineral oil, 36mmol) was added in portions over 20 minutes to a solution of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (8.46g, 30mmol), (prepared as described for the starting material in Example 1), in DMF (70ml) and the mixture was stirred for 1.5 hours. Chloromethyl pivalate (5.65g, 37.5mmol) was added dropwise and the mixture stirred for 2 hours at ambient temperature. The mixture was diluted with ethyl acetate (100ml) and poured onto ice/water (400ml) and 2M hydrochloric acid (4ml). The organic layer was separated and the aqueous layer extracted with ethyl acetate, the combined extracts were washed with brine, dried (MgSO₄) and the solvent removed by evaporation. The residue was triturated with a mixture of ether and petroleum ether, the solid was collected by filtration and dried under vacuum to give 7-
benzyloxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (10g, 84%).

^1^H NMR Spectrum: (DMSO_d6) 1.11(s, 9H); 3.89(s, 3H); 5.3(s, 2H); 5.9(s, 2H); 7.27(s, 1H); 7.35(m, 1H); 7.47(t, 2H); 7.49(d, 2H); 7.51(s, 1H); 8.34(s, 1H)

A mixture of 7-benzyloxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-  
dihydroquinazolin-4-one (7g, 17.7mmol) and 10% palladium-on-charcoal catalyst (700mg) in  
ethyl acetate (250ml), DMF (50ml), methanol (50ml) and acetic acid (0.7ml) was stirred  
under hydrogen at atmospheric pressure for 40 minutes. The catalyst was removed by  
filtration and the solvent removed from the filtrate by evaporation. The residue was triturated  
with ether, collected by filtration and dried under vacuum to give 7-hydroxy-6-methoxy-3-  
((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (4.36g, 80%).

^1^H NMR Spectrum: (DMSO_d6) 1.1(s, 9H); 3.89(s, 3H); 5.89(s, 2H); 7.0(s, 1H); 7.48(s, 1H); 8.5(s, 1H)

A suspension of 7-hydroxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-  
dihydroquinazolin-4-one (6.12g, 20mmol) potassium carbonate (5.52g, 40mmol) in DMF  
(60ml) was stirred at ambient temperature for 30 minutes. 4-(4-  
Methylphenylsulphonyloxy)methyl)-1-tert-butyloxy carbonylpiperidine (8.86g, 24mmol),  
(prepared as described for the starting material in Example 10), was added and the mixture  
was stirred at 100°C for 2 hours. After cooling, the mixture was poured onto water/ice  
(400ml, 1:1) containing 2M hydrochloric acid (10ml). The precipitate was collected by  
filtration, washed with water and dried under vacuum over phophorus pentoxide. The solid  
was triturated in a mixture of ether/pentane (1:1), collected by filtration and dried to give 6-  
methoxy-3-((pivaloyloxy)methyl)-7-((1-tert-butyloxy carbonylpiperidin-4-yl)methoxy)-3,4-  
dihydroquinazolin-4-one (7.9g, 78.5%).

^1^H NMR Spectrum: (DMSO_d6) 1.1(s, 9H); 1.1-1.3(m, 2H); 1.42(s, 9H); 1.73(d, 2H); 1.93-  
2.1(br s, 1H); 2.65-2.9(br s, 2H); 3.9(s, 3H); 3.9-4.1(m, 4H); 5.9(s, 2H); 7.2(s, 1H); 7.5(s, 1H); 8.35(s, 1H)

MS (ESI): 526 [MNa]+

A solution of 6-methoxy-3-((pivaloyloxy)methyl)-7-((1-tert-  
butyloxy carbonylpiperidin-4-yl)methoxy)-3,4-dihydroquinazolin-4-one (7.9g, 16mmol) in  
methylene chloride (80ml) containing 5.5M hydrogen chloride in isopropanol (80ml) was  
stirred for 1 hour at ambient temperature. Ether was added and the solid was collected by
filtration, washed with ether and dried under vacuum at 60°C to give 6-methoxy-7-
(piperidin-4-yl)methoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one
hydrochloride (6.9g, 100%).

\[ \text{H NMR Spectrum: (DMSO}_d_6, \text{ CF}_3\text{CO}_2\text{D}) 1.15(s, 9H); 1.5-1.7(m, 2H); 2.0(d, 2H); 2.2-2.3(br}
\text{s, 1H); 3.0(t, 2H); 3.4(d, 2H); 3.94(s, 3H); 4.15(d, 2H); 5.97(s, 2H); 7.3(s, 1H); 7.6(s, 1H);
8.65(s, 1H)
\]

MS (ESI): 404 [MH]^+

To a solution of 6-methoxy-7-((piperidin-4-yl)methoxy)-3-((pivaloyloxy)methyl)-3,4-
dihydroquinazolin-4-one hydrochloride (0.88g, 2mmol) and triethylamine (0.3ml, 2.1mmol)
in methanol (10ml) and methylene chloride (10ml) was added potassium carbonate (280mg,
2mmol) and methyl vinyl sulfone (0.4ml, 2.1mmol). After stirring for 2 hours at ambient
temperature, the volatiles were removed under vacuum. The residue was partitioned between
ethyl acetate and water. The organic layer was washed with brine, dried (MgSO_4) and
evaporated to give 6-methoxy-7-((1-(2-methylsulphonylethyl)piperidin-4-yl)methoxy)-3-
((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (0.55g, 54%).

\[ \text{H NMR Spectrum: (DMSO}_d_6) 1.09(s, 9H); 1.25-1.4(m, 2H); 1.7-1.9(m, 3H); 2.0(t, 2H);
2.7(t, 2H); 2.95(d, 2H); 3.02(s, 3H); 3.25-3.45(m, 2H); 3.9(s, 3H); 4.0(d, 2H); 5.9(s, 2H);
7.15(s, 1H); 7.49(s, 1H); 8.35(s, 1H)
\]


To a suspension of 6-methoxy-7-((1-(2-methylsulphonylethyl)piperidin-4-
yl)methoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (90mg, 0.18mmol) in
methanol (3ml) was added 2M aqueous sodium hydroxide (180μl, 0.35mmol). After stirring
for 2 hours at ambient temperature, the mixture was adjusted to pH 10 with 2M hydrochloric
acid. The volatiles were removed under vacuum and the residue was suspended in water,
filtered, washed with water followed by ether and dried under vacuum at 60°C to give 6-
methoxy-7-((1-(2-methylsulphonylethyl)piperidin-4-yl)methoxy)-3,4-dihydroquinazolin-4-
one (55mg, 79%).

\[ \text{H NMR Spectrum: (DMSO}_d_6) 1.2-1.4(m, 2H); 1.7-1.85(m, 3H); 2.0(t, 2H); 2.7(t, 2H); 2.9(d,
2H); 3.02(s, 3H); 3.3-3.5(m, 2H); 3.9(s, 3H); 4.0(d, 2H); 7.11(s, 1H); 7.45(s, 1H); 7.97(s, 1H)
\]

MS (ESI): 396 [MH]^+

A solution of 6-methoxy-7-((1-(2-methylsulphonylethyl)piperidin-4-yl)methoxy)-3,4-
dihydroquinazolin-4-one (335mg, 0.85mmol) in thionyl chloride (5ml) containing DMF
(50µl) was refluxed for 1 hour. After cooling, the volatiles were removed under vacuum and the residue was triturated with ether and filtered. The solid was suspended in methylene chloride and sodium hydrogen carbonate was added. The organic layer was washed with water, brine, dried (MgSO₄) and evaporated. The residue was triturated with ether, filtered and dried under vacuum to give 4-chloro-6-methoxy-7-((1-(2-methylsulphonylethyl)piperidin-4-ylmethoxy)quinazoline (335mg, 95%).

$^1$H NMR Spectrum: (DMSO-d$_6$) 1.25-1.45(m, 2H); 1.75-1.90(m, 3H); 2.00(t, 2H); 2.70(t, 2H); 2.92(d, 2H); 3.03(s, 3H); 3.20-3.35(m, 2H); 4.00(s, 3H); 4.10(d, 2H); 7.40(s, 1H); 7.45(s, 1H); 8.90(s, 1H)

MS (ESI): 414 [MH]$^+$

**Example 13**

Using a procedure analogous to that described for Example 10, 4-chloro-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (130mg, 0.4mmol), (prepared as described for the starting material in Example 10), was reacted with 4-methyl-7-hydroxyquinoline (80mg, 0.5mmol), (Chem. Ber. 1967, 100, 2077), to give 6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)-4-(4-methylquinolin-7-yloxy)quinazoline (160mg, 90%).

$^1$H NMR Spectrum: (DMSO-d$_6$) 1.30-1.50(m, 2H); 1.70-1.90(m, 3H); 1.90(t, 2H); 2.15(s, 3H); 2.70(s, 3H); 2.80(d, 2H); 4.00(s, 3H); 4.10(d, 2H); 7.40(m, 2H); 7.65(dd, 1H); 7.65(s, 1H); 7.90(s, 1H); 8.20(d, 1H); 8.54(s, 1H); 8.70(d, 1H)

MS (ESI): 445 [MH]$^+$

**Example 14**

A solution of 4-chloro-6-methoxy-7-((1-(2-methylsulphonylethyl)piperidin-4-yl)methoxy)quinazoline (115mg, 0.28mmol), (prepared as described for the starting material in Example 12), 5-hydroxy-2-methylindole (50mg, 0.33mmol) and potassium carbonate (60mg, 0.42mmol) in DMF (1.5ml) was stirred at 100°C for 2 hours. After cooling, the mixture was partitioned between ethyl acetate and water. The organic layer was washed with water, brine, dried (MgSO₄) and evaporated. The residue was purified by chromatography eluting with ethyl acetate/methylene chloride (1/1) followed by methanol/ethyl acetate/methylene chloride (1/4/5 and 1/0/9) to give 6-methoxy-4-(2-methylindol-5-yloxy)-7-((1-(2-methylsulphonylethyl)piperidin-4-yl)methoxy)quinazoline (60mg, 41%).
- 111 -

\(^1\)H NMR Spectrum: (DMSO\(_d_6\)) 1.3-1.45 (m, 2H); 1.75-1.92 (m, 3H); 2.02 (t, 2H); 2.4 (s, 3H); 2.7 (t, 2H); 2.95 (d, 2H); 3.05 (s, 3H); 4.0 (s, 3H); 4.05 (d, 2H); 6.15 (s, 1H); 6.85 (dd, 1H); 7.25 (s, 1H); 7.3 (d, 1H); 7.38 (s, 1H); 7.6 (s, 1H); 8.45 (s, 1H)

MS (ESI): 525 [MH]^+

5 Elemental analysis: Found C 60.7 H 6.2 N 10.5
C\(_{27}\)H\(_{32}\)O\(_3\)S 0.5H\(_2\)O Requires C 60.8 H 6.2 N 10.5%

Example 15

Using a procedure analogous to that described for Example 9, 4-chloro-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline (0.13g, 0.4mmol), (prepared as described for the starting material in Example 9), was reacted with 7-hydroxy-4-methylquinoline (80mg, 0.5mol), (Chem. Berich. 1967, 100, 2077), to give 6-methoxy-4-(4-methylquinolin-7-yl)oxy)-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline (155mg, 87%).

\(^1\)H NMR Spectrum: (DMSO\(_d_6\)) 1.7 (br s, 4H); 2.05 (m, 2H); 2.5 (br s, 4H); 2.6 (t, 2H); 2.75 (s, 3H); 4.02 (s, 3H); 4.3 (t, 2H); 7.41 (s, 1H); 7.45 (d, 1H); 7.65 (s, 1H); 7.65 (d, 1H); 7.95 (s, 1H); 8.25 (d, 1H); 8.55 (s, 1H); 8.8 (d, 1H)

MS (ESI): 445 [MH]^+

Example 16

Using a procedure analogous to that described for Example 9, 4-chloro-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline (0.13g, 0.4mmol), (prepared as described for the starting material in Example 9), was reacted with 2,2,4-trimethyl-1,2-dihydroquinolin-6-ol (95mg, 0.5mmol), (IZV. ACAD. NAVK. SSSR. Ser. Khim. 1981, 9, 208), to give 6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)-4-(2,2,4-trimethyl-1,2-dihydroquinolin-6-yloxy)quinazoline (90mg, 47%).

\(^1\)H NMR Spectrum: (DMSO\(_d_6\)) 1.23 (s, 6H); 1.7 (br s, 4H); 1.85 (s, 3H); 2.0 (m, 2H); 2.45 (br s, 4H); 2.57 (t, 2H); 3.95 (s, 3H); 4.25 (t, 2H); 5.35 (s, 1H); 5.9 (s, 1H); 6.5 (d, 1H); 6.8 (dd, 1H); 6.85 (s, 1H); 7.32 (s, 1H); 7.52 (s, 1H); 8.5 (s, 1H)

MS (ESI): 475 [MH]^+

Example 17

Using a procedure analogous to that described for Example 9, 4-chloro-6-methoxy-7-
(()-1-methylpyridin-4-yl)methoxy)quinazoline (0.13 g, 0.4 mmol), (prepared as described for the starting material in Example 10), was reacted with 2,2,4-trimethyl-1,2-dihydroquinolin-6-ol (95 mg, 0.5 mmol), (IZV. ACAD. NAVK. SSSR. Ser. Khim. 1981, 9, 2008), to give 6-methoxy-7-(()-1-methylpyridin-4-yl)methoxy)-4-(2,2,4-trimethyl-1,2-dihydroquinolin-6-yl)oxy)quinazoline (140 mg, 74%).

1H NMR Spectrum: (DMSO-d6) 1.15 (s, 6 H); 1.3-1.45 (m, 2 H); 1.7-2.0 (m, 8 H); 2.16 (s, 3 H); 2.65-2.85 (d, 2 H); 4.0 (s, 3 H); 4.05 (d, 2 H); 5.35 (s, 1 H); 5.9 (s, 1 H); 6.5 (d, 1 H); 6.80 (d, 1 H); 6.82 (s, 1 H); 7.33 (s, 1 H); 7.5 (s, 1 H); 8.52 (s, 1 H)

MS (ESI): 475 [MH]+

**Example 18**

Using a procedure analogous to that described for Example 9, 4-chloro-6-methoxy-7-(()-1-methylpyridin-4-yl)methoxy)quinazoline (0.13 g, 0.4 mmol), (prepared as described for the starting material in Example 10), was reacted with 2,4-dimethyl-7-hydroxyquinoline (87 mg, 0.5 mmol), (Chem. Berichte, 1903, 36, 4016), to give 4-(2,4-dimethylquinolin-7-yloxy)-6-methoxy-7-(()-1-methylpyridin-4-yl)methoxy)quinazoline (61 mg, 33%).

1H NMR Spectrum: (DMSO-d6) 1.3-1.5 (m, 2 H); 1.7-1.95 (m, 5 H); 2.2 (s, 3 H); 2.65 (s, 3 H); 2.7 (s, 3 H); 2.75-2.9 (br d, 2 H); 4.05 (s, 3 H); 4.1 (d, 2 H); 7.3 (s, 1 H); 7.4 (s, 1 H); 7.52 (d, 1 H); 7.65 (s, 1 H); 7.8 (s, 1 H); 8.15 (d, 1 H); 8.55 (s, 1 H)

MS (ESI): 459 [MH]+

**Example 19**

Using a procedure analogous to that described for Example 9, 4-chloro-6-methoxy-7-(()-1-methylpyridin-4-yl)methoxy)quinazoline (0.13 g, 0.4 mmol), (prepared as described for the starting material in Example 10), was reacted with 6-hydroxy-2H-4H-1,4-benzoxazin-3-one (83 mg, 0.5 mmol), (J. Chem. Soc. C, 1971, 2696), to give 6-methoxy-7-(()-1-methylpyridin-4-yl)methoxy)-4-(3-oxo-2H-4H-1,4-benzoxazin-6-yl)oxy)quinazoline (158 mg, 88%).

1H NMR Spectrum: (DMSO-d6) 1.25-1.45 (m, 2 H); 1.8 (d, 2 H); 1.7-1.9 (m, 1 H); 1.9 (t, 2 H); 2.2 (s, 3 H); 2.8 (d, 2 H); 3.97 (s, 3 H); 4.05 (d, 2 H); 4.65 (s, 2 H); 6.8 (s, 1 H); 6.85 (d, 1 H); 7.05 (d, 1 H); 7.35 (s, 1 H); 7.52 (s, 1 H); 8.55 (s, 1 H)

MS (ESI): 451 [MH]+
Example 20
Using a procedure analogous to that described for Example 9, 4-chloro-6-methoxy-7-((3-(pyrrolidin-1-yl)propoxy)quinazoline (0.13g, 0.4mmol), (prepared as described for the starting material in Example 9), was reacted with 6-hydroxy-2H-4H-1,4-benzoxazin-3-one (83mg, 0.5mmol), (J. Chem. Soc. C, 1971, 2696), to give 6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)-4-(3-oxo-2H-4H-1,4-benzoxazin-6-yl)oxyquinazoline (170mg, 94%).

^1H NMR Spectrum: (DMSO_d6, CF3CO2D) 1.8-2.0(m, 2H); 2.0-2.15(m, 2H); 2.2-2.35(m, 2H); 3.0-3.2(m, 2H); 3.4(t, 2H); 3.6-3.75(m, 2H); 4.05(s, 3H); 4.35(t, 2H); 4.65(s, 2H); 6.85(s, 1H); 6.9(d, 1H); 7.1(d, 1H); 7.5(s, 1H); 7.7(s, 1H); 8.9(s, 1H)

MS (ESI): 451 [MH]^+

Example 21
Using a procedure analogous to that described for Example 10, 4-chloro-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (74mg, 0.23mmol), (prepared as described for the starting material in Example 10), was reacted with 6-hydroxyquinoline (41mg, 0.28mol) to give 6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)-4-(quolinin-6-yl)oxyquinazoline (89mg, 94%).

^1H NMR Spectrum: (DMSO_d6) 1.3-1.5(m, 2H); 1.8(d, 2H); 1.9(t, 2H); 1.8-1.9(m, 1H); 2.2(s, 3H); 2.82(d, 2H); 4.02(s, 3H); 4.1(d, 2H); 7.4(s, 1H); 7.6(dd, 1H); 7.65(s, 1H); 7.75(d, 1H);

7.95(s, 1H); 8.15(d, 1H); 8.4(d, 1H); 8.55(s, 1H); 8.95(d, 1H)

MS (ESI): 431 [MH]^+

Example 22
To 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (250mg, 0.74mmol), (prepared as described for the starting material in Example 1), in suspension in DMF (4ml) were successively added 4-chloro-7-hydroxyquinoline (133mg, 0.74mmol) and potassium carbonate (153mg, 1mmol) and the reaction mixture heated to 100°C. More 4-chloro-7-hydroxyquinoline (27mg, 0.15mmol) was added after one hour and heating was continued for a further 30 minutes. The product precipitated upon cooling to ambient temperature. The reaction mixture was diluted with water, the product was collected by filtration and washed with more water. The dried solid was triturated with ether and filtered to give 4-(4-chloroquinolin-7-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline (166mg, 47%).
- 114 -

\(^1\)H NMR Spectrum: (DMSOd\(_6\), CF\(_3\)CO\(_2\)D) 2.3 (m, 2H); 3.2 (m, 2H); 3.4 (m, 2H); 3.5 (m, 2H);
3.7 (m, 2H); 4.0 (m, 2H); 4.1 (s, 3H); 4.4 (m, 2H); 7.55 (s, 1H); 7.75 (s, 1H); 7.90 (dd, 1H);
7.95 (d, 1H); 8.15 (d, 1H); 8.45 (d, 1H); 8.80 (s, 1H); 9.05 (d, 1H)

MS - ESI: 481 [MH]\(^+\)

5 Elemental analysis:

<table>
<thead>
<tr>
<th></th>
<th>Found</th>
<th>Requires</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(<em>{22})H(</em>{25})ClN(_4)O(_4)</td>
<td>C 61.8 H 5.1 N 11.5</td>
<td>C 62.4 H 5.2 N 11.7%</td>
</tr>
</tbody>
</table>

The starting material was prepared as follows:

A solution of 7-benzyloxy-4-chloroquinoline (17g, 56mmol), (Konishi et al. WO 96/11187), in TFA (170ml) was heated at reflux for 2 hours. The solvent was removed under vacuum and the residue was triturated with ether, filtered and washed with ether. The solid was suspended in an aqueous solution of sodium hydrogen carbonate (5.5g, 65mmol in 200ml of water) and stirred at ambient temperature for 30 minutes. The solid was collected by filtration, washed with water and dried overnight under vacuum and over phosphorus pentoxide to give 4-chloro-7-hydroxyquinoline (9.85g, 98%).

\(^1\)H NMR Spectrum: (DMSOd\(_6\)) 7.37 (s, 1H); 7.39 (d, 1H); 7.62 (d, 1H); 8.15 (d, 1H); 8.8 (d, 1H)

MS - EI: m/z 179 [M.]\(^+\)

Example 23

A solution of 4-chloro-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (74mg, 0.23mmol), (prepared as described for the starting material in Example 10), and 2-hydroxynaphthalene (40mg, 0.28mmol) in DMF (1.5ml) containing potassium carbonate (48mg, 0.35mmol) was stirred at 100°C for 3.5 hours. After cooling, methylene chloride (4.5ml) was added and the mixture was poured onto a column of silica (SiO\(_2\) Isolute\(^\circledR\)) and eluted with, successively, methylene chloride, methylene chloride/methanol (9/1), methylene chloride/methanol/3M ammonia in methanol (75/20/5). The fractions containing the product were evaporated under vacuum. The residues was triturated with ether, filtered and dried under vacuum to give 6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)-4-(2-naphthyloxy)quinazoline (80mg, 83%).

MS - ESI: 430 [MH]\(^+\)

\(^1\)H NMR Spectrum: (DMSOd\(_6\)) 1.35-1.45 (m, 2H), 1.8 (d, 2H), 2.0 (t, 1H), 2.2 (s, 3H), 2.85
Example 24

A solution of 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (74mg, 0.23mmol), (prepared as described for the starting material in Example 1), and 3,4-(methylene dioxy)aniline (53mg, 0.24mmol) in a solution of isopropanol (3.5ml) containing 5.5M hydrogen chloride in isopropanol (42μl) was heated for 3 hours. After cooling to ambient temperature, the reaction mixture was cooled to 0°C and maintained at this temperature overnight. The precipitate was collected by filtration, washed with ethyl acetate and dried under vacuum to give 4-(1,3-benzodioxol-5-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline (82mg, 76%).

MS - ESI: 439 [MH]+

1H NMR Spectrum: (DMSO-d6) 2.3-2.4 (m, 2H), 3.05-3.2 (m, 2H), 3.25-3.35 (m, 2H), 3.5 (d, 2H), 3.82 (t, 2H), 4.0 (d, 2H), 4.05 (s, 3H), 4.32 (t, 2H), 6.1 (s, 2H), 7.02 (d, 1H), 7.1 (dd, 1H), 7.3 (s, 1H), 7.4 (s, 1H), 8.32 (s, 1H), 8.8 (s, 1H)

Examples 25-29

Using an analogous procedure to that described in Example 24, 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline, (prepared as described for the starting material in Example 1), was used in the synthesis of the compounds described in Table I hereinafter as detailed in the notes a)-e) to Table I.

Table I

<table>
<thead>
<tr>
<th>Example No.</th>
<th>Weight (mg)</th>
<th>yield %</th>
<th>MS-ESI [MH]+</th>
<th>note</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>104</td>
<td>90</td>
<td>435.1</td>
<td>a</td>
<td>1-H-indazol-6-yl</td>
</tr>
</tbody>
</table>
a) 4-Chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (74mg) was reacted with 6-aminoindazole (32mg) to give 4-(1\textit{-H}-indazol-6-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline.

\[ ^1H \text{ NMR Spectrum: (DMSO}_{d_6}) 2.3-2.4 (m, 2H), 3.05-3.2 (m, 2H), 3.2-3.3 (m, 2H), 3.52 (d, 2H), 3.85 (t, 2H), 4.0 (d, 2H), 4.05 (s, 3H), 4.32 (t, 2H), 7.42 (s, 1H), 7.45 (d, 1H), 7.85 (d, 1H), 7.98 (s, 1H), 8.1 (s, 1H), 8.42 (s, 1H), 8.85 (s, 1H) \]

b) 4-Chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (74mg) was reacted with 5-aminoindazole (32mg) to give 4-(1\textit{-H}-indazol-5-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline.

\[ ^1H \text{ NMR Spectrum: (DMSO}_{d_6}) 2.3-2.4 (m, 2H), 3.05-3.2 (m, 2H), 3.25-3.3 (m, 2H), 3.45-3.55 (m, 2H), 3.8-3.9 (m, 2H), 3.9-4.02 (m, 2H), 4.05 (s, 3H), 4.32 (t, 2H), 7.42 (s, 1H), 7.65 (m, 2H), 8.05 (s, 1H), 8.15 (s, 1H), 8.4 (s, 1H), 8.75 (s, 1H) \]

c) 4-Chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (74mg) was reacted with 6-aminothiazole (36mg) to give 4-(1,3-benzothiazol-6-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline.

\[ ^1H \text{ NMR Spectrum: (DMSO}_{d_6}) 2.3-2.4 (m, 2H), 3.05-3.2 (m, 2H), 3.2-3.3 (m, 2H), 3.55 (d, 2H), 3.8 (t, 2H), 4.0 (d, 2H), 4.08 (s, 3H), 4.32 (t, 2H), 7.4 (s, 1H), 7.88 (dd, 1H), 8.2 (d, 1H), 8.4 (s, 1H), 8.55 (s, 1H), 8.85 (s, 1H), 9.42 (s, 1H) \]

d) 4-Chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (74mg) was reacted with 6-amino-2-methylthiazole (57mg) to give 6-methoxy-4-(2-methyl-1,3-benzothiazol-5-ylamino)-7-(3-morpholinopropoxy)quinazoline.

\[ ^1H \text{ NMR Spectrum: (DMSO}_{d_6}) 2.3-2.4 (m, 2H), 2.85 (s, 3H), 3.05-3.2 (m, 2H), 3.3 (t, 2H), 3.4-3.5 (m, 2H), 3.85 (t, 2H), 4.0 (d, 2H), 4.05 (s, 3H), 4.35 (t, 2H), 7.42 (s, 1H), 7.75 (dd,
1H), 8.15 (d, 1H), 8.3 (s, 1H), 8.42 (s, 1H), 8.85 (s, 1H)

e) 4-Chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (74mg) was reacted with 5-
aminoindan (32mg) to give 4-(2,3-dihydro-1H-inden-5-ylamino)-6-methoxy-7-(3-
morpholinopropoxy)quinazoline.

1H NMR Spectrum: (DMSO-d₆) 2.08 (m, 2H), 2.3-2.4 (m, 2H), 2.9 (m, 4H), 3.05-3.2 (m, 2H),
3.2-3.3 (m, 2H), 3.5 (d, 2H), 3.82 (t, 2H), 4.0 (d, 2H), 4.05 (s, 3H), 4.3 (t, 2H), 7.32 (d, 1H),
7.4 (m, 2H), 7.55 (s, 1H), 8.32 (s, 1H), 8.8 (s, 1H)

Example 30

A suspension of 4-chloro-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline
(130mg, 0.4mmol), (prepared as described for the starting material in Example 10), 7-
hydroxy-2-methylchromone (88mg, 0.5 mmol), (Bull Soc. Chim. Fr. 1995, 132, 233), and
potassium carbonate (83mg, 0.6 mmol) was heated at 100°C for 1.5 hours. After cooling, the
mixture was partitioned between water and ethyl acetate. The organic layer was washed with
water, brine, dried (MgSO₄), and the volatiles were removed by evaporation. The residue was
triturated with ether, collected by filtration, washed with ether and dried under vacuum to give
6-methoxy-4-(2-methyl-4-oxo-4H-chromen-7-yl)oxy)-7-(1-methylpiperidin-4-
ylmethoxy)quinazoline (170mg, 92%).

MS - ESI: 462 [MH]+
1H NMR Spectrum: (DMSO-d₆) 1.3-1.5 (m, 2H); 1.75-1.95 (m, 5H); 2.2 (s, 3H), 2.42 (s, 3H);
4.0 (s, 3H); 4.1 (d, 2H); 6.3 (s, 2H); 7.4 (s, 1H); 7.45 (dd, 1H); 7.6 (s, 1H); 7.7 (s, 1H); 8.15
(d, 1H); 8.61 (s, 1H)

Examples 31-33

Using an analogous procedure to that described in Example 30, the compounds
described in Table II hereinafter and detailed in the notes a)-c) to Table II, were made.

Table II

![Table II](image)
Table II

<table>
<thead>
<tr>
<th>Example No.</th>
<th>Weight (mg)</th>
<th>yield</th>
<th>MS-ESI [MH]+</th>
<th>note</th>
<th>Q</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>180</td>
<td>85</td>
<td>451</td>
<td>a</td>
<td>1-methylpiperidin-4-ylmethoxy</td>
<td>4-methyl-3,4-dihydro-2H-1,4-benzoxazin-6-ylmethoxy</td>
</tr>
<tr>
<td>32</td>
<td>160</td>
<td>87</td>
<td>462</td>
<td>b</td>
<td>3-pyrrolidin-1-ylpropoxy</td>
<td>2-methyl-4-oxo-4H-chromen-7-ylmethoxy</td>
</tr>
<tr>
<td>33</td>
<td>100</td>
<td>56</td>
<td>451</td>
<td>c</td>
<td>3-pyrrolidin-1-ylpropoxy</td>
<td>4-methyl-3,4-dihydro-2H-1,4-benzoxazin-6-ylmethoxy</td>
</tr>
</tbody>
</table>

a) 4-Chloro-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (130mg), (prepared as described for the starting material in Example 10), was reacted with 3,4-dihydro-4-methyl-2H-1,4-benzoxazin-6-ol (83mg), (J. Org. Chem. 1971, 36 (1)), to give 6-methoxy-4-(4-methyl-3,4-dihydro-2H-1,4-benzoxazin-6-ylmethoxy)-7-(1-methylpiperidin-4-ylmethoxy)quinazoline.

^1H NMR Spectrum: (DMSOd₆) 1.6-1.75 (m, 2H); 1.9-2.3 (m, 5H); 2.8 (s, 3H); 2.9 (s, 3H); 3.0-3.15 (m, 2H); 3.3 (br s, 2H); 3.5-3.6 (d, 2H); 4.1 (s, 3H); 4.2 (d, 2H); 4.3 (t, 2H); 6.55 (m, 1H); 6.75 (s, 1H); 6.8 (d, 1H); 7.6 (s, 1H); 7.75 (s, 1H); 9.15 (s, 1H)

b) 4-Chloro-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (130mg), (prepared as described for the starting material in Example 9), was reacted with 7-hydroxy-2-methylchromone (88mg), (Bull Soc. Chim Fr. 1995, 132, 233). After cooling, water was added (20ml) and the precipitate was collected by filtration and dried under vacuum over phosphorus pentoxide at 60°C to give 6-methoxy-4-(2-methyl-4-oxo-4H-chromen-7-ylmethoxy)-7-(3-pyrrolidin-1-ylpropoxy)quinazoline.

^1H NMR Spectrum: (DMSO_d₆, CF₃COOD) 1.8-2.0 (m, 2H); 2.0-2.15 (m, 2H); 2.2-2.3 (m, 2H); 2.4 (s, 3H); 3.05-3.15 (m, 2H); 3.3-3.4 (m, 2H); 3.6-3.7 (m, 2H); 4.05 (s, 3H); 4.35 (t, 2H); 6.3 (s, 1H); 7.45 (d, 1H); 7.5 (s, 1H); 7.65 (s, 1H); 7.72 (s, 1H); 8.15 (d, 1H); 8.75 (s, 1H)
c) 4-Chloro-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (130mg), (prepared as described for the starting material in Example 9), was reacted with 3,4-dihydro-4-methyl-2H-1,4-benzoxazin-6-ol (83mg), (J. Org. Chem. 1971, 36 (1)), to give \textbf{6-methoxy-4-(4-methyl-3,4-dihydro-2H-1,4-benzoxazin-6-yloxy)-7-(3-pyrrolidin-1-ylpropoxy)quinazoline}.

$^1$H NMR Spectrum: (DMSOd$_6$) 1.85-2.0 (m, 2H); 2.0-2.15 (m, 2H); 2.25-2.35 (m, 2H); 2.83 (s, 3H); 3.05-3.15 (m, 2H); 3.3 (t, 2H); 3.4 (t, 2H); 3.7 (br m, 2H); 4.1 (s, 3H); 4.3 (t, 2H); 4.4 (t, 2H); 6.52 (d, 1H); 6.7 (s, 1H); 6.8 (d, 1H); 7.55 (s, 1H); 7.75 (s, 1H); 9.1 (s, 1H)

**Example 34**

A solution of 4-chloro-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (110mg, 0.34mmol), (prepared as described for the starting material in Example 10), and 5-hydroxyindole (55mg, 0.41mmol) in DMF (1.5ml) containing potassium carbonate (70mg, 0.51mmol) was heated at 100°C for 2 hours. After cooling, water was added and the precipitate was collected by filtration, washed with water followed by ether, and dried under vacuum over phosphorus pentoxide to give \textbf{4-(indol-5-yloxy)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline} (90mg, 64%).

MS - ESI: 419 [MH]$^+$

$^1$H NMR Spectrum: (DMSOd$_6$) 1.35-1.5 (m, 2H); 1.8 (d, 2H); 1.95 (t, 2H); 1.7-2.0 (m, 1H); 2.2 (s, 3H); 2.85 (d, 2H); 4.02 (s, 3H); 4.1 (d, 2H); 6.45 (s, 1H); 7.0 (d, 1H); 7.35 (s, 1H); 7.4-7.5 (m, 3H); 7.6 (s, 1H); 8.5 (s, 1H)

Elemental analysis: Found C 67.4 H 6.5 N 13.1

C$_{24}$H$_{26}$N$_4$O$_5$ 0.5H$_2$O Requires C 67.4 H 6.4 N 13.1%

**Example 35**

Using an analogous procedure to that described in Example 34, 4-chloro-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (110mg, 0.34mmol), (prepared as described for the starting material in Example 10), was reacted with 2,3-dimethyl-5-hydroxyindole (66mg, 0.41mmol), (Arch. Pharm. 1972, 305, 159). The crude product was purified by column chromatography eluting with methanol/methylene chloride (1/9) followed by 3M ammonia in methanol/methanol/methylene chloride (5/15/80) to give \textbf{4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline} (60mg, 40%).

MS - ESI: 447 [MH]$^+$
Example 36

Using an analogous procedure to that described in Example 34, 4-chloro-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (110mg, 0.34mmol), (prepared as described for the starting material in Example 9), was reacted with 5-hydroxyindole (55mg, 0.41mmol). The crude product was purified by chromatography on alumina, eluting with methanol/ethyl acetate/methylene chloride (5/45/50) to give 4-(indol-5-yl oxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (70mg, 50%).

MS - ESI 419 [MH]+

Example 37

A suspension of 4-chloro-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (100mg, 0.31mmol), (prepared as described for the starting material in Example 10), and 5-amino-2,3-dimethylindole (55mg, 0.34mmol) in isopropanol (6ml) containing 5.5M hydrogen chloride in isopropanol (60μL) was heated for 30 minutes at 70°C. After cooling, the solid was collected by filtration, washed with isopropanol, followed by ether and dried under vacuum to give 4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline hydrochloride (118mg, 74%).

MS - ESI: 446 [MH]+
1H); 11.25 (br s, 1H)
Elemental analysis:
\[
\text{Found C} \ 58.5 \ \text{H} \ 6.8 \ \text{N} \ 12.9 \\
\text{C}_{26}\text{H}_{31}\text{N}_5\text{O}_2 \ \text{1H}_2\text{O} \ 1.9\text{HCl} \\
\text{Requires C} \ 58.6 \ \text{H} \ 6.6 \ \text{N} \ 13.1\%
\]

5 Example 38

Using an analogous procedure to that described in Example 37, 4-chloro-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (100mg, 0.31mmol), (prepared as described for the starting material in Example 9), was reacted with 5-amino-2,3-dimethylindole (55mg, 0.34mmol) to give 4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(3-pyrrolidin-1-

10 ylpropoxy)quinazoline hydrochloride (114mg, 72%).

MS - ESI: 446 [MH]+

\(^1\)H NMR Spectrum: (DMSO\_d\_6, CF\_3COOD) 1.85-2.0 (m, 2H); 2.05-2.15 (m, 2H); 2.1 (s, 3H); 2.2 (s, 3H); 2.25-2.35 (m, 2H); 2.35 (s, 3H); 3.0-3.15 (m, 2H); 3.32-3.42 (m, 2H); 3.6-3.7 (m, 2H); 4.05 (s, 3H); 4.3 (t, 2H); 7.2 (d, 1H); 7.3 (s, 1H); 7.35 (d, 1H); 7.57 (s, 1H); 8.2 (s, 1H); 8.8 (s, 1H)

Elemental analysis:
\[
\text{Found C} \ 58.8 \ \text{H} \ 7.0 \ \text{N} \ 12.5 \\
\text{C}_{30}\text{H}_{31}\text{N}_5\text{O} \ \text{1.9H}_2\text{O} \ \text{1.9HCl} \ \text{0.1isopropanol} \\
\text{Requires C} \ 58.6 \ \text{H} \ 7.1 \ \text{N} \ 12.9\%
\]

Example 39

Using an analogous procedure to that described in Example 38, 4-chloro-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (100mg, 0.31mmol), (prepared as described for the starting material in Example 9), was reacted with 5-amino-2-methylindole (50mg, 0.34mmol) to give 6-methoxy-4-(2-methylindol-5-ylamino)-7-(3-pyrrolidin-1-ylpropoxy)quinazoline hydrochloride (138mg, 89%).

MS - ESI: 432 [MH]+

\(^1\)H NMR Spectrum: (DMSO\_d\_6) 1.8-1.9 (m, 2H); 2.0-2.1 (m, 2H); 2.15-2.35 (m, 2H); 2.4 (s, 3H); 3.0-3.1 (m, 2H); 3.2-3.3 (m, 2H); 3.5-3.6 (m, 2H); 4.0 (s, 3H); 4.32 (t, 2H); 6.2 (s, 1H); 7.2 (d, 1H); 7.3 (m, 2H); 7.65 (s, 1H); 8.25 (s, 1H); 8.75 (s, 1H); 10.75 (br s, 1H); 11.15 (s, 1H); 11.25 (br s, 1H)

Elemental analysis:
\[
\text{Found C} \ 58.9 \ \text{H} \ 6.6 \ \text{N} \ 13.5 \\
\text{C}_{25}\text{H}_{29}\text{N}_5\text{O}_2 \ \text{2.2HCl} \ \text{0.1isopropanol} \\
\text{Requires C} \ 58.7 \ \text{H} \ 6.2 \ \text{N} \ 13.5\%
\]
Example 40

A mixture of 4-chloro-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (100mg, 0.31mmol), (prepared as described for the starting material in Example 9), and 7-hydroxy-2,4-dimethylquinoline (64mg, 0.36mmol), (Chem. Berichte, 1903, 26, 4016), in DMF (3ml) containing potassium carbonate (86mg, 0.62mmol) was heated at 90°C for 3 hours. After cooling, the mixture was poured onto a column of silica and eluted with 2.5M ammonia in methanol/methylene chloride (5/95) to give 4-(2,4-dimethylquinolin-7-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (50mg, 35%).

MS - ESI: 459 [MH]+

¹H NMR Spectrum: (CDCl₃) 1.8 (br s, 4H); 2.2 (m, 4H); 2.55 (br s, 4H); 2.7 (2s, 6H); 2.68 (m, 2H); 4.05 (s, 3H); 4.3 (t, 2H); 7.15 (s, 1H); 7.35 (s, 1H); 7.45 (d, 1H); 7.6 (s, 1H); 7.9 (s, 1H); 8.05 (d, 1H); 8.6 (s, 1H)

Elemental analysis: Found C 70.4 H 7.1 N 12.1

Example 41

Using an analogous procedure to that described in Example 37, 4-chloro-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (50mg, 0.155mmol), (prepared as described for the starting material in Example 10), was reacted with 5-amino-2-methylindole (0.171mmol) to give 6-methoxy-4-(2-methylindol-5-ylamino)-7-(1-methylpiperidin-4-ylmethoxy)quinazoline hydrochloride (72mg, quant.).

MS - ESI: 432 [MH]+

¹H NMR Spectrum: (DMSO₆, CF₃COOD) 1.5-1.7 (m, 2H); 2.05 (d, 2H); 2.1-2.2 (m, 1H); 2.45 (s, 3H); 2.8 (s, 3H); 3.05 (t, 2H); 3.5 (d, 2H); 4.0 (s, 3H); 4.1 (d, 2H); 6.2 (s, 1H); 7.2 (d, 1H); 7.32 (d, 1H); 7.4 (d, 1H); 7.6 (s, 1H); 8.2 (s, 1H); 8.85 (s, 1H)

Elemental analysis: Found C 53.9 H 6.8 N 12.4

Example 42

A suspension of 4-chloro-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (100mg, 0.31 mmol), (prepared as described for the starting material in Example 9), and 7-hydroxy-2-methylquinoline (54mg, 0.34mmol), (J. Med. Chem. 1998, 41, 4062), in DMF
(3ml) containing potassium carbonate (86mg, 0.62mmol) was heated at 90°C for 2 hours. After cooling, the mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water, brine, dried and the volatiles were removed by evaporation. The residue was triturated with minimal ether, collected by filtration and dried under vacuum to give 6-methoxy-4-(2-methylquinolin-7-yl)oxy)-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (95mg, 69%).

MS - ESI: 445 [MH]+

1H NMR Spectrum: (CDCl3) 1.8 (br s, 4H); 2.2 (m, 2H); 2.5 (br s, 4H); 2.7 (t, 2H); 2.8 (s, 3H); 4.1 (s, 3H); 4.3 (t, 2H); 7.3 (d, 1H); 7.35 (s, 1H); 7.45 (dd, 1H); 7.6 (s, 1H); 7.85 (d, 1H); 7.9 (s, 1H); 8.1 (d, 1H); 8.6 (s, 1H)

Example 43

Using an analogous procedure to that described in Example 42, 4-chloro-6-methoxy-7-(1-(2-methyllumophonyethyl)piperidin-4-ylmethoxy)quinazoline (156mg, 0.38mmol), (prepared as described for the starting material in Example 12), was reacted with 7-hydroxy-2-methylquinoline (66mg, 0.4 mmol), (J. Med. Chem. 1998, 41, 4062), to give 6-methoxy-7-(1-(2-methylsulphonylethyl)piperidin-4-ylmethoxy)-4-(2-methylquinolin-7-yl)oxy)quinazoline (166mg, 82%).

MS - ESI: 537 [MH]+

1H NMR Spectrum: (DMSOd6) 1.3-1.5 (m, 2H); 1.75-1.95 (m, 3H); 1.95-2.15 (m, 2H); 2.7 (s, 3H); 2.7-2.8 (m, 2H); 2.9-3.0 (m, 2H); 3.05 (s, 3H); 3.2-3.35 (m, 2H); 4.02 (s, 3H); 4.1 (d, 2H); 7.4 (s, 1H); 7.45 (d, 1H); 7.55 (d, 1H); 7.65 (s, 1H); 7.8 (s, 1H); 8.05 (d, 1H); 8.35 (d, 1H); 8.55 (s, 1H)

Elemental analysis: Found C 62.2 H 6.3 N 10.4

Example 44

A suspension of 4-chloro-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (50mg, 0.155mmol), (prepared as described for the starting material in Example 10), and 5-hydroxy-2-trifluoromethylinol (34mg, 0.17mmol) in DMF (1.5ml) containing potassium carbonate (43mg, 0.31mmol) was heated at 90°C for 2 hours. After cooling, the mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with
brine, dried (MgSO₄) and the volatiles were removed by evaporation. The residue was purified by column chromatography eluting with methanol/ethyl acetate/methylene chloride (10/50/40) followed by 2.5M ammonia in methanol/ethyl acetate/methylene chloride (10/50/40) to give 6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)-4-(2-trifluoromethylindol-5-yl oxy)quinazoline (35mg, 48%).

MS - ESI: 487 [MH]+

¹H NMR Spectrum: (DMSO_d₆) 1.25-1.4 (m, 2H); 1.75 (d, 2H); 1.8 (t, 2H); 1.7-2.0 (m, 1H); 2.2 (s, 3H); 2.75 (d, 2H); 4.0 (s, 3H); 4.1 (d, 2H); 7.0 (s, 1H); 7.25 (d, 1H); 7.4 (s, 1H); 7.6 (d, 1H); 7.8 (s, 1H); 8.5 (s, 1H); 12.5 (s, 1H)

Elemental analysis:

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</tr>
<tr>
<td>N</td>
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C₂₅H₂₂F₃N₄O₃ 0.7H₂O 0.2ether

The starting material was prepared as follows:

A solution of (4-methoxy-2-methylphenyl)-carbamic acid-1,1-dimethylethyl ester (2g, 8.43mmol), (J. Med. Chem. 1996, 39, 5119), in dry THF (25ml) was cooled to -40°C and sec-butyllithium (15ml, 19.5mmol) was added. After stirring for 15 minutes at this temperature, N-methyl-N-methoxytrifluoroacetamide (1.32g, 8.43mmol) in THF (20ml) was added in portions. Stirring was continued for 1 hour at -40°C and then the mixture was allowed to warm to ambient temperature. The mixture was poured onto ether/1M hydrochloric acid. The organic layer was separated, washed with water, brine, dried (MgSO₄) and the volatiles were removed by evaporation.

The crude residue (1.4g) was dissolved in methylene chloride (8ml) and TFA was added (1.5ml). After stirring for 3 hours at ambient temperature, the volatiles were removed under vacuum. The crude product was partitioned between methylene chloride and water. The organic layer was separated, washed with water, brine, dried (MgSO₄) and the volatiles were removed by evaporation. The residue was purified by column chromatography, eluting with ether/petroleum ether (1/9) to give 5-methoxy-2-trifluoromethylindole (845mg, 47% over 2 steps).

¹H NMR Spectrum: (CDCl₃) 3.83 (s, 3H), 6.82 (s, 1H), 7.0 (dd, 1H), 7.1 (s, 1H), 7.3 (d, 1H), 8.15 (br s, 1H)

A solution of 5-methoxy-2-trifluoromethylindole (800mg, 3.7mmol) in methylene chloride (6ml) was cooled to -15°C and a solution of 1M boron tribromide in methylene
chloride (7.44 ml, 7.4 mmol) was added in portions. The mixture was allowed to warm to ambient temperature and was stirred for 45 minutes. After cooling to 0°C, saturated aqueous sodium hydrogen carbonate (25 ml) was added. The mixture was extracted with ethyl acetate. The organic layer was dried (MgSO₄) and the volatiles were removed by evaporation. The residue was purified by column chromatography eluting with ethyl acetate/petroleum ether. After removal of the volatiles by evaporation, the solid was triturated with pentane, collected by filtration and dried under vacuum to give 5-hydroxy-2-trifluoromethylindole (290 mg, 39%).

MS - EI: 201 [M]+

1H NMR Spectrum: (CDCl₃) 4.64 (s, 1H), 6.8 (s, 1H), 6.92 (dd, 1H), 7.1 (s, 1H), 7.3 (d, 1H), 8.3 (br s, 1H)

Elemental analysis:

C₁₀H₇F₃NO 0.1 H₂O

Found C 53.3 H 2.9 N 6.8
Requires C 53.3 H 3.1 N 6.9%

Example 45

Using an analogous procedure to that described in Example 44, 4-chloro-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (100 mg, 0.3 mmol), (prepared as described for the starting material in Example 9), was reacted with 5-hydroxy-2-trifluoromethylindole (75 mg, 0.37 mmol), (prepared as described for the starting material in Example 44), to give 6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)-4-(2-trifluoromethylindol-5-yloxy)quinazoline (105 mg, 70%).

MS - ESI: 487 [MH]+

1H NMR Spectrum: (CDCl₃) 1.8 (m, 4H); 2.1-2.3 (m, 2H); 2.55 (br s, 4H); 2.7 (t, 2H); 4.1 (s, 3H); 4.3 (t, 2H); 6.95 (s, 1H); 7.2 (dd, 1H); 7.35 (s, 1H); 7.5 (d, 1H); 7.55 (s, 1H); 7.6 (s, 1H); 8.6 (s, 1H); 8.8 (s, 1H)

Elemental analysis:

C₂₅H₂₅F₃N₄O₃

Found C 61.7 H 5.5 N 11.5
Requires C 61.7 H 5.2 N 11.5%

Example 46

Using an analogous procedure to that described in Example 42, 4-chloro-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (100 mg, 0.31 mmol), (prepared as described for the starting material in Example 10), was reacted with 7-hydroxy-2-methylquinoline (54 mg,
- 126 -

0.34 mmol), (J. Med. Chem. 1998, 41, 4062), to give 6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)-4-(2-methylquinolin-7-yloxy)quinazoline (86mg, 63%).

MS - ESI: 445 [MH]+

1H NMR Spectrum: (CDCl₃) 1.4-1.6 (m, 2H); 1.95 (d, 2H); 2.05 (t, 2H); 1.9-2.1 (m, 1H); 2.35 (s, 3H); 2.8 (s, 3H); 2.95 (d, 2H); 4.1 (s, 3H); 4.15 (d, 2H); 7.3 (m, 2H); 7.45 (dd, 1H); 7.6 (s, 1H); 7.9 (d, 1H); 7.95 (s, 1H); 8.1 (d, 1H); 8.6 (s, 1H)

Elemental analysis: Found C 69.7 H 6.5 N 12.8

C₂₀H₂₈N₄O₃ 0.2H₂O Requires C 69.7 H 6.4 N 12.5%

Example 47

A suspension of 4-chloro-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (110mg, 0.34 mmol), (prepared as described for the starting material in Example 9), and 2,3-dimethyl-5-hydroxyindole (66mg, 0.41 mmol), (Arch. Pharm. 1972, 305, 159), in DMF (1.5ml) containing potassium carbonate (70mg, 0.51 mmol) was heated at 100°C for 2 hours.

After cooling, the residue was purified by chromatography, eluting with methanol/methylene chloride (1/9) followed by 2.5M ammonia in methanol/methanol/methylene chloride (5/10/85) to give 4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (50mg, 33%).

MS - ESI: 447 [MH]+

1H NMR Spectrum: (DMSO-d₆, CF₃COOD) 1.9-2.0 (m, 2H); 2.05-2.15 (m, 2H); 2.15 (s, 3H); 2.3-2.4 (m, 2H); 2.4 (s, 3H); 3.05-3.15 (m, 2H); 3.35-3.45 (t, 2H); 3.7 (br s, 2H); 4.1 (s, 3H); 4.4 (t, 2H); 6.95 (d, 1H); 7.3 (s, 1H); 7.35 (d, 1H); 7.55 (s, 1H); 7.85 (s, 1H); 9.15 (s, 1H)

Elemental analysis: Found C 67.7 H 6.8 N 12.2

C₂₀H₂₈N₄O₃ 0.8H₂O Requires C 67.8 H 6.9 N 12.2%

Example 48

Using an analogous procedure to that described in Example 32, 7-benzylxoxy-4-chloro-6-methoxyquinazoline (1g, 3.33 mmol), (prepared as described for the starting material in Example 1), was reacted with 5-hydroxy-2-methylindole (0.59g, 4nmol) to give 7-benzylxoxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (1.25g, 91%).

MS - ESI: 412 [MH]+

1H NMR Spectrum: (DMSO-d₆) 2.4 (s, 3H); 4.0 (s, 3H); 5.35 (s, 2H); 6.15 (s, 1H); 6.85 (s,
1H); 7.2-7.6 (m, 9H); 8.5 (s, 1H)

Elemental analysis:

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</tr>
<tr>
<td>N</td>
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<td>10.1%</td>
</tr>
</tbody>
</table>

The starting material may be prepared as follows:

A solution of boron tribromide (32.5ml, 341mmol) in methylene chloride (60ml) was added in portions to a solution of 5-methoxy-2-methylindole (25g, 155mmol) in methylene chloride (250ml) cooled at -45°C. After stirring for 15 minutes at -30°C, the mixture was warmed up to ambient temperature and stirred for 1 hour. Methylene chloride (300ml) was added in portions and the mixture was cooled to 0°C. Water was added in portions and the mixture was adjusted to pH6 with 4N sodium hydroxide. The organic layer was separated. The aqueous layer was extracted with methylene chloride and the organic layers were combined, washed with water, brine, dried (MgSO₄) and the volatiles were removed by evaporation. The residue was purified by column chromatography eluting with ethyl acetate/methylene chloride (1/9 followed by 15/85) to give 5-hydroxy-2-methylindole (21.2g, 93%).

^1H NMR Spectrum: (DMSO_d₆) 2.35 (s, 3H); 5.95 (s, 1H); 6.5 (dd, 1H); 6.7 (s, 1H); 7.05 (d, 1H); 8.5 (s, 1H)

**Example 49**

A solution of 7-benzyloxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (0.2g, 0.5mmol), (prepared as described in Example 48), in a mixture of methylene chloride (5ml) and DMF (2ml) containing 10% palladium-on-charcoal (50mg) was treated with hydrogen at 1.8 atmospheres pressure for 2 hours. The suspension was filtered and the catalyst was washed with methanol followed by methylene chloride. The volatiles were removed from the filtrate by evaporation. The residue was triturated with water. The resulting solid was washed with water and dried under vacuum over phosphorus pentoxide at 60°C to give 7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (140mg, 89%).

MS - ESI: 322 [MH]^+

^1H NMR Spectrum: (DMSO_d₆) 2.4 (s, 3H); 4.0 (s, 3H); 6.15 (s, 1H); 6.9 (d, 1H); 7.2 (s, 1H); 7.25 (s, 1H); 7.3 (d, 1H); 7.6 (s, 1H); 8.4 (s, 1H)
**Example 50**

A suspension of 4-chloro-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline (150mg, 0.45mmol) and 5-hydroxy-2-trifluoromethylindole (109mg, 0.54mmol), (prepared as described for the starting material in Example 44), in DMF (1.5ml) containing potassium carbonate (94mg, 0.67mmol) was heated at 100°C for 1 hour. After cooling, the precipitate was collected by filtration, washed with ether, and dried under vacuum to give 6-methoxy-7-(3-methylsulphonylpropoxy)-4-(2-trifluoromethylindol-5-yloxy)quinazoline (195mg, 87%).

MS - ESI: 496 [MH]^+

1H NMR Spectrum: (DMSO_d6, CF3COOD) 2.25-2.4 (m, 2H), 3.1 (s, 3H), 3.35 (t, 2H), 4.1 (s, 3H), 4.4 (t, 2H), 7.1 (s, 1H), 7.3 (d, 1H), 7.5 (s, 1H), 7.6 (d, 1H), 7.7 (s, 1H), 7.78 (s, 1H), 8.9 (s, 1H)

The starting material was prepared as follows:

A solution of 3-(methylthio)-1-propanol (5.3g, 50mmol) in methanol (500ml) was added to a solution of OXONE, (trade mark of E.I. du Pont de Nemours & Co., Inc), (30g) in water (150ml) and the mixture stirred at ambient temperature for 24 hours. The precipitated solid was removed by filtration and the methanol removed from the filtrate by evaporation. The aqueous residue was saturated with sodium chloride and extracted with methylene chloride (4x25ml). The aqueous residue was then saturated with ammonium chloride and extracted with ethyl acetate (4x25ml). The extracts were combined, dried (MgSO4) and the solvent removed by evaporation to give 3-(methylsulphonyl)-1-propanol (610mg, 9%) as an oil.

1H NMR Spectrum: (CDCl3) 2.10(m, 2H); 2.96(s, 3H); 3.20(t, 2H); 3.80(t, 2H)

MS - ESI: 139 [MH]^+

Alternatively the 3-(methylsulphonyl)-1-propanol may be prepared as follows:

m-Chloroperoxybenzoic acid (67%, 25 g, 97.2 mmol) was added in portions to 3-(methylthio)-1-propanol (5 ml, 48.6 mmol) in solution in dichloromethane. Some m-chlorobenzoic acid precipitated out and was removed by filtration. The filtrate was evaporated and the residue was purified over alumina using first dichloromethane (100%) then dichloromethane/methanol (95/5) to give 3-(methylsulphonyl)-1-propanol (4.18 g, 62%) as an oil.
Triphenylphosphine (8.9g, 35.2mmol) was added to a suspension of 7-hydroxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (6g, 19.6mmol), (prepared as described for the starting material in Example 12), in methylene chloride (150ml). This was followed by the addition of 3-(methylsulphonyl)-1-propanol (3.5g, 25.4mmol) and diethyl azodicarboxylate (5.5ml, 35.2mmol) in portions. The reaction was complete once the reaction became homogeneous. Silica was added and the volatiles were removed by evaporation. The free flowing powder was placed on the top of a flash chromatography column pre-equilibrated with ethyl acetate (100%). Elution was done using ethyl acetate (100%) followed by methylene chloride/ethyl acetate/methanol (60/35/5). The volatiles were removed by evaporation to give 6-methoxy-7-(3-methylsulphonylpropoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (7.58 g, 91%) as a white solid.

$^1$H NMR Spectrum: (CDCl$_3$) 1.2(s, 9H); 2.4-2.5(m, 2H); 3.0(s, 3H); 3.25-3.35(t, 2H); 5.95(s, 1H); 7.1(s, 1H); 7.65(s, 1H); 8.2(s, 1H)

6-Methoxy-7-(3-methylsulphonylpropoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (7g, 17mmol) was suspended in methanol and 2M sodium hydroxide (3.3ml, 6.6mmol) was added with continuous stirring. The reaction mixture became homogeneous after 15 minutes. After a further 45 minutes water was added (7ml) and the reaction mixture was adjusted to pH10 with 2M hydrochloric acid. The precipitate (a white solid) was collected by filtration, washed with water and dried over phosphorus pentoxide under vacuum to give 6-methoxy-7-(3-methylsulphonylpropoxy)-3,4-dihydroquinazolin-4-one (5 g, 90%).

$^1$H NMR Spectrum: (DMSO$_d_6$) 2.2-2.3(m, 2H); 3.05(s, 3H); 3.35(t, 2H); 3.9(s, 3H); 4.25(t, 2H); 7.15(s, 1H); 7.5(s, 1H); 8.0(s, 1H)

6-Methoxy-7-(3-methylsulphonylpropoxy)-3,4-dihydroquinazolin-4-one (3.6g, 11.5mmol) was suspended in thionyl chloride (40ml). DMF (1.8ml) was added under argon and the mixture was heated at reflux for 1.5 hours. The thionyl chloride was eliminated by several azeotropic distillations using toluene. The solid residue was suspended in ice/water and a saturated solution of sodium hydrogen carbonate was added to adjust the mixture to pH7. The solid was collected by filtration, washed with water and dried in a vacuum dessicator over phosphorus pentoxide to give 4-chloro-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline (3.35g, 88%).
Examples 51-52

Using an analogous procedure to that described in Example 50, 4-chloro-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline, (prepared as described for the starting material in Example 50), was reacted with the appropriate phenol to give the compounds described in Table III:

**Table III**

<table>
<thead>
<tr>
<th>Example No.</th>
<th>Weight (mg)</th>
<th>Yield %</th>
<th>MS-ESI [M+H]^+</th>
<th>Ar</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>51</td>
<td>189</td>
<td>92</td>
<td>454</td>
<td>2-methylquinolin-7-yl</td>
<td>a</td>
</tr>
<tr>
<td>52</td>
<td>175</td>
<td>90</td>
<td>428</td>
<td>indol-5-yl</td>
<td>b</td>
</tr>
</tbody>
</table>

a) 4-Chloro-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline (150mg, 0.45mmol) was reacted with 7-hydroxy-2-methylquinoline (86.6mg, 0.54mmol), (J. Med. Chem. 1998, 41, 4062). After cooling, water was added and the precipitate was collected by filtration, washed with water, followed by ether and dried under vacuum to give 6-methoxy-7-(3-methylsulphonylpropoxy)-4-(2-methylquinolin-7-yloxy)quinazoline.

^H NMR Spectrum: (DMSO-d<sub>6</sub>, CF<sub>3</sub>COOD) 2.2-2.35 (m, 2H), 2.95 (s, 3H), 3.1 (s, 3H), 3.35 (m, 2H), 4.05 (s, 3H), 4.4 (t, 2H), 7.5 (s, 1H), 7.7 (s, 1H), 7.95 (dd, 1H), 8.02 (d, 1H), 8.2 (s, 1H), 8.48 (d, 1H), 8.7 (s, 1H), 9.12 (d, 1H)

b) Using an analogous procedure to that described in note a), 4-chloro-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline (150mg, 0.45mmol) was reacted with 5-hydroxyindole (72.4mg, 0.54mmol) to give 4-(indol-5-yloxy)-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline.

^H NMR Spectrum: (DMSO-d<sub>6</sub>) 2.2-2.35 (m, 2H), 3.1 (s, 3H), 3.3-3.4 (t, 2H), 4.0 (s, 3H), 4.4 (t, 2H), 6.5 (s, 1H), 7.0 (dd, 1H), 7.4 (s, 1H), 7.4-7.5 (m, 3H), 7.6 (s, 1H), 8.5 (s, 1H), 11.25
Example 53

0.5M Triphenylphosphine in methylene chloride and diisopropyl azodicarboxylate (150μl, 0.75mmol) were added in portions to a suspension of 7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (112mg, 0.35mmol), (prepared as described in Example 49), and N,N-dimethylethanolamine (62mg, 0.7mmol) in methylene chloride (2ml). After stirring for 2 hours at ambient temperature, the reaction mixture was poured onto an isolute® column (10g of silica) and eluted with ethyl acetate/methylene chloride (1/1) followed by methanol/ethyl acetate/methylene chloride (10/40/50), methanol/methylene chloride (10/90), and 3M ammonia in methanol/methanol/methylene chloride (5/15/80). After removal of the volatiles by evaporation, the residue was dissolved in the minimum amount of methylene chloride (about 3ml) and ether and petroleum ether (about 10ml) was added. The resulting precipitate was collected by filtration and dried under vacuum to give 7-(2-(N,N-dimethylamino)ethoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (52mg, 38%).

MS - ESI: 393 [MH]^+

1H NMR Spectrum: (DMSO_d6) 2.25 (s, 6H), 2.4 (s, 3H), 2.75 (t, 2H), 4.0 (s, 3H), 4.3 (t, 2H), 6.15 (s, 1H), 6.87 (d, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 7.5 (s, 1H)

Examples 54-56

Using an analogous procedure to that described in Example 53, the appropriate alcohols were reacted with 7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline, (prepared as described in Example 49), in analogous proportions to give the compounds described in Table IV:

Table IV

<table>
<thead>
<tr>
<th>Example</th>
<th>Weight</th>
<th>Yield</th>
<th>MS-ESI</th>
<th>R</th>
<th>Note</th>
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</thead>
</table>

![Chemical Structure Image]
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<th>No.</th>
<th>(mg)</th>
<th>%</th>
<th>[MH]+</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>54</td>
<td>25</td>
<td>17</td>
<td>419</td>
<td>2-pyrrolidin-1-yloethoxy</td>
</tr>
<tr>
<td>55</td>
<td>112</td>
<td>74</td>
<td>433</td>
<td>1-methylpiperidin-3-yloethoxy</td>
</tr>
<tr>
<td>56</td>
<td>115</td>
<td>72</td>
<td>456</td>
<td>2-(N-methyl-N-(4-pyridyl)amino)ethoxy</td>
</tr>
</tbody>
</table>

a) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline was reacted with 1-(2-hydroxyethyl)pyrrolidine (81mg) to give **6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-pyrrolidin-1-yloethoxy)quinazoline**.

1H NMR Spectrum: (DMSO-d6) 1.65-1.8 (m, 4H), 2.4 (s, 3H), 2.6 (br s, 4H), 2.9 (t, 2H), 4.0 (s, 3H), 4.3 (t, 2H), 6.15 (s, 1H), 6.9 (d, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

b) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline was reacted with 1-methyl-3-piperidinemethanol (90mg) to give **6-methoxy-4-(2-methylindol-5-yloxy)-7-(1-methylpiperidin-3-yloethoxy)quinazoline**.

1H NMR Spectrum: (DMSO-d6) 1.45-2.2 (m, 7H), 2.18 (s, 3H), 2.4 (s, 3H), 2.6 (br d, 1H), 2.85 (br d, 1H), 4.0 (s, 3H), 4.1 (d, 2H), 6.15 (s, 1H), 6.9 (d, 1H), 7.25 (d, 1H), 7.3 (d, 1H), 7.35 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

c) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline was reacted with 2-(N-methyl-N-(4-pyridyl)amino)ethanol (106mg), (EP 0359389), to give **6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(N-methyl-N-(4-pyridyl)amino)ethoxy)quinazoline**.

1H NMR Spectrum: (DMSO-d6) 2.4 (s, 3H), 3.1 (s, 3H), 3.9 (t, 2H), 3.97 (s, 3H), 4.4 (t, 2H), 6.15 (s, 1H), 6.75 (d, 2H), 6.87 (dd, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.35 (s, 1H), 7.6 (s, 1H), 8.15 (d, 2H), 8.5 (s, 1H)

**Examples 57-66**

Using an analogous procedure to that described in Example 53, except that ammonia in methanol was not necessary during the column chromatography, the appropriate alcohols were reacted with 7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline, (prepared as described in Example 49), in analogous proportions to give the compounds described in Table V:
Table V

<table>
<thead>
<tr>
<th>Example No.</th>
<th>Weight (mg)</th>
<th>Yield %</th>
<th>MS-ESI [MH]+</th>
<th>R</th>
<th>Note</th>
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</thead>
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<tr>
<td>57</td>
<td>115</td>
<td>76</td>
<td>435</td>
<td>2-morpholinoethoxy</td>
<td>a</td>
</tr>
<tr>
<td>58</td>
<td>64</td>
<td>42</td>
<td>433</td>
<td>2-piperidinoethoxy</td>
<td>b</td>
</tr>
<tr>
<td>59</td>
<td>66</td>
<td>43</td>
<td>437</td>
<td>2-(N-(2-methoxyethyl)-N-methylamino)ethoxy</td>
<td>c</td>
</tr>
<tr>
<td>60</td>
<td>118</td>
<td>75</td>
<td>449</td>
<td>3-morpholinopropoxy</td>
<td>d</td>
</tr>
<tr>
<td>61</td>
<td>101</td>
<td>68</td>
<td>424</td>
<td>2-(2-methoxyethoxy)ethoxy</td>
<td>e</td>
</tr>
<tr>
<td>62</td>
<td>81</td>
<td>57</td>
<td>407</td>
<td>3-(N,N-dimethylamino)propoxy</td>
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<tr>
<td>63</td>
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<td>92</td>
<td>497</td>
<td>3-(1,1-dioxothiomorpholino)propoxy</td>
<td>g</td>
</tr>
<tr>
<td>64</td>
<td>121</td>
<td>83</td>
<td>417</td>
<td>2-(1H-1,2,4-triazol-1-yl)ethoxy</td>
<td>h</td>
</tr>
<tr>
<td>65</td>
<td>38</td>
<td>22</td>
<td>492</td>
<td>2-(2-(4-methylpiperazin-1-yl)ethoxy)ethoxy</td>
<td>i</td>
</tr>
<tr>
<td>66</td>
<td>80</td>
<td>48</td>
<td>479</td>
<td>2-(2-morpholinoethoxy)ethoxy</td>
<td>j</td>
</tr>
</tbody>
</table>

a) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline was reacted with 4-(2-hydroxyethyl)morpholine (92mg) to give 6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-morpholinoethoxy)quinazoline.

¹H NMR Spectrum: (DMSO₆) 2.4 (s, 3H), 2.5-2.7 (m, 4H), 2.8 (t, 2H), 3.6 (t, 4H), 4.0 (s, 3H), 4.35 (t, 2H), 6.15 (s, 1H), 6.87 (dd, 1H), 7.25 (s, 1H), 7.32 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

b) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline was reacted with 1-(2-hydroxyethyl)piperidine (90mg) to give 6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-
piperedinoethoxy)quinazoline.

$^1$H NMR Spectrum: (DMSO$_d_6$) 1.3-1.45 (m, 2H), 1.4-1.6 (m, 4H), 2.4 (s, 3H), 2.4-2.5 (m, 4H), 2.75 (t, 2H), 3.97 (s, 3H), 4.3 (t, 2H), 6.15 (s, 1H), 6.9 (d, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

c) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline was reacted with 2-(N-(2-methoxyethyl)-N-methylamino)ethanol (93mg) to give 6-methoxy-7-(2-(N-(2-methoxyethyl)-N-methylamino)ethoxy)-4-(2-methylindol-5-yloxy)quinazoline.

$^1$H NMR Spectrum: (DMSO$_d_6$) 2.35 (s, 3H), 2.4 (s, 3H), 2.65 (t, 2H), 2.85 (t, 2H), 3.25 (s, 3H), 3.45 (t, 2H), 3.97 (s, 3H), 4.25 (t, 2H), 6.15 (s, 1H), 6.9 (dd, 1H), 7.25 (s, 1H), 7.32 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

The starting material was prepared as follows:

A mixture of 2-(methylamino)ethanol (5.4g, 72 mmol), 2-bromoethyl methyl ether (10g, 72 mmol) and triethylamine (10ml, 72 mmol) in acetonitrile (70ml) was refluxed overnight. After cooling, the solid was filtered and the filtrate was evaporated. The residue was triturated with ether. The ether layer was separated and evaporated to give 2-(N-(2-methoxyethyl)-N-methylamino)ethanol (3g, 31%).

MS-ESI: 134 [MH]+

$^1$H NMR Spectrum: (CDCl$_3$) 2.35 (s, 3H), 2.6 (t, 2H), 2.65 (t, 2H), 3.35 (s, 3H), 3.5 (t, 2H), 3.6 (t, 2H)

d) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline was reacted with 4-(3-hydroxypropyl)morpholine (102mg) to give 6-methoxy-4-(2-methylindol-5-yloxy)-7-(3-morpholinopropoxy)quinazoline.

$^1$H NMR Spectrum: (DMSO$_d_6$) 1.9-2.1 (m, 2H), 2.4 (s, 3H), 2.45 (t, 2H), 2.45-2.6 (s, 4H), 3.6 (t, 4H), 4.0 (s, 3H), 4.25 (t, 2H), 6.15 (s, 1H), 6.9 (d, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.38 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

The starting material was prepared as follows:

Morpholine (94g, 1.08mol) was added dropwise to a solution of 3-bromo-1-propanol (75g, 0.54mol) in toluene (750ml) and the reaction then heated at 80°C for 4 hours. The
mixture was allowed to cool to ambient temperature and the precipitated solid was removed by filtration. The volatiles were removed from the filtrate and the resulting yellow oil was purified by distillation at 0.4-0.7 mmHg to give 4-(3-hydroxypropyl)morpholine (40g, 50%) as a colourless oil.

b.p. 68-70°C (~0.5mmHg)

\[ {^1}H \text{ NMR Spectrum: (DMSO}_d_6) 1.65-1.78 (m, 2H); 2.50 (t, 4H); 2.60 (t, 2H); 3.68 (t, 4H); 3.78 (t, 2H); 4.90 (br d, 1H) \]

e) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline was reacted with 2-(2-methoxyethoxy)ethanol (84mg) to give 6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-4-(2-methylindol-5-yloxy)quinazoline.

\[ {^1}H \text{ NMR Spectrum: (DMSO}_d_6) 2.42 (s, 3H), 3.27 (s, 3H), 3.5 (t, 2H), 3.65 (t, 2H), 3.85 (t, 2H), 4.0 (s, 3H), 4.32 (t, 2H), 6.15 (s, 1H), 6.9 (d, 1H), 7.3 (s, 1H), 7.35 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H) \]

f) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline was reacted with 3-(N,N-dimethylamino)propanol (72mg) to give 7-(3-N,N-dimethylaminopropoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline.

\[ {^1}H \text{ NMR Spectrum: (DMSO}_d_6) 1.9-2.0 (m, 2H), 2.17 (s, 6H), 2.4 (s, 3H), 3.98 (s, 3H), 4.22 (t, 2H), 6.14 (s, 1H), 6.88 (dd, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.35 (s, 1H), 7.6 (s, 1H), 8.47 (s, 1H) \]

g) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline was reacted with 3-(1,1-dioxothiomorpholino)-1-propanol (135mg), (prepared as described for the starting material in Example 5), to give 7-(3-(1,1-dioxothiomorpholino)propoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline.

\[ {^1}H \text{ NMR Spectrum: (DMSO}_d_6) 1.9-2.0 (m, 2H), 2.38 (s, 3H), 2.65 (t, 2H), 2.9 (br s, 4H), 3.1 (br s, 4H), 3.96 (s, 3H), 4.25 (t, 2H), 6.12 (s, 1H), 6.85 (dd, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.37 (s, 1H), 7.56 (s, 1H), 8.46 (s, 1H) \]

h) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline was reacted with 2-(1H-1,2,4-triazol-1-yl)ethanol (79mg), (Ann. Phar. Fr. 1977, 35, 503-508), to give 6-methoxy-4-
(2-methylindol-5-yloxy)-7-(2-(1H-1,2,4-triazol-1-yl)ethoxy)quinazoline.

\(^1\)H NMR Spectrum: (DMSO\(_d_6\)) 2.42 (s, 3H), 3.96 (s, 3H), 4.62 (m, 2H), 4.75 (m, 2H), 6.15 (s, 1H), 6.9 (dd, 1H), 7.27 (s, 1H), 7.32 (d, 1H), 7.47 (s, 1H), 7.63 (s, 1H), 8.03 (s, 1H), 8.51 (s, 1H), 8.60 (s, 1H)

i) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline was reacted with 2-(2-(4-methylpiperazin-1-yl)ethoxy)ethanol (132mg), (Arzneim. Forsch. 1966, 16, 1557-1560), to give 6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(4-methylpiperazin-1-yl)ethoxy)ethoxy)quinazoline.

\(^1\)H NMR Spectrum: (DMSO\(_d_6\)) 2.15 (s, 3H), 2.2-2.6 (m, 10H), 2.4 (s, 3H), 3.65 (t, 2H), 3.85 (t, 2H), 4.03 (s, 3H), 4.35 (m, 2H), 6.16 (s, 1H), 6.9 (dd, 1H), 7.3 (s, 1H), 7.35 (d, 1H), 7.4 (s, 1H), 7.61 (s, 1H), 8.5 (s, 1H)

j) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline was reacted with 2-(2-morpholinoethoxy)ethanol (123mg) to give 6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(2-morpholinoethoxy)ethoxy)quinazoline.

\(^1\)H NMR Spectrum: (DMSO\(_d_6\)) 2.40 (s, 3H), 2.4-2.5 (m, 4H), 2.4-2.6 (m, 2H), 3.55 (t, 4H), 3.6 (t, 2H), 3.85 (t, 2H), 3.97 (br s, 3H), 4.15 (br s, 2H), 6.15 (s, 1H), 6.9 (d, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 8.48 (s, 1H)

The starting material was prepared as follows:

2-(2-Chloroethoxy)ethanol (1.25g, 10mmol) was added to a mixture of morpholine (2.58g, 30mmol) and potassium carbonate (5.5g, 40mmol) in acetonitrile (50ml). The mixture was heated at reflux for 6 hours and then stirred for 18 hours at ambient temperature. The insolubles were removed by filtration and the volatiles were removed from the filtrate by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol (95/5 followed by 90/10 and then 80/20) to give 2-(2-morpholinoethoxy)ethanol (600mg, 34%).

MS - (EI): 175 [M+]

\(^1\)H NMR Spectrum: (CDCl\(_3\)) 2.5(br s, 4H); 2.59(t, 2H); 3.6-3.85(m, 10H)

Example 67
A solution of 4-chloro-6-methoxy-7-(3-piperidinopropoxy)quinazoline (100mg, 0.29mmol), 5-hydroxy-2-methylindole (53mg, 0.36mmol), (prepared as described for the starting material in Example 48), and potassium carbonate (62mg, 0.44mmol) in DMF (2ml) was heated at 85°C for 3 hours, followed by heating at 95°C for 2 hours. After cooling, ice/water (15ml) was added and the precipitate was collected by filtration and dried under vacuum. The solid was purified by column chromatography eluting with methylene chloride/methanol (95/5) followed by methylene chloride/methanol/3M ammonia in methanol (95/3.2) to give 6-methoxy-4-(2-methylindol-5-yl-oxy)-7-(3-piperidinopropoxy)quinazoline (71mg, 54%).

MS - ESI: 447 [MH]^+

1H NMR Spectrum: (DMSO_d6) 1.35-1.4 (m, 2H), 1.45-1.55 (m, 4H), 1.92-2.0 (m, 2H), 2.3-2.4 (m, 4H), 2.40 (s, 3H), 2.4-2.5 (m, 2H), 3.97 (s, 3H), 4.22 (t, 2H), 6.15 (s, 1H), 6.9 (d, 1H), 7.27 (s, 1H), 7.8 (d, 1H), 7.35 (s, 1H), 7.58 (s, 1H), 8.48 (s, 1H)

The starting material was prepared as follows:

Diethyl azodicarboxylate (3.9ml, 24.5mmol) was added in portions to a suspension of 7-hydroxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (5g, 16.3mmol), (prepared as described for the starting material in Example 12), 3-bromo-1-propanol (2.21ml, 24.5mmol) and triphenylphosphine (6.42g, 24.5mmol) in methylene chloride (50ml). After stirring for 2 hours at ambient temperature, the volatiles were removed under vacuum and the residue was purified by column chromatography eluting with methylene chloride followed by methylene chloride/methanol (95/5) to give 7-(3-bromopropoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (6g, 86%).

MS - ESI: 427-429 [MH]^+

1H NMR Spectrum: (DMSO_d6) 1.12 (s, 9H), 2.32 (t, 2H), 3.7 (t, 2H), 3.9 (s, 3H), 4.25 (t, 2H), 5.9 (s, 2H), 7.20 (s, 1H), 7.51 (s, 1H), 8.36 (s, 1H)

Elemental analysis: Found C 50.1 H 5.4 N 6.4
Requires C 50.2 H 5.5 N 6.5%

C_{19}H_{23}BrN_{2}O_{3}, 0.2H_2O

A solution of 7-(3-bromopropoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (2.89g, 6.78mmol) in piperidine (10ml) was heated at 100°C for 1 hour. After cooling, the volatiles were removed under vacuum. The residue was dissolved in methylene chloride, and washed with saturated ammonium chloride and brine. The organic
layer was dried (MgSO₄) and the volatiles were removed by evaporation. The residue was
dried under vacuum to give 6-methoxy-7-(3-piperidinopropoxy)-3-((pivaloyloxy)methyl)-3,4-
dihydroquinazolin-4-one (2.4g, 83%).
MS - ESI: 432 [MH]+

1H NMR Spectrum: (DMSOd₆) 1.15 (s, 9H), 1.35-1.5 (m, 1H), 1.6-1.8 (m, 3H), 1.8-1.9 (d,
2H), 2.2-2.3 (m, 2H), 2.95 (t, 2H), 3.25 (t, 2H), 3.55 (d, 2H), 3.95 (s, 3H), 4.25 (t, 2H), 5.94
(s, 2H), 7.24 (s, 1H), 7.56 (s, 1H), 8.46 (s, 1H)

A solution of 6-methoxy-7-(3-piperidinopropoxy)-3-((pivaloyloxy)methyl)-3,4-
dihydroquinazolin-4-one (2.35g, 5.45mmol) in 7M ammonia in methanol (50ml) was stirred
overnight at ambient temperature. The volatiles were removed under vacuum and the residue
was triturated with ether, filtered and washed with ether followed by ether/methylene chloride
(1/1) and dried under vacuum to give 6-methoxy-7-(3-piperidinopropoxy)-3,4-
dihydroquinazolin-4-one (1.65g, 95%).
MS - ESI: 318 [MH]+

1H NMR Spectrum: (DMSOd₆) 1.3-1.4 (m, 2H), 1.4-1.55 (m, 4H), 1.85-1.95 (m, 2H), 2.35 (br
s, 4H), 2.4 (t, 2H), 3.9 (s, 3H), 4.15 (t, 2H), 7.11 (s, 1H), 7.44 (s, 1H), 7.9 (s, 1H)
Elemental analysis:

\[ \text{C}_{17}\text{H}_{23}\text{N}_{2}\text{O}_{6} \cdot 0.2\text{H}_{2}\text{O} \]

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<td>H 7.4</td>
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<tr>
<td>N 13.1</td>
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A solution of 6-methoxy-7-(3-piperidinopropoxy)-3,4-dihydroquinazolin-4-one (1.5g,
4.7mmol) in thionyl chloride (15ml) containing DMF (1.5ml) was heated at reflux for 3 hours.
After cooling, the volatiles were removed under vacuum. The residue was azeotroped with
toluene. The solid was partitioned between methylene chloride and sodium hydrogen
carbonate. The aqueous layer was adjusted to pH10 with 6M aqueous sodium hydroxide. The
organic layer was separated, washed with brine, dried (MgSO₄) and the volatiles were
removed by evaporation. The residue was purified by column chromatography to give 4-
chloro-6-methoxy-7-(3-piperidinopropoxy)quinazoline (1.21g, 76%).
MS - ESI: 336 [MH]+

1H NMR Spectrum: (DMSOd₆) 1.35-1.45 (m, 2H), 1.5-1.6 (m, 4H), 1.9-2.05 (m, 2H), 2.4 (br
s, 4H), 2.45 (t, 2H), 4.0 (s, 3H), 4.29 (t, 2H), 7.41 (s, 1H), 7.46 (s, 1H), 8.9 (s, 1H)

**Example 68**

Using an analogous procedure to that described in Example 67, 4-chloro-6-methoxy-7-
(3-piperidinopropoxy)quinazoline (100mg), (prepared as described for the starting material in Example 67), was reacted with 5-hydroxyindole (48mg, 0.36mmol) to give **4-(indol-5-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline** (57mg, 45%).

MS - ESI: 433 [MH]^+

1H NMR Spectrum: (DMSO_d6) 1.4 (br s, 2H), 1.45-1.6 (br s, 4H), 1.9-2.1 (m, 2H), 2.4 (br s, 4H), 2.45 (t, 2H), 4.0 (s, 3H), 4.25 (t, 2H), 6.47 (s, 1H), 7.0 (d, 1H), 7.35 (s, 1H), 7.45 (s, 2H), 7.47 (d, 1H), 7.61 (s, 1H), 8.49 (s, 1H)

**Example 69**

A solution of 7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (161mg, 0.5mmol), (prepared as described in Example 49), 4-(4-methylphenylsulphonyloxy)methyl-1-tert-butoxycarbonylpiperidine (222mg, 0.6mmol), (prepared as described for the starting material in Example 10), and potassium carbonate (188mg, 1mol) in DMF (1.6ml) was heated at 100°C for 2 hours. After cooling, water was added. The precipitate was collected by filtration, washed with water, and dried under vacuum over phosphorus pentoxide at 60°C. The solid was triturated with petroleum ether, collected by filtration, washed with a mixture of ether/petroleum ether (1/1) and dried under vacuum to give **6-methoxy-4-(2-methylindol-5-yloxy)-7-(1-tert-butoxycarbonylpiperidin-4-ylmethoxy)quinazoline** (200mg, 77%).

MS - ESI: 541 [MNa]^+

1H NMR Spectrum: (DMSO_d6) 1.1-1.3 (m, 2H), 1.4 (s, 9H), 1.8 (d, 2H), 1.95-2.1 (m, 1H), 2.4 (s, 1H), 2.7-2.85 (br s, 2H), 3.95 (s, 3H), 4.05 (d, 2H), 6.12 (s, 1H), 6.85 (d, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.35 (s, 1H), 7.55 (s, 1H), 8.45 (s, 1H)

**Example 70**

A solution of 6-methoxy-4-(2-methylindol-5-yloxy)-7-(1-tert-butoxycarbonylpiperidin-4-ylmethoxy)quinazoline (155mg, 0.3mmol), (prepared as described in Example 69), in methylene chloride (5ml) containing TFA (1ml) was stirred at ambient temperature for 30 minutes. The volatiles were removed under vacuum and the residue was treated with water and adjusted to pH12 with 2M sodium hydroxide. The mixture was extracted with methylene chloride. The organic layer was dried (MgSO4), and the volatiles were removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/ethyl acetate/methanol (5/4/1) followed by methylene
chloride/methanol (9/1) and by 3M ammonia in methanol/methanol/methylene chloride (5/15/80). After removal of the solvent by evaporation, the residue was dissolved in the minimum of methylene chloride, ether was added followed by petroleum ether. The precipitate was collected by filtration, washed with ether and dried under vacuum to give 6-methoxy-4-(2-methylindol-5-yl)-7-(piperidin-4-ylmethoxy)quinazoline (120mg, 96%).

MS - ESI: 419 [M+H]+

1H NMR Spectrum: (DMSO-d6, CF3COOD) 1.5-1.7 (m, 2H), 2.05 (br d, 2H), 2.3-2.4 (m, 1H), 2.4 (s, 3H), 3.05 (t, 2H), 3.4 (d, 2H), 4.09 (s, 3H), 4.25 (d, 2H), 6.95 (dd, 1H), 7.35 (s, 1H), 7.4 (d, 1H), 7.6 (s, 1H), 7.85 (s, 1H), 9.15 (s, 1H)

Example 71

Methoxyacetaldehyde (368mg, 3.47mmol) (freshly distilled) followed by sodium triacetoxyborohydride (552mg, 2.6mmol) were added to a solution of 6-methoxy-4-(2-methylindol-5-yl)-7-(piperidin-4-ylmethoxy)quinazoline (726mg, 1.74mmol), (prepared as described in Example 70), in a mixture of methylene chloride (15ml) and methanol (15ml). After stirring for 1.5 hours at ambient temperature, saturated sodium hydrogen carbonate was added. The volatiles were removed under vacuum and the residue was partitioned between methylene chloride and water. The organic layer, was separated, washed with water, brine, dried (MgSO4) and the volatiles were removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol (80/20). After removal of the solvent, the residue was triturated with ether, collected by filtration, washed with ether and dried under vacuum at 60°C to give 6-methoxy-7-(1-(2-methoxyethyl)piperidin-4-ylmethoxy)-4-(2-methylindol-5-yl)quinazoline (392mg, 47%).

MS - ESI 477 [M+H]+

1H NMR Spectrum: (DMSO-d6, CF3COOD) 1.6-1.8 (m, 2H), 2.05 (br d, 2H), 2.15-2.3 (m, 1H), 2.4 (s, 3H), 3.05 (t, 2H), 3.3 (br s, 2H), 3.32 (s, 3H), 3.58 (d, 2H), 3.65 (br s, 2H), 4.05 (s, 3H), 4.18 (d, 2H), 6.2 (s, 0.5 H (partly exchanged)), 6.92 (dd, 1H), 7.32 (s, 1H), 7.35 (d, 1H), 7.55 (s, 1H), 7.8 (s, 1H), 9.15 (s, 1H)

Elemental analysis:

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<tr>
<td>N</td>
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</table>

C27H32N4O4

The starting material was prepared as follows:
A solution of 1,1,2-trimethoxyethane (90g, 750mmol) in water (570ml) containing 12 N hydrochloric acid (3.75ml) was stirred at 40°C for 1.5 hours. After cooling, solid sodium chloride was added and the mixture was extracted with ether. The organic layer was dried (MgSO₄). The organic layer was distilled and the fraction from 70-90°C was collected to give methoxyacetaldehyde (20.3g) which was used directly in the next step.

**Example 72**

Diphenylphosphoryl azide (83mg, 0.3mmol) was added in portions to a solution of 7-(2-carboxyvinyl)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (75mg, 0.2mmol), triethylamine (40mg, 0.4mmol) and 1-(2-aminoethyl)pyrrolidine (46mg, 0.4mmol) in DMF (1.5ml). After stirring for 5 hours at ambient temperature, the mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water, brine, dried (MgSO₄) and the volatiles were removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol (9/1) followed by methylene chloride/3M ammonia in methanol (9/1). After removal of the solvent, the solid was triturated with ether, collected by filtration, washed with ether and dried under vacuum to give 6-methoxy-4-(2-methylindol-5-yloxy)-7-((2-(2-pyrrolidin-1-ythyl)carbamoyl)vinyl)quinazoline (25mg, 26%).

MS - ESI: 472 [MH]⁺

H NMR Spectrum: (DMSO-d₆, CF₃COOD) 1.8-1.95 (m, 2H), 1.95-2.1 (m, 2H), 2.48 (s, 3H), 3.0-3.2 (m, 2H), 3.35 (t, 2H), 3.6 (t, 2H), 3.65 (br s, 2H), 4.11 (s, 3H), 6.18 (s, 0.5H, partially exchanged), 6.95 (dd, 1H), 7.05 (d, 1H), 7.35 (s, 1H), 7.37 (d, 1H), 7.8 (s, 1H), 7.86 (d, 1H), 8.2 (s, 1H), 8.76 (s, 1H)

The starting material was prepared as follows:

Trifluoromethanesulphonic anhydride (338mg, 1.2mmol) was added to a suspension of 4-(4-chloro-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline (320mg, 1mmol), (prepared as described for the starting material in Example 5), in methylene chloride (2ml) containing pyridine (2ml) cooled at 5°C. When the addition was complete, the mixture was left to warm to ambient temperature and stirred for 1 hour. After removal of the volatiles by evaporation, the residue was partitioned between ethyl acetate/ether and water. The organic layer was separated, washed with 0.5M hydrochloric acid, followed by water, brine, dried
(MgSO₄) and evaporated to give 4-(4-chloro-2-fluorophenoxy)-6-methoxy-7-(trifluoromethylsulphonyloxy)quinazoline (400mg, 88%).

MS - ESI: 453 - 455 [MH]^+

^1H NMR Spectrum: (DMSO_d₆) 4.15 (s, 3H), 7.5 (d, 1H), 7.62 (t, 1H), 7.78 (d, 1H), 8.02 (s, 1H), 8.27 (s, 1H), 8.77 (s, 1H)

Triethylamine (33mg, 0.33mmol) and tert-butyl acrylate (77mg, 0.6mmol) followed by diphenylpropylphosphine (3.4mg, 0.008mmol) and palladium(II) acetate (1.7mg, 0.0075mmol) were added to a solution of 4-(4-chloro-2-fluorophenoxy)-6-methoxy-7-(trifluoromethylsulphonyloxy)quinazoline (136mg, 0.3mmol) in DMF (1.5ml) under argon.

When the addition was complete the reaction flask was purged with argon. The mixture was stirred at 80-85°C for 6 hours. After cooling, the mixture was partitioned between ethyl acetate and water. The aqueous layer was adjusted to pH6 with 2M hydrochloric acid. The organic layer was separated, washed with water, brine, dried (MgSO₄) and evaporated. The residue was purified by column chromatography eluting with methylene chloride/ether (95/5). After removal of the solvent under vacuum, the solid was triturated with pentane/ether, collected by filtration and dried under vacuum to give 4-(4-chloro-2-fluorophenoxy)-6-methoxy-7-(2-(tert-butoxycarbonyl)vinyl)quinazoline (63mg, 49%).

MS - ESI: 431 [MH]^+

^1H NMR Spectrum: (DMSO_d₆) 1.51 (s, 9H), 4.07 (s, 3H), 6.87 (d, 1H), 7.45 (d, 1H), 7.6 (t, 1H), 7.7 (s, 1H), 7.75 (d, 1H), 7.91 (d, 1H), 8.39 (s, 1H), 8.65 (s, 1H)

Elemental analysis:

Found C 61.1 H 4.8 N 6.6

Requires C 61.3 H 4.7 N 6.5%

A solution of 4-(4-chloro-2-fluorophenoxy)-6-methoxy-7-(2-(tert-butoxycarbonyl)vinyl)quinazoline (581mg, 1.31mmol) in a mixture of methylene chloride/TFA (2.5ml/2.5ml) was stirred at ambient temperature for 1.5 hours. After removal of the volatiles under vacuum, the residue was partitioned between ethyl acetate and water. The aqueous layer was adjusted to pH3 with 0.5M sodium hydroxide. The organic layer was separated and the aqueous layer was further extracted with ethyl acetate. The combined organic layers were washed with brine, dried (MgSO₄) and evaporated to give 7-(2-carboxyvinyl)-4-(4-chloro-2-fluorophenoxy)-6-methoxyquinazoline (430mg, 85%).

^1H NMR Spectrum: (DMSO_d₆) 4.08 (s, 3H), 6.9 (d, 1H), 7.45 (s, 1H), 7.6 (t, 1H), 7.70 (s,
1H), 7.73 (d, 1H), 7.95 (d, 1H), 8.39 (s, 1H), 8.66 (s, 1H)

1M Sodium HMDS in THF (0.84ml, 8.4mmol) was added to a suspension of 7-(2-carboxyvinyl)-4-(4-chloro-2-fluorophenoxy)-6-methoxyquinazoline (105mg, 0.28mmol) and 5-hydroxy-2-methylindole (82mg, 0.56mmol), (prepared as described for the starting material in Example 48), in DMSO (1.5ml). After stirring for 2 hours at ambient temperature, the mixture was partitioned between ethyl acetate and water. The aqueous layer was adjusted to pH3 with 2M hydrochloric acid. The organic layer was washed with water, brine, dried (MgSO₄) and evaporated. The residue was purified by column chromatography eluting with methylene chloride/methanol (95/5 followed by 90/10 and 70/30) to give 7-(2-carboxyvinyl)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (75mg, 71%).

^H NMR Spectrum: (DMSO_d₆) 2.4 (s, 3H), 4.06 (s, 3H), 6.15 (s, 1H), 6.82 (d, 1H), 6.9 (dd, 1H), 7.3 (s, 1H), 7.35 (d, 1H), 7.68 (s, 1H), 7.84 (d, 1H), 8.25 (s, 1H), 8.55 (s, 1H)

**Example 73**

A suspension of 7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (321mg, 1mmol), (prepared as described in Example 49), 1-bromo-3-chloropropane (120µl, 1.2mmol) and potassium carbonate (359mg, 2.6mmol) in DMF (5ml) was stirred at ambient temperature overnight. After addition of water, the precipitate was collected by filtration, washed with water and dried over phosphorus pentoxide at 60°C to give 7-(3-chloropropoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (280mg, 70%).

MS - ESI: 398 [MH]^+

^H NMR Spectrum: (DMSO_d₆) 2.2-2.35 (m, 2H), 2.4 (s, 3H), 3.85 (t, 2H), 4.0 (s, 3H), 4.32 (t, 2H), 6.15 (s, 1H), 6.88 (d, 1H), 7.27 (s, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

**Example 74**

A solution of 7-(3-chloropropoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (150mg, 0.38mmol), (prepared as described in Example 73), in 1-methylpiperazine (2ml) was heated at 100°C for 2 hours. After cooling, the mixture was partitioned between ethyl acetate and aqueous 5% sodium hydrogen carbonate. The organic layer was separated, washed with water, brine, dried (MgSO₄) and evaporated. The residue was purified by column chromatography on an isolute column eluting with methanol/ethyl acetate/methylene chloride (1/4/5 followed by 1/9/0) and 3M ammonia in methanol/methanol/methylene chloride
After removal of the solvent under vacuum, the solid was dissolved in the minimum of methylene chloride and ether/petroleum ether was added. The precipitate was collected by filtration, and dried under vacuum to give 6-methoxy-4-(2-methylindol-5-yloxy)-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline (55mg, 32%).

MS - ESI: 462 [MH]^+

^1H NMR Spectrum: (DMSO-d_6, CF_3COOD, 60^oC) 2.2-2.3 (m, 2H), 2.4 (s, 3H), 2.9 (s, 3H), 3.4-3.5 (m, 4H), 3.5-3.8 (m, 6H), 4.07 (s, 3H), 4.4 (t, 2H), 6.95 (d, 1H), 7.35 (s, 1H), 7.4 (d, 1H), 7.55 (s, 1H), 7.8 (s, 1H), 8.95 (s, 1H)

Example 75

Triphenylphosphine (262mg, 1mmol) and N,N-diethylethanolamine (88mg, 0.75mmol) were added to a suspension of 7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (160mg, 0.5mmol), (prepared as described in Example 49), in methylene chloride (5ml), followed by the addition, in portions, of diethyl azodicarboxylate (165μl, 1mmol). After stirring for 1 hour at ambient temperature, the volatiles were removed under vacuum. The residue was purified by column chromatography eluting with methylene chloride/methanol (95/5) followed by methylene chloride/3M ammonia in methanol (90/10) to give 7-(2-(N,N-diethylamino)ethoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (147mg, 70%).

MS - ESI 421 [MH]^+

^1H NMR Spectrum: (DMSO-d_6) 1.0 (t, 6H), 2.41 (s, 3H), 2.6 (q, 4H), 2.88 (t, 2H), 3.97 (s, 3H), 4.24 (t, 2H), 6.14 (s, 1H), 6.89 (dd, 1H), 7.25 (s, 1H), 7.32 (d, 1H), 7.38 (s, 1H), 7.58 (s, 1H), 8.48 (s, 1H)

Elemental analysis: Found C 66.2 H 6.9 N 13.1 Requires C 66.3 H 6.9 N 12.9%

Example 76

Using an analogous procedure to that described in Example 75, 7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (321mg, 1mmol), (prepared as described in Example 49), was reacted with 2-((1-tertbutoxycarbonyl)piperidin-4-yloxy)ethanol (294mg, 1.2mmol) to give 6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-((1-tertbutoxycarbonyl)piperidin-4-yloxy)ethoxy)quinazoline (420mg, 76%).
MS - ESI: 549 [MH]^+

1H NMR Spectrum: (DMSO-d_6) 1.4 (s, 9H), 1.3-1.5 (m, 2H), 1.7-1.9 (m, 2H), 2.38 (s, 3H), 3.0 (br t, 2H), 3.5-3.7 (m, 3H), 3.85 (m, 2H), 3.98 (s, 3H), 4.3 (t, 2H), 6.12 (s, 1H), 6.85 (d, 1H), 7.22 (s, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 7.55 (s, 1H), 8.48 (s, 1H)

The starting material was prepared as follows:

 tert-Butoxycarbonyl anhydride (1.52g, 7mmol) in acetone (3.5ml) was added to a solution of 4,4-(ethylenedioxy)piperidine (1g, 7mmol) in acetone/trichloromethane (3.5ml/3.5ml) cooled at 0°C. After stirring for 4 hours at ambient temperature, the volatiles were removed under vacuum. The residue was dissolved in ether and the ether solution was washed with water, brine, dried (MgSO_4) and evaporated to give 4,4-(ethylenedioxy)-1-tert-butoxycarbonylpiperidine (1.7g, quant.).

1H NMR Spectrum: (CDCl_3): 1.46 (s, 9H), 1.65 (t, 4H), 3.5 (t, 4H), 3.97 (s, 4H)

Freshly distilled boron trifluoride etherate (52µl, 0.41mmol), followed by sodium cyanoborohydride (38mg, 0.6mmol) were added to a solution of 4,4-(ethylenedioxy)-1-tert-butoxycarbonylpiperidine (100mg, 0.41mmol) in THF (1.4ml) cooled at 0°C. After stirring for 6 hours at ambient temperature, boron trifluoride etherate (52µl) and sodium cyanoborohydride (26mg, 0.41mmol) were added. After stirring overnight at ambient temperature, the mixture was partitioned between ethyl acetate and 2M sodium hydroxide.

The organic layer was washed with water, brine, dried (MgSO_4) and evaporated. The residue was purified by column chromatography eluting with methylene chloride/methanol (95/5) followed by methylene chloride/methanol/3M ammonia in methanol (80/15/5) to give 2-((1-tert-butoxycarbonyl)piperidin-4-yloxy)ethanol (42mg, 42%).

MS - ESI: 268 [MNa]^+

1H NMR Spectrum: (CDCl_3) 1.48 (s, 9H), 1.5-1.6 (m, 2H), 1.8-1.9 (m, 2H), 2.0 (t, 1H), 3.05-3.15 (m, 2H), 3.5 (m, 1H), 3.57 (t, 2H), 3.7-3.9 (m, 4H)

Example 77

A solution of 6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-((1-tert-butoxycarbonyl)piperidin-4-yloxy)ethoxy)quinazoline (379 mg, 0.69 mmol), (prepared as described in Example 76), in methylene chloride (7ml) containing TFA (2.5ml) was stirred for 1.5 hours at ambient temperature. After removal of the volatiles under vacuum, the residue
was partitioned between ethyl acetate and water. Solid sodium hydrogen carbonate and 2N sodium hydroxide were added to adjust the aqueous layer to about pH10. The organic layer was washed with water, followed by brine, dried (MgSO₄) and evaporated. The residue was triturated with ether, filtered, washed with ether and dried under vacuum to give 6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(piperidin-4-yloxy)ethoxy)quinazoline (164 mg, 53%).

'H NMR Spectrum: (DMSO-d₆) 1.2-1.4 (m, 2H), 1.8-1.9 (m, 2H), 2.47 (s, 3H), 2.4-2.5 (m, 2H), 2.9-3.0 (d, 2H), 3.3-3.5 (m, 1H), 3.95 (s, 2H), 4.0 (s, 3H), 4.35 (s, 2H), 6.15 (s, 1H), 6.9 (dd, 1H), 7.28 (s, 1H), 7.32 (d, 1H), 7.41 (s, 1H), 7.60 (s, 1H), 8.49 (s, 1H)

MS-ESI : 448 [M]+

Example 78

A solution of 7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (193 mg, 0.6 mmol), (prepared as described in Example 49), 4-(2-hydroxyethoxy)pyridine (166 mg, 1.2 mmol), (J. Chem. Soc. Perkin II, 1987, 1867), in methylene chloride (5 ml) containing triphenylphosphine (330 mg, 1.26 mmol) and diisopropyl azodicarboxylate (255 mg, 1.26 mmol) was stirred at ambient temperature for 2 hours. The precipitate was filtered, triturated with ether followed by ethyl acetate, and dried under vacuum to give 6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(4-pyridyloxy)ethoxy)quinazoline (142 mg, 54%).

'H NMR Spectrum: (DMSO-d₆) 2.40 (s, 3H), 3.97 (s, 3H), 4.52 (t, 2H), 4.58 (t, 2H), 6.14 (s, 1H), 6.89 (dd, 1H), 7.07 (d, 2H), 7.26 (s, 1H), 7.31 (d, 1H), 7.46 (s, 1H), 7.61 (s, 1H), 8.41 (d, 2H), 8.5 (s, 1H)

MS-ESI : 443 [MH]+

Elemental analysis

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<td>H 5.0</td>
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<td>N 12.5</td>
<td>N 12.4%</td>
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</table>

Example 79

A suspension of 6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(N-methyl-N-tertbutoxycarbonylamino)ethoxy)quinazoline (148 mg, 0.31 mmol), (prepared as described in Example 149), in methylene chloride (4 ml) containing TFA (1 ml) was stirred for 1 hour. After removing the volatiles under vacuum, the residue was azeotroped with toluene. The residue was dissolved in methylene chloride (3 ml) and triethylamine (215 µl, 1.5 mmol) was added followed by methanesulphonyl chloride (48 µl, 0.62 mmol). After stirring for 1 hour at
ambient temperature, the mixture was partitioned between methylene chloride and water. The organic layer was separated, washed with water, brine, dried (MgSO₄) and evaporated. The residue was purified by column chromatography eluting with ethylacetate/methanol (99/1 followed by 97/3). After evaporation of the solvent, the solid was triturated with ether, filtered, washed with ether and dried under vacuum to give 6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(N-methyl-N-methylsulphonylamino)ethoxy)quinazoline (54 mg, 38%).

\(^1\)H NMR Spectrum: (DMSO\(_d_6\)) 2.4 (s, 3H), 2.93 (s, 3H), 3.0 (s, 3H), 3.62 (t, 2H), 4.0 (s, 3H), 4.38 (t, 2H), 6.14 (s, 1H), 6.88 (dd, 1H), 7.26 (s, 1H), 7.3 (d, 1H), 7.43 (s, 1H), 7.61 (s, 1H), 8.49 (s, 1H).

MS-ESI : 457 [MH]⁺

**Example 80**

A solution of 6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(piperidin-4-yloxy)ethoxy)quinazoline (76 mg, 0.17 mmol), (prepared as described in Example 77), in acrylonitrile (0.5 ml), methylene chloride (1 ml) and methanol (1 ml) was stirred overnight at ambient temperature. After removal of the volatiles under vacuum the residue was purified by column chromatography eluting with methylene chloride/methanol (98/2 followed by 95/5 and 90/10). The residue was triturated with ethyl acetate and ether. The resulting solid was filtered and dried under vacuum to give 7-(2-(1-(2-cyanoethyl)piperidin-4-yloxy)ethoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (73 mg, 86%).

\(^1\)H NMR Spectrum: (DMSO\(_d_6\)) 1.4-1.55 (m, 2H), 1.8-1.9 (m, 2H), 2.15 (t, 2H), 2.4 (s, 3H), 2.55 (t, 2H), 2.65 (t, 2H), 2.7-2.8 (m, 2H), 3.4-3.5 (m, 1H), 3.85 (m, 2H), 4.0 (s, 3H), 4.3 (t, 2H), 6.15 (s, 1H), 6.9 (dd, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

MS-ESI : 502 [MH]⁺

Elemental analysis

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<td>H 6.2</td>
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**Example 81**

A solution of 4-chloro-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (100 mg, 0.31 mmol), (prepared as described for the starting material in Example 9), 6-hydroxyindole (50 mg, 0.37 mmol) and potassium carbonate (64 mg, 0.466 mmol) in DMF (1 ml) was heated at 95°C for 4 hours. After cooling, the mixture was diluted with methylene chloride and
poured onto a silica column. The product was eluted with methylene chloride, followed by methylene chloride/methanol (80/20 followed by 70/30 and 50/50). After removal of the solvent by evaporation, the precipitate was triturated with ether, filtered and dried under vacuum to give **6-methoxy-4-(indol-6-yloxy)-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline** (90 mg, 69%).

1H NMR Spectrum: (DMSOd₆) 1.85 (br s, 4H), 2.15-2.25 (m, 2H), 2.85-3.15 (m, 6H), 4.01 (s, 3H), 4.32 (t, 2H), 6.5 (s, 1H), 6.95 (dd, 1H), 7.32 (s, 1H), 7.4 (s, 2H), 7.6 (d, 1H), 7.65 (s, 1H), 8.52 (s, 1H)

MS-ESI : 419 [MH]⁺

**Example 82**

Diisopropyl azodicarboxylate (146 mg, 0.72 mmol) was added to a solution of 7-hydroxy-4-(2-methylindol-5-yloxy)quinazoline (100 mg, 0.34 mmol), triphenyl phosphine (189 mg, 0.72 mol), and 3-pyrrolidinopropan-1-ol (89 mg, 0.686 mmol), (J. Org. Chem. 1988, 53, 3164), in methylene chloride (2.5 ml). After stirring overnight at ambient temperature, the solid was filtered. The filtrate was purified by column chromatography eluting with ethyl acetate/methylene chloride (1/1) followed by ethyl acetate/methylene chloride/methanol (4/5/1), methylene chloride/methanol (9/1) and 3N ammonia in methanol/methylene chloride (1/9). After removal of the solvent, the residue was triturated with ether, filtered, and dried under vacuum to give **4-(2-methylindol-5-yloxy)-7-(3-(pyrrolidin-yl)propoxy)quinazoline** (49 mg, 35%).

1H NMR Spectrum: (DMSOd₆) 1.8-2.0 (m, 2H), 2.0-2.15 (m, 2H), 2.2-2.32 (m, 2H), 2.41 (s, 3H), 3.0-3.2 (m, 2H), 3.4 (t, 2H), 3.6-3.7 (m, 2H), 4.35 (t, 2H), 6.2 (s, 1H), 6.95 (dd, 1H), 7.3 (s, 1H), 7.35 (d, 1H), 7.5 (s, 1H), 7.57 (dd, 1H), 8.5 (d, 1H), 9.15 (s, 1H)

MS-ESI : 403 [MH]⁺

The starting material was prepared as follows:

Sodium (368mg, 16mmol) was added to benzyl alcohol (10ml, 96mmol) and the mixture was heated at 148°C for 30 minutes. 7-Fluoro-3,4-dihydroquinazolin-4-one (656mg, 4mmol), (J. Chem. Soc. section B 1967, 449), was added and the mixture maintained at 148°C for 24 hours. The reaction mixture was allowed to cool, the solution was poured on to water (170ml) and the aqueous mixture adjusted to pH3 with concentrated hydrochloric acid. The
precipitate was collected by filtration, washed with water, ether and dried under vacuum to give 7-benzyloxy-3,4-dihydroquinazolin-4-one (890mg, 89%) as a white solid.

m.p. 267-269°C

\[^1\text{H}\text{ NMR Spectrum: (DMSO}_d_6; \text{CF}_3\text{COOD})\] 5.32(s, 2H); 7.25(d, 1H); 7.32-7.52(m, 6H); 8.12(d, 1H); 8.99(s, 1H)

MS - ESI: 252 [MH]\(^+\)

Elemental analysis:

Found:  C 71.4  H 4.9  N 10.7

Required: C 71.2  H 4.8  N 11.1%

A mixture of 7-benzyloxy-3,4-dihydroquinazolin-4-one (11g, 43.6mmol) and DMF (1ml) in thionyl chloride (100ml) was heated at reflux for 1.5 hours. Excess thionyl chloride was removed by evaporation and the residue azeotroped with toluene. The residue was partitioned between methylene chloride and water and saturated aqueous sodium hydrogen carbonate was added until the aqueous layer was at about pH9. The organic layer was separated, washed with water, brine, dried (MgSO\(_4\)) and evaporated to give 7-benzyloxy-4-chloroquinazoline (10.5g, 89%).

\[^1\text{H}\text{ NMR Spectrum: (DMSO}_d_6)\] 5.4 (s, 2H); 7.35-7.65 (m, 6H); 8.2 (d, 1H); 9.0 (s, 1H)

MS - ESI: 270 [MH]\(^+\)

A solution of 7-benzyloxy-4-chloroquinazoline (2g, 7.4mmol), 5-hydroxy-2-methylindole (1.3 g, 8.9 mmol), (prepared as described for the starting material in Example 48), in DMF (20 ml) containing potassium carbonate (1.53 g, 11.1 mmol) was stirred at 80°C for 3 hours. After cooling, the mixture was poured in portions into ice/water. The precipitate was filtered and washed with water and dried under vacuum. The solid was dissolved in methylene chloride and was purified by column chromatography eluting with ethyl acetate and methylene chloride (1/1) to give 7-benzyloxy-4-(2-methylindol-5-yloxy)quinazoline (2.28 g, 81%).

MS-ESI : 382 [MH]\(^+\)

\[^1\text{H}\text{ NMR Spectrum: (DMSO}_d_6)\] 2.41 (s, 3H), 5.4 (s, 2H), 6.15 (s, 1H), 6.9 (dd, 1H), 7.3 (s, 1H), 7.35 (d, 1H), 7.4 (d, 1H), 7.4-7.5 (m, 4H), 7.55 (d, 2H), 8.32 (d, 1H), 8.6 (s, 1H).

10% Palladium on charcoal (200 mg) followed by ammonium formate (4.34 g, 69 mmol) were added to a solution of 7-benzyloxy-4-(2-methylindol-5-yloxy)quinazoline (1.75 g, 4.58 mmol) in DMF (60 ml). After stirring for 1 hour at ambient temperature, the mixture
was filtered. The filtrate was evaporated. The residue was triturated with water, filtered, washed with ethyl acetate, and dried under vacuum to give 7-hydroxy-4-(2-methylindol-5-yloxy)quinazoline (1.24 g, 93%).

^1^H NMR Spectrum: (DMSO-d$_6$) 2.4 (s, 3H), 6.14 (s, 1H), 6.88 (dd, 1H), 7.17 (s, 1H), 7.25-7.3 (m, 2H), 7.30 (d, 1H), 8.24 (d, 1H), 8.5 (s, 1H)

**Examples 83-89**

Using an analogous procedure to that described in Example 82, the appropriate alcohols were reacted with 7-hydroxy-4-(2-methylindol-5-yloxy)quinazoline, (prepared as described for the starting material in Example 82), to give the compounds described in Table VI below.

**Table VI**

<table>
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<th>Example number</th>
<th>Weight (mg)</th>
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<td>24</td>
<td>412</td>
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<td>87</td>
<td>63</td>
<td>44</td>
<td>419</td>
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a) 7-Hydroxy-4-(2-methylindol-5-yloxy)quinazoline (100 mg) was reacted with 3-(methylsulphonyl)-1-propanol (95 mg), (prepared as described for the starting material in Example 50), to give 7-(3-(methylsulphonyl)propoxy)-4-(2-methylindol-5-ylxy)quinazoline.

$^1$H NMR Spectrum: (DMSO$_d_6$, CF$_3$COOD) 2.2-2.3 (m, 2H), 2.4 (s, 3H), 3.05 (s, 3H), 3.3-3.45 (m, 2H), 4.4 (t, 2H), 6.2 (s, 1H), 6.95 (dd, 1H), 7.38 (s, 1H), 7.4 (d, 1H), 7.5 (s, 1H), 7.6 (dd, 1H), 8.5 (d, 1H), 9.2 (s, 1H)

Elemental analysis

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b) 7-Hydroxy-4-(2-methylindol-5-ylxy)quinazoline (100 mg) was reacted with 4-(2-hydroxyethyl)morpholine (90 mg) to give 4-(2-methylindol-5-ylxy)-7-(2-morpholinoethoxy)quinazoline.

$^1$H NMR Spectrum: (DMSO$_d_6$, CF$_3$COOD) 2.4 (s, 3H), 3.1-3.3 (m, 2H), 3.62 (d, 2H), 3.7-3.9 (m, 4H), 4.05 (d, 2H), 4.7 (t, 2H), 6.2 (s, 0.5 H, partially exchanged), 6.95 (dd, 1H), 7.35 (s, 1H), 7.39 (d, 1H), 7.6 (s, 1H), 7.65 (dd, 1H), 8.55 (d, 1H), 9.15 (s, 1H)

Elemental analysis

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</tr>
<tr>
<td>N 13.5</td>
<td>N 13.7%</td>
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</table>

c) 7-Hydroxy-4-(2-methylindol-5-ylxy)quinazoline (100 mg) was reacted with 1-(3-hydroxypropyl)piperidine (98 mg) to give 4-(2-methylindol-5-ylxy)-7-(3-(piperidin-1-yl)propoxy)quinazoline.

$^1$H NMR Spectrum: (DMSO$_d_6$, CF$_3$COOD) 1.2-1.5 (m, 2H), 1.6-1.8 (m, 2H), 1.8-1.9 (m, 2H), 2.25-2.35 (m, 2H), 2.45 (s, 3H), 2.95 (t, 2H), 3.25-3.3 (m, 2H), 3.55 (d, 2H), 4.4 (t, 2H), 6.95 (dd, 1H), 7.4 (s, 1H), 7.45 (d, 1H), 7.5 (s, 1H), 7.6 (d, 1H), 8.55 (d, 1H), 9.15 (s, 1H)
d) 7-Hydroxy-4-(2-methylindol-5-yloxy)quinazoline (100 mg) was reacted with 3-(1,1-dioxothiomorpholino)-1-propanol (133 mg), (prepared as described for the starting material in Example 5), to give 4-(2-methylindol-5-yloxy)-7-(3-(1,1-dioxothiomorpholino)propoxy)quinazoline.

1H NMR Spectrum: (DMSOd$_6$) 1.9-2.0 (m, 2H), 2.4 (s, 3H), 1.6-1.7 (m, 2H), 2.9 (br s, 4H), 3.1 (br s, 4H), 4.25 (t, 2H), 6.12 (s, 1H), 6.85 (d, 1H), 7.22 (s, 1H), 7.3 (d, 1H), 7.3-7.4 (m, 2H), 8.25 (d, 1H), 8.55 (s, 1H)

\[ \text{Elemental analysis} \quad \text{Found} \quad \text{C 66.5} \quad \text{H 6.2} \quad \text{N 12.7} \]
\[ \text{C$_{24}$H$_{26}$N$_4$O$_3$} \quad 0.14 \text{CH$_2$Cl$_2$} \quad 0.7 \text{H$_2$O} \quad \text{Requires} \quad \text{C 66.7} \quad \text{H 6.4} \quad \text{N 13.0\%} \]

e) 7-Hydroxy-4-(2-methylindol-5-yloxy)quinazoline (100 mg) was reacted with 4-(3-hydroxypropyl)morpholine (100 mg), (prepared as described for the starting material in Example 60), to give 4-(2-methylindol-5-yloxy)-7-(3-morpholinopropoxy)quinazoline.

1H NMR Spectrum: (DMSOd$_6$) 1.95-2.05 (m, 2H), 2.42 (s, 3H), 2.5 (t, 2H), 2.55 (t, 4H), 3.6 (t, 4H), 4.3 (t, 2H), 6.18 (s, 1H), 6.9 (dd, 1H), 7.3 (s, 1H), 7.35 (d, 1H), 7.3-7.4 (m, 2H), 8.3 (d, 1H), 8.6 (s, 1H)

\[ \text{Elemental analysis} \quad \text{Found} \quad \text{C 69.0} \quad \text{H 6.6} \quad \text{N 13.4} \]
\[ \text{C$_{24}$H$_{30}$N$_4$O$_2$} \quad 0.8 \text{H$_2$O} \quad \text{Requires} \quad \text{C 69.1} \quad \text{H 6.7} \quad \text{N 13.4\%} \]

f) 7-Hydroxy-4-(2-methylindol-5-yloxy)quinazoline (100 mg) was reacted with 1-(2-hydroxyethyl)piperidine (89 mg) to give 4-(2-methylindol-5-yloxy)-7-(2-(piperidin-1-yI)ethoxy)quinazoline.

1H NMR Spectrum: (DMSOd$_6$) 1.4-1.5 (br s, 2H), 1.5-1.7 (br s, 4H), 2.42 (s, 3H), 2.5-2.7 (br s, 4H), 2.8-3.0 (br s, 2H), 4.35 (br s, 2H), 6.18 (s, 1H), 6.9 (dd, 1H), 7.3 (s, 1H), 7.35 (d, 1H), 7.4 (d, 1H), 7.42 (s, 1H), 8.3 (d, 1H), 8.6 (s, 1H)

\[ \text{Elemental analysis} \quad \text{Found} \quad \text{C 63.7} \quad \text{H 4.8} \quad \text{N 21.5} \]
\[ \text{C$_{24}$H$_{30}$N$_4$O$_2$} \quad 0.8 \text{H$_2$O} \quad \text{Requires} \quad \text{C 63.7} \quad \text{H 4.8} \quad \text{N 21.5\%} \]

g) 7-Hydroxy-4-(2-methylindol-5-yloxy)quinazoline (100 mg) was reacted with 2-(1H-1,2,4-triazol-1-yl)ethanol (78 mg), (Ann. Pharr. Fr. 1977, 35, 503-508), to give 4-(2-methylindol-5-yloxy)-7-(2-(1H-1,2,4-triazol-1-yl)ethoxy)quinazoline.

1H NMR Spectrum: (DMSOd$_6$) 2.4 (s, 3H), 4.6 (m, 2H), 4.7 (m, 2H), 6.15 (s, 1H), 6.9 (dd, 1H), 7.28 (s, 1H), 7.3 (d, 2H), 7.4 (s, 1H), 8.02 (s, 1H), 8.3 (d, 1H), 8.6 (s, 1H), 8.65 (s, 1H)

\[ \text{Elemental analysis} \quad \text{Found} \quad \text{C 63.7} \quad \text{H 4.8} \quad \text{N 21.5} \]
Example 90

A solution of 7-hydroxy-4-(2-methylindol-5-yloxy)quinazoline (423 mg, 1.45 mmol), (prepared as described for the starting material in Example 82), triphenylphosphine (685 mg, 2.61 mmol), 4-hydroxymethyl-1-tert-butoxycarbonylpiperidine (500 mg, 2.32 mmol), (prepared as described for the starting material in Example 10), and diisopropyl azodicarboxylate (528 mg, 2.61 mmol) in methylene chloride (18 ml) was stirred overnight at ambient temperature. The mixture was then poured onto a column of silica and eluted with ethyl acetate. After evaporation of the solvent, the residue was triturated with ether, filtered, and dried under vacuum to give 7-(1-tert-butoxycarbonylpiperidin-4-ylmethoxy)-4-(2-methylindol-5-yloxy)quinazoline (478 mg, 68 %).

$^1$H NMR Spectrum: (DMSO$_d_6$) 1.3-1.4 (m, 2H), 1.42 (s, 9H), 1.85 (d, 2H), 2.0-2.1 (m, 1H), 2.42 (s, 3H), 2.7-2.9 (br s, 2H), 3.95-4.05 (m, 2H), 4.1 (d, 2H), 6.15 (s, 1H), 6.9 (dd, 1H), 7.3 (s, 1H), 7.33 (d, 1H), 7.38 (s, 1H), 7.35-7.4 (m, 1H), 8.3 (d, 1H), 8.6 (s, 1H)

MS-ESI : 489 [MH]$^+$

Elemental analysis

C$_{21}$H$_{18}$N$_6$O$_2$ 0.5 H$_2$O Requires C 63.8 H 4.8 N 21.3%

C$_{28}$H$_{32}$N$_4$O$_4$ Requires C 68.8 H 6.6 N 11.5%

Example 91

To a suspension of 4-(2,3-dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (124 mg, 0.32 mmol) in methylene chloride (2.5 ml) was added triphenylphosphine (179 mg, 0.628 mmol), 1-(2-hydroxyethyl)pyrroldine (75 mg, 0.65 mmol) followed by diisopropyl azodicarboxylate (134 µl, 0.68 mmol) in portions. After stirring overnight at ambient temperature the mixture was poured onto a column of silica and eluted with ethyl acetate/methylene chloride (1/1) followed by ethyl acetate/methylene chloride/methanol (4/5/1) followed by methylene chloride/methanol (9/1). After removal of the solvent, the solid was triturated with ether, filtered, washed with ether and dried under vacuum to give 4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(2-(pyrroldin-1-yl)ethoxy)quinazoline (51 mg, 37 %).

$^1$H NMR Spectrum: (DMSO$_d_6$) 1.6-1.75 (m, 4H), 2.12 (s, 3H), 2.28 (s, 3H), 2.52 (br s, 4H), 3.85 (t, 2H), 3.93 (s, 3H), 4.25 (t, 2H), 6.8 (d, 1H), 7.17 (s, 1H), 7.22 (d, 1H), 7.33 (s, 1H),
7.54 (s, 1H), 8.43 (s, 1H)

The starting material was prepared as follows:

To a solution of 2,3-dimethyl-5-methoxyindole (175mg, 1 mmol), (J. Chem. Soc. 1957, 3175-3180) in methylene (5 ml) cooled at -60°C was added boron tribromide (210 μl, 2.2 mmol) dropwise. After completion of addition, the mixture was left to warm up to ambient temperature and was stirred for 1 hour. Water was added and the pH was adjusted to 6 with 2N sodium hydroxide. The mixture was extracted with ethyl acetate and the organic layer was separated, washed with brine, dried (MgSO₄) and evaporated to give 2,3-dimethyl-5-hydroxyindole (124mg, 77%).

¹H NMR Spectrum: (DMSO-d₆) 2.1 (s, 3H); 2.3 (s, 3H); 6.5 (dd, 1H); 6.65 (d, 1H); 7.0 (d, 1H); 8.45 (s, 1H)

Under nitrogen, to a solution of 2,3-dimethyl-5-hydroxyindole (643mg, 4 mmol), in DMF (10 ml) was added potassium carbonate (690mg, 5 mmol). After stirring for 15 minutes at ambient temperature, 7-benzoxyl-4-chloro-6-methoxyquinazoline (1g, 3.33 mmol), (prepared as described for the starting material in Example 1), was added. The mixture was heated at 90°C for 2 hours followed by 30 minutes at 95°C. After cooling, the mixture was poured onto water (100ml) cooled at 5°C. The precipitate was filtered, washed with water, followed by ether and dried under vacuum to give 7-benzyloxy-4-(2,3-dimethylindol-5-yloxy)-6-methoxyquinazoline (1.4 g, 95%).

¹H NMR Spectrum: (DMSO-d₆) 2.15 (s, 3H); 2.35 (s, 3H); 4.02 (s, 3H); 5.4 (s, 2H); 6.9 (dd, 1H); 7.22 (d, 1H); 7.3 (d, 1H); 7.35-7.6 (m, 6H); 7.65 (s, 1H); 8.5 (s, 1H)

A solution of 7-benzyloxy-4-(2,3-dimethylindol-5-yloxy)-6-methoxyquinazoline (2g, 4.7 mmol) in DMF (120 ml) containing ammonium formate (11gr, 174 mmol) and 10% palladium on charcoal (200mg) was stirred for 2.5 hours at ambient temperature. The mixture was filtered, and the filtrate was evaporated under vacuum. The residue was triturated with ether and the solid was washed with water followed by ether and dried under vacuum at 50°C to give 4-(2,3-dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (1.1 g, 69%).

¹H NMR Spectrum: (DMSO-d₆) 2.1 (s, 3H); 2.32 (s, 3H); 3.97 (s, 3H); 7.85 (dd, 1H); 7.2 (bs, 2H); 7.25 (d, 1H); 7.58 (s, 1H); 8.4 (s, 1H)

Examples 92-106
Using an analogous procedure to that described in Example 91, the appropriate alcohol was reacted with 4-(2,3-dimethylindol-5-ylxyloxy)-7-hydroxy-6-methoxyquinazoline, (prepared as described for the starting material in Example 91), to give the compounds described in the Table VII below.

### Table VII

<table>
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* HPLC conditions 2) as described hereinbefore.

a) 4-(2,3-Dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (124 mg) was reacted with 2-(1H-1,2,4-triazol-1-yl)ethanol (74 mg), (Ann. Pharm. Fr. 1977, 35, 503-508), to give 4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(2-(1H-1,2,4-triazol-1-yl)ethoxy)quinazoline.

'H NMR Spectrum: (DMSO-d₆) 2.10 (s, 3H), 2.30 (s, 3H), 3.93 (s, 3H), 4.52 (m, 2H), 4.55-4.65 (m, 2H), 6.85 (d, 1H), 7.2 (s, 1H), 7.25 (d, 1H), 7.4 (d, 1H), 7.58 (s, 1H), 8.0 (s, 1H), 8.48 (s, 1H), 8.58 (s, 1H)

b) 4-(2,3-Dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (124 mg) was reacted with 2-(2-methoxyethoxy)ethanol (78 mg) to give 4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)quinazoline.

'H NMR Spectrum: (DMSO-d₆) 2.14 (s, 3H), 2.35 (s, 3H), 3.3 (s, 3H), 3.5 (t, 2H), 3.65 (t, 2H), 3.85 (t, 2H), 4.0 (s, 3H), 4.32 (t, 2H), 6.9 (d, 1H), 7.25 (d, 1H), 7.28 (d, 1H), 7.4 (s, 1H), 7.6
c) 4-(2,3-Dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (97 mg) was reacted with N,N-diethylethanolamine (68 mg) to give 7-(2-(N,N-diethylamino)ethoxy)-4-(2,3-dimethylindol-5-yloxy)-6-methoxyquinazoline.

1H NMR Spectrum: (DMSO$_d_6$) 1.05 (t, 6H), 2.15 (s, 3H), 2.35 (s, 3H), 2.6-2.7 (m, 4H), 2.92 (br s, 2H), 4.0 (s, 3H), 4.25 (t, 2H), 6.9 (dd, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

d) 4-(2,3-Dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (97 mg) was reacted with N,N-dimethylethanolamine (52 mg) to give 7-(2-(N,N-dimethylamino)ethoxy)-4-(2,3-dimethylindol-5-yloxy)-6-methoxyquinazoline.

1H NMR Spectrum: (DMSO$_d_6$) 2.15 (s, 3H), 2.35 (s, 9H), 2.85 (br s, 2H), 4.0 (s, 3H), 4.35 (t, 2H), 6.87 (dd, 1H), 7.22 (s, 1H), 7.3 (d, 1H), 7.42 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

e) 4-(2,3-Dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (97 mg) was reacted with 4-(2-hydroxyethyl)morpholine (59 mg) to give 4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(2-morpholinoethoxy)quinazoline.

1H NMR Spectrum: (DMSO$_d_6$) 2.15 (s, 3H), 2.35 (s, 3H), 3.25-3.4 (m, 2H), 3.65 (d, 2H), 3.7-3.8 (m, 4H), 4.0-4.1 (m, 2H), 4.1 (s, 3H), 4.7 (t, 2H), 6.95 (dd, 1H), 7.3 (s, 1H), 7.35 (d, 1H), 7.6 (s, 1H), 7.8 (s, 1H), 9.0 (s, 1H)

f) 4-(2,3-Dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (97 mg) was reacted with 3-(N,N-dimethylamino)propan-1-ol (60 mg) to give 7-(3-(N,N-dimethylamino)propoxy)-4-(2,3-dimethylindol-5-yloxy)-6-methoxyquinazoline.

1H NMR Spectrum: (DMSO$_d_6$) 1.95-2.05 (m, 2H), 2.15 (s, 3H), 2.2 (s, 6H), 2.35 (s, 3H), 2.45 (t, 2H), 4.0 (s, 3H), 4.25 (t, 2H), 6.9 (dd, 1H), 7.22 (d, 1H), 7.3 (d, 1H), 7.37 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

g) 4-(2,3-Dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (97 mg) was reacted with 1-(2-hydroxyethyl)-2-pyrrolidinone (75 mg) to give 4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(2-(2-oxopyrrolidin-1-yl)ethoxy)quinazoline.
- 158 -

1H NMR Spectrum: (DMSOd₆) 1.9-2.05 (m, 4H), 2.15 (s, 3H), 2.25 (t, 2H), 2.35 (s, 3H), 3.65 (t, 2H), 4.0 (s, 3H), 4.35 (t, 2H), 6.9 (d, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.45 (s, 1H), 7.62 (s, 1H), 8.5 (s, 1H)

h) 4-(2,3-Dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (97 mg) was reacted with 2-(2-hydroxyethyl)piperidine (75 mg) to give 4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(2-(piperidin-2-yl)ethoxy)quinazoline.

1H NMR Spectrum: (DMSOd₆) 1.0-1.15 (m, 1H), 1.25-1.4 (m, 2H), 1.5 (br s, 1H), 1.65 (d, 1H), 1.7-1.8 (m, 1H), 1.8-1.9 (m, 2H), 2.15 (s, 3H), 2.35 (s, 3H), 2.5 (d, 1H), 2.6-2.7 (m, 1H), 2.9-3.0 (m, 1H), 4.0 (s, 3H), 4.2-4.35 (m, 2H), 6.88 (dd, 1H), 7.2 (s, 1H), 7.27 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

i) 4-(2,3-Dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (97 mg) was reacted with 1-(2-hydroxyethyl)pyrrolidin-2,5-dione (83 mg) to give 4-(2,3-dimethylindol-5-yloxy)-7-(2,5-dioxopyrrolidin-1-yl)ethoxy)-6-methoxyquinazoline.

1H NMR Spectrum: (DMSOd₆) 2.12 (s, 3H), 2.35 (s, 3H), 2.68 (s, 4H), 3.85 (t, 2H), 3.95 (s, 3H), 4.35 (t, 2H), 6.88 (dd, 1H), 7.22 (s, 1H), 7.25 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

j) 4-(2,3-Dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (97 mg) was reacted with 1-methyl-3-piperidinemethanol (75 mg) to give 4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(1-methylpiperidin-3-ylmethoxy)quinazoline.

k) 4-(2,3-Dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (97 mg) was reacted with 4-(3-hydroxypropyl)morpholine (75 mg), (prepared as described for the starting material in Example 60), to give 4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline.

1H NMR Spectrum: (DMSOd₆) 1.95-2.05 (m, 2H), 2.15 (s, 3H), 2.35 (s, 3H), 2.42 (br s, 4H), 2.5 (t, 2H), 3.6 (m, 4H), 4.0 (s, 3H), 4.25 (t, 2H), 6.85 (dd, 1H), 7.25 (d, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H).

l) 4-(2,3-Dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (97 mg) was reacted with 2-(N-(2-methoxyethyl)-N-methylamino)ethanol (77 mg), (prepared as described for the
starting material in Example 59), to give 4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(2-(N-(2-methoxyethyl)-N-methylamino)ethoxy)quinazoline.

\(^1\)H NMR Spectrum: (DMSO\(_d_6\)) 2.15 (s, 3H), 2.35 (s, 6H), 2.65 (t, 2H), 2.9 (t, 2H), 3.25 (s, 3H), 3.45 (t, 2H), 4.0 (s, 3H), 4.3 (t, 2H), 6.9 (dd, 1H), 7.22 (s, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

m) 4-(2,3-Dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (97 mg) was reacted with 3-(1,1-dioxothiomorpholinol)-1-propanol (112 mg), (prepared as described for the starting material in Example 5), to give 4-(2,3-dimethylindol-5-yloxy)-7-(3-(1,1-dioxothiomorpholinol)propoxy)-6-methoxyquinazoline.

\(^1\)H NMR Spectrum: (DMSO\(_d_6\)) 1.95-2.05 (m, 2H), 2.15 (s, 3H), 2.35 (s, 3H), 2.7 (t, 2H), 2.95 (br s, 4H), 3.15 (br s, 4H), 4.0 (s, 3H), 4.29 (t, 2H), 6.9 (dd, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 7.61 (s, 1H), 8.5 (s, 1H)

n) 4-(2,3-Dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (97 mg) was reacted with 2-(4-pyridyloxy)ethanol (81 mg), (J. Chem. Soc. Perkin Trans 2, 1987, 12, 1867), to give 4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(2-(4-pyridyloxy)ethoxy)quinazoline.

\(^1\)H NMR Spectrum: (DMSO\(_d_6\)) 2.15 (s, 3H), 2.35 (s, 3H), 4.0 (s, 3H), 4.55 (m, 2H), 4.6 (m, 2H), 6.88 (dd, 1H), 7.08 (d, 2H), 7.22 (s, 1H), 7.28 (d, 1H), 7.48 (s, 1H), 7.6 (s, 1H), 8.42 (d, 2H), 8.5 (s, 1H), 10.78 (s, 1H)

o) 4-(2,3-Dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (97 mg) was reacted with 3-(methylsulphonyl)-1-propanol (80 mg), (prepared as described for the starting material in Example 50), to give 4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline.

\(^1\)H NMR Spectrum: (DMSO\(_d_6\)) 1.8-1.9 (m, 2H), 2.15 (s, 3H), 2.25-2.35 (m, 2H), 2.35 (s, 3H), 3.0 (s, 3H), 4.02 (s, 3H), 4.35 (t, 2H), 6.9 (dd, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 7.7 (s, 1H), 8.52 (s, 1H)

30 Example 107

Using an analogous procedure to that described in Example 91, 7-hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (89mg) was reacted with 2-(2-methoxyethoxy)ethanol (70mg)
to give 4-(indol-5-yl oxy)-6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)quinazoline (50mg, 42%).

$^1$H NMR Spectrum: (DMSO$_d_6$) 3.3 (s, 3H), 3.5 (m, 2H), 3.65 (m, 2H), 3.85 (m, 2H), 4.02 (s, 3H), 4.35 (t, 2H), 6.58 (s, 1H), 7.0 (dd, 1H), 7.4 (s, 1H), 7.45 (br s, 2H), 7.47 (d, 1H), 7.61 (s, 1H), 8.5 (s, 1H)

MS-ESI : 410 [MH]$^+$

The starting material was prepared as follows:

A mixture of 7-benzyloxy-4-chloro-6-methoxyquinazoline (3g, 10 mmol), (prepared as described for the starting material in Example 1), 5-hydroxyindole (1.46g, 11 mmol) in DMF (30ml) containing potassium carbonate (2.75g, 20 mmol) was heated at 95°C for 2 hours. After cooling the mixture was poured onto water (100ml). The precipitate was filtered, washed with water and dried under vacuum at 50°C over phosphorus pentoxide. The solid was triturated with ether, filtered, washed with ether and dried under vacuum to give 7-benzyloxy-4-(indol-5-yl oxy)-6-methoxyquinazoline (3.5g, 88%).

$^1$H NMR Spectrum: (DMSO$_d_6$) 4.02 (s, 3H), 5.4 (s, 2H), 6.5 (s, 1H), 7.0 (dd, 1H), 7.4-7.6 (m, 9H), 7.65 (s, 1H), 8.5 (s, 1H), 11.23 (s, 1H)

MS-ESI : 398 [MH]$^+$

A solution of 7-benzyloxy-4-(indol-5-yl oxy)-6-methoxyquinazoline (8 g, 20 mmol) in DMF (50 ml) and methylene chloride (100 ml) containing 10% palladium on charcoal (2 g) was hydrogenated at 1.8 atmospheres pressure until uptake of hydrogen had ceased. The solution was filtered, the catalyst was washed with DMF and the filtrate was evaporated. The residue was purified by column chromatography eluting with methylene chloride, followed by methylene chloride/methanol (95/5 and 90/10). After evaporation of the solvent, the residue was triturated with ether, filtered and dried under vacuum to give 7-hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (2.7 g; 44%).

$^1$H NMR Spectrum: (DMSO$_d_6$) 4.0 (s, 3H), 6.46 (s, 1H), 7.01 (dd, 1H), 7.2 (s, 1H), 7.4-7.5 (m, 3H), 7.6 (s, 1H), 8.41 (s, 1H)

30 Examples 108-118

Using an analogous procedure to that described in Example 107, the appropriate alcohol was reacted with 7-hydroxy-4-(indol-5-yl oxy)-6-methoxyquinazoline, (prepared as
described for the starting material in Example 107), to give the compounds described in the Table VIII below.

**Table VIII**

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r) 7-Hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (89 mg) was reacted with N,N-diethylethanolamine (68 mg) to give 7-(2-(N,N-diethylamino)ethoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline.

s) 7-Hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (89 mg) was reacted with N,N-dimethylethanolamine (52 mg) to give 7-(2-(N,N-dimethylamino)ethoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline.

1H NMR Spectrum: (DMSO_d6) 2.3 (s, 6H), 2.8 (t, 2H), 4.0 (s, 3H), 4.3 (t, 2H), 6.45 (s, 1H), 7.0 (dd, 1H), 7.4-7.5 (m, 4H), 7.6 (s, 1H), 8.5 (s, 1H)

t) 7-Hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (89 mg) was reacted with 3-(N,N-dimethylamino)propan-1-ol (60 mg) to give 7-(3-(N,N-dimethylamino)propoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline.

1H NMR Spectrum: (DMSO_d6) 1.9-2.05 (m, 2H), 2.21 (s, 6H), 2.45 (t, 2H), 4.02 (s, 3H), 4.25 (t, 2H), 6.47 (s, 1H), 7.0 (dd, 1H), 7.38 (s, 1H), 7.35-7.4 (m, 2H), 7.45 (d, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

u) 7-Hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (89 mg) was reacted with (2S)-2-(hydroxymethyl)-1-methylpyrrolidine (67 mg) to give (2S)-4-(indol-5-yloxy)-6-methoxy-7-(1-methylpyrrolidin-2-yl)quinazoline.

v) 7-Hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (89 mg) was reacted with 3-(N,N-diethylamino)-1-propanol (76 mg) to give 7-(3-(N,N-diethylamino)propoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline.

1H NMR Spectrum: (DMSO_d6) 0.95 (t, 6H), 1.9-2.0 (m, 2H), 2.5 (m, 4H), 2.6 (t, 2H), 4.0 (s, 3H), 4.25 (t, 2H), 6.48 (s, 1H), 7.0 (dd, 1H), 7.38 (s, 1H), 7.42-7.5 (m, 3H), 7.6 (s, 1H), 8.5 (s, 1H)
w) 7-Hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (89 mg) was reacted with 2-(2-hydroxyethyl)piperidine (75 mg) to give 4-(indol-5-yloxy)-6-methoxy-7-(2-(piperidin-2-y1)ethoxy)quinazoline.

1H NMR Spectrum: (DMSO-d6) 1.45-1.75 (m, 3H), 1.75-1.85 (m, 2H), 2.0-2.1 (m, 1H), 2.1-2.2 (m, 1H), 2.25-2.35 (m, 1H), 2.95 (t, 1H), 3.3-3.4 (m, 2H), 4.1 (s, 3H), 4.4-4.5 (m, 2H), 6.5 (s, 1H), 7.05 (dd, 1H), 7.45-7.6 (m, 4H), 7.75 (s, 1H), 9.0 (s, 1H)

x) 7-Hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (89 mg) was reacted with 1-(2-hydroxyethyl)piperidine (75 mg) to give 4-(indol-5-yloxy)-6-methoxy-7-(2-(piperidin-1-y1)ethoxy)quinazoline.

1H NMR Spectrum: (DMSO-d6) 1.1-1.3 (m, 1H), 1.35-1.5 (m, 1H), 1.65-1.8 (m, 2H), 1.8-1.9 (m, 2H), 3.1 (t, 2H), 3.6 (d, 2H), 3.65(t,2H), 4.1 (s, 3H), 4.7 (t, 2H), 6.5 (d, 1H), 7.05 (dd, 1H), 7.45 (s, 1H), 7.5-7.55 (m, 2H), 7.61 (s, 1H), 7.8 (s, 1H), 9.0 (m, 1H)

y) 7-Hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (89 mg) was reacted with 4-(3-hydroxypropyl)morpholine (84 mg), (prepared as described for the starting material in Example 60), to give 4-(indol-5-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline.

1H NMR Spectrum: (DMSO-d6) 1.9-2.1 (m, 2H), 2.4 (br s, 4H), 2.5 (t, 2H), 3.6 (t, 4H), 4.0 (s, 3H), 4.25 (t, 2H), 6.45 (s, 1H), 7.0 (dd, 1H), 7.4 (s, 1H), 7.4-7.45 (m, 2H), 7.47 (d, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

z) 7-Hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (89 mg) was reacted with 2-(N-(2-methoxyethyl)-N-methylamino)ethanol (77 mg), (prepared as described for the starting material in Example 59), to give 4-(indol-5-yloxy)-6-methoxy-7-(2-(N-(2-methoxyethyl)-N-methylamino)ethoxy)quinazoline.

1H NMR Spectrum: (DMSO-d6) 2.35 (s, 3H), 2.65 (t, 2H), 2.9 (t, 2H), 3.25 (s, 3H), 3.45 (t, 2H), 4.0 (s, 3H), 4.3 (t, 2H), 6.45 (s, 1H), 7.05 (dd, 1H), 7.4-7.5 (m, 4H), 7.6 (s, 1H), 8.5 (s, 1H)

aa) 7-Hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (89 mg) was reacted with 3-(1,1-dioxothiomorpholino)-1-propanol (112 mg), (prepared as described for the starting material in
Example 5), to give 7-(3-(1,1-dioxothiomorpholino)propoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline.

^H NMR Spectrum: (DMSO_d6) 2.0 (m, 2H), 2.65 (m, 2H), 2.9 (br s, 4H), 3.15 (br s, 4H), 4.0 (s, 3H), 4.25 (t, 2H), 6.5 (s, 1H), 7.0 (dd, 1H), 7.35-7.5 (m, 4H), 7.65 (s, 1H), 8.5 (s, 1H)

bb) 7-Hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (89 mg) was reacted with 2-(4-pyridyloxy)ethanol (81 mg), ( J. Chem. Soc. Perkin Trans 2, 1987, 12, 1867), to give 4-(indol-5-yloxy)-6-methoxy-7-(2-(4-pyridyloxy)ethoxy)quinazoline.

Example 119

A solution of 4-chloro-6-methoxy-7-(3-piperidinopropoxy)quinazoline (200 mg, 0.59 mmol), (prepared as described for the starting material in Example 67), 6-hydroxyindole (96 mg, 0.715 mmol) in DMF (3 ml) containing cesium carbonate (291 mg, 0.894 mmol) was heated at 90°C for 4 hours. After cooling, the mixture was diluted with water, the precipitate was filtered, washed with water and dried under vacuum. The solid was purified by column chromatography eluting with methylene chloride/methanol (90/10 increasing to 50/50) to give 4-(indol-6-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline (240 mg, 93 %).

^H NMR Spectrum: (DMSO_d6) 1.35-1.45 (m, 2H), 1.45-1.55 (m, 4H), 1.9-2.05 (m, 2H), 2.3-2.4 (m, 4H), 2.45 (t, 2H), 4.0 (s, 3H), 4.22 (t, 2H), 6.5 (s, 1H), 6.9 (dd, 1H), 7.3 (s, 1H), 7.35-7.40 (m, 2H), 7.55-7.65 (m, 2H), 8.5 (s, 1H)

MS-ESI : 433 [MH]^+

Elemental analysis

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Example 120

A solution of 4-chloro-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline (200 mg, 0.6 mmol), (prepared as described for the starting material in Example 50), and 6-hydroxyindole (97 mg, 0.73 mmol) in DMF (3 ml) containing potassium carbonate (125 mg, 0.91 mmol) was heated at 90°C for 2.5 hours. After cooling, water was added. The precipitate was filtered, washed with water and dried under vacuum. The residue was triturated with ether, filtered, washed with ether and dried under vacuum to give 4-(indol-6-yloxy)-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline (130 mg, 50 %).
\(-\text{165}\)-

\(^1\)H NMR Spectrum: (DMSO\(_d_6\)) 2.2-2.35 (m, 2H), 3.05 (s, 3H), 3.3 (m, 2H), 4.0 (s, 3H), 4.35 (t, 2H), 6.48 (s, 1H), 6.9 (dd, 1H), 7.3 (s, 1H), 7.4 (2s, 2H), 7.6 (d, 1H), 7.65 (s, 1H), 7.9 (s, 1H)

MS-ESI : 428 [MH]\\(^+\)

Elemental analysis

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**Example 121**

Using an analogous procedure to that described for Example 120, 4-chloro-6-methoxy-7-(3-morpholinoproxy)quinazoline (200 mg, 0.59 mmol), (prepared as described for the starting material in Example 1), was reacted with 6-hydroxyindole (95 mg, 0.71 mmol) to give 4-(indol-6-yloxy)-6-methoxy-7-(3-morpholinoproxy)quinazoline (155 mg, 60%).

\(^1\)H NMR Spectrum: (DMSO\(_d_6\)) 1.95-2.05 (m, 2H), 2.4 (br s, 4H), 2.48 (t, 2H), 3.6 (t, 4H), 4.0 (s, 3H), 4.27 (t, 2H), 6.5 (s, 1H), 6.93 (dd, 1H), 7.3 (s, 1H), 7.4 (br s, 2H), 7.6 (d, 1H), 7.61 (s, 1H), 8.5 (s, 1H)

MS-ESI : 435 [MH]\\(^+\)

Elemental analysis

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**Example 122**

A suspension of 7-(1-\text{-}1\text{-}tert\text{-}butoxycarbonylpiperidin\text{-}4\text{-}ylmethoxy)\text{-}4\text{-}(2\text{-}methylindol\text{-}5\text{-}yloxy)quinazoline (150 mg, 0.31 mmol), (prepared as described in Example 90), in methylene chloride (2 ml) and TFA (1.5 ml) was stirred for 1 hour at ambient temperature. After removal of the volatiles under vacuum the residue was azeotroped with toluene. The residue was partitioned between methylene chloride and water and the aqueous layer was adjusted to pH11. The organic layer was separated, washed with brine, dried (MgSO\(_4\)), and evaporated. The residue was triturated with ether, filtered, washed with ether and dried under vacuum to give 4-(2-methylindol-5-yloxy)-7-(piperidin-4-ylmethoxy)quinazoline (80 mg, 67%).

\(^1\)H NMR Spectrum: (DMSO\(_d_6\), CF\(_3\)COOD) 1.5-1.65 (m, 2H), 2.0 (d, 2H), 2.15-2.3 (m, 1H), 2.4 (s, 3H), 2.95 (t, 2H), 3.38 (d, 2H), 4.2 (d, 2H), 6.2 (s, 0.5H, partially exchanged), 6.9 (dd, 1H), 7.35 (s, 1H), 7.4 (d, 1H), 7.5 (s, 1H), 7.58 (dd, 1H), 8.5 (d, 1H), 9.1 (s, 1H)

MS-ESI : 389 [MH]\\(^+\)
Elemental analysis

C_{25}H_{24}N_4O_2 0.2 H_2O 0.12 CH_2Cl_2
Requirements

Example 123

Using an analogous procedure to that described for Example 71, 4-(2-methylindol-5-yloxy)-7-(piperidin-4-ylmethoxy)quinazoline (150 mg, 0.386 mmol), (prepared as described in Example 122), was reacted with methoxyacetaldehyde (83 mg, 0.772 mmol), (prepared as described for the starting material in Example 71), to give 7-(1-(2-methoxyethyl)piperidin-4-ylmethoxy)-4-(2-methylindol-5-yloxy)quinazoline (80 mg, 46%).

\[ ^1H \text{NMR Spectrum: (DMSO-d}_6\) 1.3-1.42 (m, 2H), 1.7-1.9 (m, 3H), 2.0 (t, 2H), 2.4 (s, 3H), 2.48 (t, 2H), 2.92 (d, 2H), 3.22 (s, 3H), 3.42 (t, 2H), 4.05 (d, 2H), 6.15 (s, 1H), 6.88 (dd, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.35 (s, 1H), 7.37 (d, 1H), 8.28 (d, 1H), 8.6 (s, 1H)

MS-ESI : 447 [MH]^+

Elemental analysis

C_{25}H_{30}N_4O_3 0.5 H_2O
Requirements

Example 124

Diethyl azodicarboxylate (117 mg, 0.67 mmol) was added in portions to a solution of 7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (120 mg, 0.37 mmol), (prepared as described in Example 49), and 3-(ethylsulphonyl)-1-propanol (74 mg, 0.48 mmol) in methylene chloride (3.5 ml) and triphenylphosphine (176 mg, 0.67 mmol). After stirring for 2 hours at ambient temperature, the residue was poured onto a column of silica and eluted with ethyl acetate/methylene chloride (1/1) followed by ethyl acetate/methylene chloride/methanol (97/3 followed by 95/5). After removal of the solvent under vacuum, the residue was triturated with ether, filtered and dried under vacuum to give 7-(3-(ethylsulphonyl)propoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (93 mg, 55%).

\[ ^1H \text{NMR Spectrum: (DMSO-d}_6\) 1.25 (t, 3H), 2.2-2.3 (m, 2H), 2.4 (s, 3H), 3.2 (q, 2H), 3.3 (t, 2H), 4.0 (s, 3H), 4.35 (t, 2H), 6.15 (s, 1H), 6.9 (dd, 1H), 7.28 (s, 1H), 7.32 (d, 1H), 7.4 (s, 1H), 7.62 (s, 1H), 8.5 (s, 1H)

MS-ESI : 456 [MH]^+

Elemental analysis

C_{25}H_{25}N_4O_3S
Requirements
The starting material was prepared as follows:

A solution of ethylthiopropanol (1.2 g, 10 mmol) in methylene chloride (30 ml) containing 3-chloroperoxybenzoic acid (5 g, 20 mmol) was stirred at ambient temperature for 30 minutes. The precipitate was filtered, washed with methylene chloride and the filtrate was poured onto a column of aluminium oxide and eluted with methylene chloride, followed by methylene chloride/methanol (95/5 and 90/10). After removal of the solvent, the residue was dissolved in methylene chloride, dried (MgSO₄) and evaporated to give 3-(ethylsulphonyl)-1-propanol (1.05 g, 69%).

1H NMR Spectrum: (DMSOd₆) 1.25 (t, 3H), 1.75-1.9 (m, 2H), 3.0-3.2 (m, 4H), 3.5 (q, 2H), 4.7 (t, 1H)
MS-ESI : 153 [MH]⁺

**Example 125**

Using an analogous procedure to that described for Example 124, 4-(2,3-dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (120 mg, 0.36 mol), (prepared as described for the starting material in Example 91), was reacted with 3-(ethylsulphonyl)-1-propanol (71 mg, 0.46 mol), (prepared as described for the starting material in Example 124), to give 4-(2,3-dimethylindol-5-yloxy)-7-(3-ethylsulphonylpropoxy)-6-methoxyquinazoline (96 mg, 57%).

1H NMR Spectrum: (DMSOd₆) 1.25 (t, 3H), 2.15 (s, 3H), 2.2-2.3 (m, 2H), 2.35 (s, 3H), 3.2 (q, 2H), 3.3 (t, 2H), 4.02 (s, 3H), 4.35 (t, 2H), 6.9 (dd, 1H), 7.22 (s, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 7.63 (s, 1H), 8.51 (s, 1H)
MS-ESI : 470 [MH]⁺

**Elemental analysis**

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**Example 126**

Using an analogous procedure to that described for Example 124, 7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (128 mg, 0.4 mmol), (prepared as described in Example 49), was reacted with 4-(2-hydroxyethyl)-(1-tert-butoxycarbonyl)piperidine (119 mg, 0.52 mmol) overnight to give 7-(2-(1-tert-butoxycarbonylpiperidin-4-yl)ethoxy)-6-
methoxy-4-(2-methylindol-5-yloxy)quinazoline (34 mg, 16%).

$^1$H NMR Spectrum: (DMSOd$_6$) 1.05-1.2 (m, 2H), 1.42 (s, 9H), 1.62-1.85 (m, 5H), 2.42 (s, 3H), 2.62-2.82 (m, 2H), 3.9-4.0 (m, 2H), 4.0 (s, 3H), 4.25 (t, 2H), 6.17 (s, 1H), 6.9 (dd, 1H), 7.3 (d, 1H), 7.32 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

MS-ESI: 533 [MH]$^+$

Elemental analysis

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<td>C 67.8 H 6.9 N 10.5</td>
<td>C 67.7 H 6.8 N 10.5%</td>
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</table>

The starting material was prepared as follows:

A solution of 4-(2-hydroxyethyl)pyridine (1.8 g, 14.6 mol) in acetic acid (15 ml) containing platinum oxide (200 mg) was hydrogenated for 20 hours at 3.3-4 atmospheres pressure. After filtration, the filtrate was evaporated and azeotroped twice with toluene. The residue was triturated with 2N sodium hydroxide and solid sodium hydroxide was added to adjust the pH to 13. The volatiles were removed under vacuum and the residue was triturated with ether, filtered, washed with methylene chloride, and dried under vacuum to give 2-(piperidin-4-yl)-1-ethanol (860 mg, 46%).

$^1$H NMR Spectrum: (DMSOd$_6$, CF$_3$COOD) 1.3-1.5 (m, 4H), 1.6-1.7 (m, 1H), 1.7-1.9 (d, 2H), 1.75 (t, 2H), 3.25 (d, 2H), 3.55 (t, 2H)

A solution of 2-(piperidin-4-yl)-1-ethanol (830 mg, 6.4 mmol) in DMF (5 ml) containing tertbutyl dicarbonate anhydride (1.4 g, 6.4 mmol) was stirred at ambient temperature for 48 hours. After removal of the volatiles under vacuum, the residue was partitioned between ether and water. The organic layer was separated, washed with water, brine, dried (MgSO$_4$) and evaporated to give 4-(2-hydroxyethyl)-(1-tert-butoxycarbonyl)piperidine (1 g, 68%).

$^1$H NMR Spectrum: (DMSOd$_6$) 0.9-1.1 (m, 2H), 1.3-1.6 (m, 3H), 1.4 (s, 9H), 1.6 (d, 2H), 2.5-2.8 (br s, 2H), 3.45 (dd, 2H), 3.9 (d, 2H), 4.35 (t, 1H)

Example 127

Using an analogous procedure to that described for Example 121, 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (160 mg, 0.47 mol), (prepared as described for the starting material in Example 1), was reacted with 6-hydroxy-2-methylindole (84 mg, 0.57 mol), (Eur. J. Med. Chem. 1975, 10, 187), to give 6-methoxy-4-(2-methylindol-6-yloxy)-7-
(3-morpholinopropoxy)quinazoline (157 mg, 73%).

\(^1\)H NMR Spectrum: (DMSO\(_d_6\), CF\(_3\)COOD) 2.25-2.35 (m, 2H), 2.38 (s, 3H), 3.15 (t, 2H), 3.35 (t, 2H), 3.5 (d, 2H), 3.68 (t, 2H), 4.0 (d, 2H), 4.05 (s, 3H), 4.35 (t, 2H), 6.18 (s, 1H), 6.9 (d, 1H), 7.22 (s, 1H), 7.45 (d, 1H), 7.52 (s, 1H), 7.8 (s, 1H), 9.05 (s, 1H)

MS-ESI : 449 [MH]^+

Elemental analysis

\[ \text{C}_{25}\text{H}_{28}\text{N}_{4}\text{O}_4 \times 0.2\text{H}_2\text{O} \]

Found C 66.4  H 6.4  N 12.4

Requires C 66.4  H 6.3  N 12.4%

Example 128

Using an analogous procedure to that described for the synthesis of 4-(2-methylindol-5-yloxy)-7-(piperidin-4-ylmethoxy)quinazoline, (prepared as described in Example 122), 7-(2-(1-tert-butoxycarbonylpiperidin-4-yl)ethoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (400 mg, 0.75 mmol), (prepared as described in Example 126), was used to give 6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(piperidin-4-yl)ethoxy)quinazoline (284 mg, 87%).

\(^1\)H NMR Spectrum: (DMSO\(_d_6\), CF\(_3\)COOD) 1.3-1.5 (m, 2H), 1.8-2.0 (m, 5H), 2.4 (s, 3H), 2.9 (t, 2H), 3.3 (d, 2H), 4.05 (s, 3H), 4.35 (t, 2H), 6.2 (s, 1H), 6.95 (dd, 1H), 7.35 (s, 1H), 7.37 (d, 1H), 7.52 (s, 1H), 7.8 (s, 1H), 9.1 (s, 1H)

MS-ESI : 433 [MH]^+

Example 129

Diethyl azodicarboxylate (65 µl, 0.4 mmol) was added in portions to a suspension of 4-(2,3-dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol), triphenylphosphine (107 mg, 0.4 mmol), (E)-4-(pyrrolidin-1-yl)but-2-en-1-ol (40 mg, 0.28 mmol) in DMF (0.4 ml) and dichloromethane (1.5 ml) cooled at 0°C. The reaction mixture was left to warm up to ambient temperature and was stirred overnight. The mixture was poured onto a column of silica and was eluted with methylene chloride followed by methylene chloride/methanol (98/2), followed by methylene chloride/3N ammonia in methanol (95/5 and 90/10) to give 4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-((E)4-(pyrrolidin-1-yl)but-2-en-1-yloxy)quinazoline (51 mg, 55%).

\(^1\)H NMR Spectrum: (DMSO\(_d_6\)) 1.6-1.7 (m, 4H), 2.15 (s, 3H), 2.3 (s, 3H), 2.4 (br s, 4H), 3.1 (d, 2H), 3.97 (s, 3H), 4.7 (d, 2H), 5.8-6.0 (m, 2H), 7.15 (s, 1H), 7.22 (d, 1H), 7.3 (d, 1H), 7.55
Thionyl chloride (9.3ml, 128mmol) was added in portions to a stirred solution of 2-butyne-1,4-diol (10g, 116mmol) in toluene (15ml) and pyridine (10.3ml) cooled at 0°C. The mixture was stirred for 3.5 hours at ambient temperature and then poured onto ice water. The mixture was extracted with ether, the organic layer was washed with saturated aqueous sodium hydrogen carbonate solution and then brine, dried (MgSO₄) and the volatiles removed by evaporation. The residue was purified by column chromatography eluting with petroleum ether/ether (7/3) to give 4-chlorobut-2-yn-1-ol (4.74g, 39%).

¹H NMR Spectrum: (CDCl₃) 1.68(t, 1H); 4.18(d, 2H); 4.33(d, 2H)

Pyrrrolidine (7.8ml, 94mmol) was added dropwise to a solution of 4-chlorobut-2-yn-1-ol (4.74g, 45mmol) in toluene (40ml) and the mixture stirred and heated at 60°C for 1 hour. The volatiles were removed by evaporation and the residue was purified by chromatography eluting with methylene chloride/methanol (96/4) to give 4-(pyrrolidin-1-yl)but-2-yn-1-ol (4.3g, 69%).

¹H NMR Spectrum: (CDCl₃) 1.82(t, 4H); 2.63(t, 4H); 3.44(t, 2H), 4.29(t, 2H)

A solution of 4-(pyrrolidin-1-yl)but-2-yn-1-ol (4.3g, 31mmol) in THF (20ml) was added dropwise to a suspension of lithium aluminium hydride (2.35g, 62mmol) in anhydrous THF (8ml) and the mixture stirred and heated at 60°C for 2 hours. The mixture was cooled to 5°C and 2M aqueous sodium hydroxide solution (28ml) was added dropwise. The resulting suspension was filtered and the volatiles removed from the filtrate by evaporation. The residue was dissolved in a mixture of methylene chloride/ethyl acetate, dried (MgSO₄) and the solvent removed by evaporation. The residue was purified by column chromatography on aluminum oxide eluting with methylene chloride/methanol (97/3) to give (E)-4-(pyrrolidin-1-yl)but-2-en-1-ol (3.09g, 70%).

¹H NMR Spectrum: (CDCl₃) 1.82(m, 4H); 2.61(m, 4H); 3.17(m, 2H); 4.13(s, 2H); 5.84(m, 2H)

A solution of 4-chloro-6-methoxy-7-benzylxyquinazoline (7g, 23mmol), (prepared as described for the starting material in Example 1), and 5-amino-2,3-dimethylindole (4.5g, 28mmol) in isopropanol (90ml) containing 6.2 N hydrogen chloride in isopropanol (380µl) was
heated at reflux for 3 hours and stirred overnight at ambient temperature. The mixture was trituted with ether and the solid was filtered, washed with ether and dried under vacuum to give 7-benzzyloxy-4-(2,3-dimethylindol-5-ylamino)-6-methoxyquinazoline (10.5 g, quant.).

\[^{1}H\text{ NMR Spectrum: (DMSO}_{d_{6}}\text{)}\] 2.16 (s, 3H), 2.33 (s, 3H), 4.0 (s, 3H), 5.34 (s, 2H), 7.2 (d, 1H), 7.32 (d, 1H), 7.35-7.55 (m, 7H), 8.2 (s, 1H), 8.7 (s, 1H), 10.9 (s, 1H), 11.15 (s, 1H)

MS-ESI : 425 [MH]^+

Ammonium formate (20g, 326 mmol) and 10% palladium on carbon (1g) were added to a solution of 7-benzzyloxy-4-(2,3-dimethylindol-5-ylamino)-6-methoxyquinazoline (10g, 22 mmol) in DMF (100ml) and methanol (300ml). After stirring for 3 hours at ambient temperature, aqueous ammonia (120ml) was added. The precipitate was filtered, washed with water and dried under vacuum. The residue was triturated with ethyl acetate and ether and was filtered, dried under vacuum and purified by column chromatography eluting with methanol/methylene chloride (5/95 followed by 10/90) to give 4-(2,3-dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (5.5g, 75%).

\[^{1}H\text{ NMR Spectrum: (DMSO}_{d_{6}}\text{)}\] 2.2 (s, 1H), 2.35 (s, 3H), 3.97 (s, 3H), 7.0 (s, 1H), 7.22 (d, 1H), 7.3 (d, 1H), 7.55 (s, 1H), 7.85 (s, 1H), 8.28 (s, 1H), 9.35 (s, 1H), 10.2 (br s, 1H), 10.62 (s, 1H)

MS-ESI : 335 [MH]^+

**Examples 130-145**

Using an analogous procedure to that described in Example 129, 4-(2,3-dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol), (prepared as described for the starting material in Example 129), was reacted with the appropriate alcohol to give the compounds described in Table IX.

**Table IX**

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a) 4-(2,3-Dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol) was reacted with 3-(5-methyl-[1,2,4]-triazol-1-yl)propan-1-ol (40 mg) to give 4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(3-(5-methyl-1H-[1,2,4]-triazol-1-yl)propoxy)quinazoline.

The starting material was prepared as follows:

Under argon, 1,2,4-triazole (13.8g, 200mmol) was added to a solution of sodium ethoxide (freshly prepared from sodium (4.6g) and ethanol (250ml)). After complete dissolution, 3-bromopropan-1-ol (18ml, 200 mmol) was added dropwise. The mixture was refluxed for 18 hours and the solid was filtered and washed with ethanol. The filtrate was evaporated and the residue was purified by column chromatography eluting with methylene chloride/methanol (9/1) to give 3-(1,2,4-triazol-1-yl)propan-1-ol (22.8 g, 90%).

$^1$H NMR Spectrum: (CDCl$_3$): 2.12 (m, 2H); 2.6 (br s, 1H); 3.65 (t, 2H); 4.35 (t, 2H); 7.95 (s, 1H); 8.1 (s, 1H)

To a solution of 3-(1,2,4-triazol-1-yl)propan-1-ol (7 g, 55 mmol) in DMF (70ml) was added tertbutyldimethylsilyl chloride (9.1g, 60 mmol) followed by DMAP (336mg, 2.7 mmol) followed by imidazole (4.5gr, 66 mmol). After stirring overnight at ambient temperature, the volatiles were removed under vacuum and the residue was partitioned between water and ethyl acetate/ether. The organic layer was separated, washed with water, brine, dried (MgSO$_4$) and evaporated. The residue was purified by column chromatography eluting with methylene chloride/ether (6/4) to give 3-(tertbutyldimethylsilyloxy)-1-(1,2,4-triazol-1-yl)propane (11.1 gr, 84%).

MS-EI : 242 [MH]+

$^1$H NMR Spectrum: (CDCl$_3$) 0.25 (s, 6H); 0.9 (s, 9H); 2.05 (m, 2H); 3.52 (t, 2H); 4.25 (t,
2H); 7.9 (s, 1H); 8.02 (s, 1H)

To a solution of 3-(tertbutyldimethylsilyloxy)-1-(1,2,4-triazol-1-yl)propane (7 g, 29 mmol) in DMF (100 ml) cooled at -70°C was added 2.5 M n-butyllithium (17.4 ml) over 45 minutes. After stirring for 90 minutes at -70°C, methyl iodide (3.6 ml, 58 mmol) was added.

After stirring for 2 hours at ambient temperature, the mixture was poured onto saturated ammonium chloride. The mixture was then diluted with ether and ethyl acetate. The organic layer was separated, washed with aqueous sodium thiosulphate followed by brine, dried (MgSO₄) and evaporated to give 3-(tertbutyldimethylsilyloxy)-1-(5-methyl-[1,2,4]-triazol-1-yl)propane (7.3 g, 98%).

MS-EI : 256 [MH]+

1H NMR Spectrum: (CDCl₃) 0.25 (s, 6H); 0.85 (s, 9H); 2.0 (t, 2H); 2.4 (s, 3H); 3.52 (t, 2H); 4.15 (t, 2H); 7.72 (s, 1H)

To a solution of ammonium fluoride (10.4 g, 280 mmol) in methanol (110 ml) was added a solution of 3-(tertbutyldimethylsilyloxy)-1-(5-methyl-[1,2,4]-triazol-1-yl)propane (7.2 g, 28 mmol) in methanol (30 ml). The mixture was refluxed for 4.5 hours. After cooling, silica (100 g) was added and the volatiles were removed under vacuum. The residue was added onto a column of silica and eluted with a mixture of methylene chloride/ethyl acetate (1/1) followed by methylene chloride/methanol (9/1) to give 3-(5-methyl-[1,2,4]-triazol-1-yl)propan-1-ol (3.65 g, 92%).

MS-ESI : 142 [MH]+

1H NMR Spectrum: (CDCl₃) 2.05 (m, 2H); 2.5 (s, 3H); 3.62 (t, 2H); 4.25 (t, 2H); 7.8 (s, 1H)

b) 4-(2,3-Dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol) was reacted with 2-(N-(2-methoxyethyl)-N-methylamino)ethanol (38 mg), (prepared as described for the starting material in Example 59), to give 4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(2-(N-(2-methoxyethyl)-N-methylamino)ethoxy)quinazoline.

1H NMR Spectrum: (DMSO-d₆) 2.15 (s, 3H), 2.35 (s, 6H), 2.65 (t, 2H), 2.85 (t, 2H), 3.25 (s, 3H), 3.45 (t, 2H), 3.95 (s, 3H), 4.2 (t, 2H), 7.15 (s, 1H), 7.22 (s, 1H), 7.3 (dd, 1H), 7.55 (s, 1H), 7.85 (s, 1H), 8.3 (s, 1H), 9.4 (s, 1H), 10.62 (s, 1H)

c) 4-(2,3-Dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol) was
reacted with 2-(1-methylimidazol-2-yl)ethanol (36 mg), (EP 06751112 A1), to give 4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(2-(1-methylimidazol-2-yl)ethoxy)quinazoline.

1H NMR Spectrum: (DMSO-d$_6$) 2.15 (s, 3H), 2.32 (s, 3H), 3.2 (t, 2H), 3.7 (s, 3H), 3.95 (s, 3H), 4.45 (t, 2H), 6.8 (s, 1H), 7.05 (s, 1H), 7.15 (s, 1H), 7.22 (d, 1H), 7.3 (dd, 1H), 7.55 (s, 1H), 7.88 (s, 1H), 8.32 (s, 1H), 9.4 (s, 1H), 10.62 (s, 1H)

d) 4-(2,3-Dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol) was reacted with 1-(3-hydroxypropyl)-4-methylpiperazine (45 mg) to give 4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline.

1H NMR Spectrum: (DMSO-d$_6$) 1.9-2.0 (m, 2H), 2.15 (2s, 6H), 2.0-2.9 (m, 8H), 2.32 (s, 3H), 2.45 (t, 2H), 3.95 (s, 3H), 4.2 (t, 2H), 7.1 (s, 1H), 7.22 (d, 1H), 7.3 (dd, 1H), 7.55 (s, 1H), 7.85 (s, 1H), 8.3 (s, 1H), 9.4 (s, 1H), 10.62 (s, 1H)

The starting material was prepared as follows:

3-Bromopropan-1-ol (20ml, 20mmol) was added dropwise to a solution of 1-methylpiperazine (29ml, 26 mmol) in ethanol (200ml). Potassium carbonate (83 gr, 60 mmol) was added and the mixture was refluxed for 20 hours. After cooling, the solid was filtered and the filtrate was evaporated. The residue was triturated with ether, filtrate and evaporated. The residue was distilled at about 60-70°C under about 0.2 mm Hg to give 1-(3-hydroxypropyl)-4-methylpiperazine (17g, 53%).

1H NMR Spectrum: (CDCl$_3$) 1.72 (m, 2H) ; 2.3 (s, 3H) ; 2.2-2.8 (m, 8H) ; 2.6 (t, 2H) ; 3.8 (t, 2H) ; 5.3 (br s, 1H)

e) 4-(2,3-Dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol) was reacted with 3-(1,1-dioxothiomorpholino)-1-propanol (55 mg), (prepared as described for the starting material in Example 5), to give 4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(3-(1,1-dioxothiomorpholino)propoxy)quinazoline.

1H NMR Spectrum: (DMSO-d$_6$) 1.9-2.0 (m, 2H), 2.5 (s, 9H), 2.65 (t, 2H), 2.9 (br s, 4H), 3.15 (br s, 4H), 3.95 (s, 3H), 4.25 (t, 2H), 7.2 (s, 1H), 7.85 (s, 1H), 8.0 (dd, 1H), 8.15 (d, 1H), 8.2 (s, 1H), 8.45 (s, 1H), 9.6 (s, 1H), 10.95 (s, 1H)
f) 4-(2,3-Dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol) was
reacted with 2-(N-methyl-N-(4-pyridyl)amino)ethanol (43 mg), (EP 0359389), to give 4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(2-(N-methyl-N-(4-pyridyl)amino)ethoxy)quinazoline.

¹H NMR Spectrum: (DMSOD₆) 2.15 (s, 3H), 2.35 (s, 3H), 3.07 (s, 3H), 3.85 (t, 2H), 3.95 (s, 3H), 4.3 (t, 2H), 6.7 (d, 2H), 7.15 (s, 1H), 7.22 (d, 1H), 7.3 (dd, 1H), 7.55 (s, 1H), 7.85 (s, 1H), 8.15 (d, 2H), 8.3 (s, 1H), 9.4 (s, 1H), 10.65 (s, 1H)

g) 4-(2,3-Dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol) was reacted with 2-furanmethanol (28 mg) to give 4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(2-furylethoxy)quinazoline.

h) 4-(2,3-Dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol) was reacted with 2-N,N-dimethylethanolamine (25 mg) to give 4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(2-(N,N-dimethylamino)ethoxy)quinazoline.

¹H NMR Spectrum: (DMSOD₆) 2.15 (s, 3H), 2.25 (s, 6H), 2.32 (s, 3H), 2.72 (t, 2H), 3.95 (s, 3H), 4.2 (t, 2H), 7.15 (s, 1H), 7.22 (d, 1H), 7.3 (dd, 1H), 7.55 (s, 1H), 7.85 (s, 1H), 8.32 (s, 1H), 9.4 (s, 1H), 10.6 (s, 1H)

i) 4-(2,3-Dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol) was reacted with 1-(2-hydroxyethyl)pyrrolidine (33 mg) to give 4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(2-(pyrrolidin-1-yl)ethoxy)quinazoline.

¹H NMR Spectrum: (DMSOD₆) 1.65-1.75 (m, 4H), 2.15 (s, 3H), 2.35 (s, 3H), 2.55-2.65 (m, 4H), 2.9 (t, 2H), 3.95 (s, 3H), 4.25 (t, 2H), 7.15 (s, 1H), 7.22 (d, 1H), 7.3 (dd, 1H), 7.55 (s, 1H), 7.85 (s, 1H), 8.32 (s, 1H), 9.4 (s, 1H), 10.62 (s, 1H)

j) 4-(2,3-Dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol) was reacted with triethylene glycol monomethyl ether (47 mg) to give 4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)ethoxy)quinazoline.

k) 4-(2,3-Dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol) was reacted with 5,5-dimethyl-1,3-dioxane-2-ethanol (46 mg) to give 7-(2-(5,5-dimethyl-1,3-dioxan-2-yl)ethoxy)-4-(2,3-dimethylindol-5-ylamino)-6-methoxyquinazoline.
1H NMR Spectrum: (DMSOd6) 0.7 (s, 3H), 1.15 (s, 3H), 2.05-2.1 (m, 2H), 2.1 (s, 3H), 2.6 (s, 3H), 3.42 (d, 2H), 3.57 (d, 2H), 4.0 (s, 3H), 4.22 (t, 2H), 4.7 (t, 1H), 7.2 (s, 1H), 7.82 (s, 1H), 8.0 (dd, 1H), 8.17 (d, 1H), 8.3 (s, 1H), 8.45 (s, 1H), 9.6 (s, 1H), 10.95 (s, 1H)

5 1) 4-(2,3-Dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol) was reacted with 1-(2-hydroxyethyl)piperidine (37 mg) to give 4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(2-piperidinoethoxy)quinazoline.

1H NMR Spectrum: (DMSOd6) 1.3-1.45 (m, 2H), 1.45-1.6 (m, 4H), 2.15 (s, 3H), 2.35 (s, 3H), 2.45 (br s, 4H), 2.75 (t, 2H), 3.95 (s, 3H), 4.25 (t, 2H), 7.15 (s, 1H), 7.22 (d, 1H), 7.3 (dd, 1H), 7.55 (s, 1H), 7.85 (s, 1H), 8.3 (s, 1H), 9.4 (s, 1H), 10.62 (s, 1H)

m) 4-(2,3-Dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol) was reacted with 2-(N-methyl-N-(pyridazin-4-yl)amino)ethanol (44 mg) to give 4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(2-(N-methyl-N-(pyridazin-4-yl)amino)ethoxy)quinazoline.

1H NMR Spectrum: (DMSOd6) 2.15 (s, 3H), 2.32 (s, 3H), 3.1 (s, 3H), 3.9 (s, 3H), 3.95 (t, 2H), 4.35 (t, 2H), 6.85 (dd, 1H), 7.15 (s, 1H), 7.20 (d, 1H), 7.28 (dd, 1H), 7.55 (s, 1H), 7.85 (s, 1H), 8.3 (s, 1H), 8.58 (d, 1H), 8.9 (d, 1H), 9.4 (s, 1H), 10.62 (s, 1H)

The starting material was prepared as follows:

A solution of 4-bromo-3,6-dichloro-pyridazine (1.11g, 5mmol), (J.Chem. Soc., Perkin Trans I, 1974, 696), and 2-(methylamino)ethanol (0.75g, 10mmol) in isopropanol (10ml) was heated at reflux for 30 minutes. The solvent was removed by evaporation, the residue was partitioned between methylene chloride and water and the aqueous layer was adjusted to pH9 with solid potassium carbonate. The organic layer was separated, washed with brine, dried (MgSO4) and the solvent removed by evaporation. The residue was triturated with ether, collected by filtration and dried under vacuum to give 2-(N-(3,6-dichloropyridazin-4-yl)-N-methylamino)ethanol (1g, 90%).

1H NMR Spectrum: (CDCl3) 2.1(br s, 1H); 3.09(s, 3H); 3.71(t, 2H); 3.93(t, 2H); 6.8(s, 1H)

MS - ESI: 221 [MH]+

A mixture of 2-(N-(3,6-dichloropyridazin-4-yl)-N-methylamino)ethanol (444mg,
2 mmol and 10% palladium-on-charcoal catalyst (150 mg) in ethanol (15 ml), methanol (5 ml) and aqueous ammonia (15 ml) was stirred under hydrogen at 3 atmospheres pressure for 4 hours. The catalyst was removed by filtration and the solvent removed from the filtrate by evaporation. The residue was dissolved in methylene chloride, the insoluble material was removed by filtration and the solvent was removed from the filtrate by evaporation. The residue was purified by column chromatography on neutral aluminum oxide eluting with methylene chloride/methanol (95/5 followed by 90/10). The purified product was triturated with petroleum ether, the solid product was collected by filtration and dried under vacuum to give 2-(N-methyl-N-(pyridazin-4-yl)amino)ethanol (275 mg, 91%).

\[ ^1H \text{ NMR Spectrum: (CDCl}_3 \text{) 3.06(s, 3H); 3.57(t, 2H); 3.89(t, 2H); 6.52(dd, 1H); 8.48(d, 1H); 8.54 (d, 1H)} \]

MS - ESI: 153 [MH]^+

n) 4-(2,3-Dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol) was reacted with 2-(2-morpholinoethoxy)ethanol (50 mg) to give 4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(2-(2-morpholinoethoxy)ethoxy)quinazoline.

\[ ^1H \text{ NMR Spectrum: (DMSO}_d\text{)} 2.18 (s, 3H), 2.35 (s, 3H), 2.35-2.45 (m, 4H), 2.45-2.5 (m, 2H), 3.5-3.55 (m, 4H), 3.65 (t, 2H), 3.8-3.85 (m, 2H), 3.95 (s, 1H), 4.25 (m, 2H), 7.15 (s, 1H), 7.22 (d, 1H), 7.3 (dd, 1H), 7.55 (s, 1H), 7.85 (s, 1H), 8.3 (s, 1H), 9.4 (s, 1H), 10.62 (s, 1H) \]

The starting material was prepared as follows:

2-(2-Chloroethoxy)ethanol (1.25 g, 10 mmol) was added to a mixture of morpholine (2.58 g, 30 mmol) and potassium carbonate (5.5 g, 40 mmol) in acetonitrile (50 ml). The mixture was heated at reflux for 6 hours and then stirred for 18 hours at ambient temperature. The insolubles were removed by filtration and the volatiles were removed from the filtrate by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol (95/5 followed by 90/10 and then 80/20) to give 2-(2-morpholinoethoxy)ethanol (600 mg, 34%).

\[ ^1H \text{ NMR Spectrum: (CDCl}_3 \text{) 2.5(br s, 4H); 2.59(t, 2H); 3.6-3.85(m, 10H)} \]

MS - (EI): 175 [M]^+
o) 4-(2,3-Dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol) was reacted with 3-(2-hydroxyethyl)pyridine (35 mg) to give 4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(2-(3-pyridyl)ethoxy)quinazoline.

$^1$H NMR Spectrum: (DMSO-d$_6$) 2.15 (s, 3H), 2.32 (s, 3H), 3.15 (t, 2H), 3.95 (s, 3H), 4.4 (t, 2H), 7.2 (s, 1H), 7.22 (d, 1H), 7.3 (dd, 1H), 7.35 (dd, 1H), 7.55 (s, 1H), 7.8 (d, 1H), 7.85 (s, 1H), 8.32 (s, 1H), 8.45 (dd, 1H), 8.6 (s, 1H), 9.4 (s, 1H), 10.68 (s, 1H)

p) 4-(2,3-Dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol) was reacted with 1-(3-hydroxypropyl)pyrrolidin-2-one (41 mg) to give 4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(3-(2-oxopyrrolidin-1-yl)propoxy)quinazoline.

$^1$H NMR Spectrum: (DMSO-d$_6$) 1.9-2.05 (m, 4H), 2.12 (s, 3H), 2.15-2.3 (m, 2H), 2.6 (s, 3H), 3.3-3.45 (m, 4H), 4.0 (s, 3H), 4.15 (t, 2H), 7.15 (s, 1H), 7.82 (s, 1H), 8.0 (dd, 1H), 8.17 (d, 1H), 8.3 (s, 1H), 8.45 (s, 1H), 9.6 (s, 1H), 10.95 (s, 1H)

**Example 146**

Using an analogous procedure to that described for Example 121, 4-chloro-6-methoxy-7-(3-pyrrolidinopropoxy)quinazoline (150 mg, 0.47 mmol), (prepared as described for the starting material in Example 9), was reacted with 6-hydroxy-2-methylindole (83 mg, 0.56 mol), (Eur. J. Med. Chem. 1975, 10, 187), to give 6-methoxy-4-(2-methylindol-6-yloxy)-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline (170 mg, 85%).

$^1$H NMR Spectrum: (DMSO-d$_6$) 1.65-1.8 (m, 4H), 1.95-2.05 (m, 2H), 2.42 (s, 3H), 2.5 (br s, 1H), 2.6 (t, 2H), 4.0 (s, 3H), 4.27 (t, 2H), 6.2 (s, 1H), 6.85 (dd, 1H), 7.2 (s, 1H), 7.4 (s, 1H), 7.45 (d, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

MS-ESI : 433 [MH$^+$]

Elemental analysis Found C 68.3 H 6.4 N 12.8

Requires C 68.3 H 6.6 N 12.7%

**Example 147**

Using an analogous procedure to that described in Example 123, 6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(piperidin-4-yl)ethoxy)quinazoline (120 mg, 0.28 mmol) was used to give 7-(2-(1-(2-methoxyethyl)piperidin-4-yl)ethoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (55 mg, 40%).
Example 148

Using an analogous procedure to that described in Example 120 OR 121 PER PP, 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (160 mg, 0.48 mmol), (prepared as described for the starting material in Example 1), was reacted with 1,2-dimethyl-5-hydroxyindole (92 mg, 0.57 mol), (Tetrahedron 1994, 50, 13433), to give 4-(1,2-dimethylindol-5-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline (163 mg, 74 %).

\[ ^1H \text{NMR Spectrum: (DMSO}_d_6) \ 1.95-2.1 \text{ (m, 2H), 2.4 \text{ (br s, 4H), 2.45 \text{ (s, 3H), 2.5 \text{ (t, 2H), 3.65 \text{ (t, 4H), 3.75 \text{ (s, 3H), 4.0 \text{ (s,3H), 4.25 \text{ (t, 2H), 6.25 \text{ (s, 1H), 6.95 \text{ (dd, 1H), 7.3 \text{ (s, 1H), 7.38 \text{ (s, 1H), 7.45 \text{ (d, 1H), 7.6 \text{ (s, 1H), 8.5 \text{ (s, 1H)}}})}}}}}}
\]
MS-ESI : 463 [MH]^+

Elemental analysis

\[ C_{26}H_{30}N_4O_4 \text{ Requires: C 67.2 H 6.5 N 12.1}\]

Example 149

Using an analogous procedure to that described in Example 124, 7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (2.3 g, 7.16 mmol), (prepared as described in Example 49), was reacted with (N-methyl-N-tert-butoxycarbonyl)ethanolamine (1.51 g, 8.6 mmol) to give 6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(N-methyl-N-tert-butoxycarbonylamino)ethoxy)quinazoline (1.93 g, 56 %).

\[ ^1H \text{NMR Spectrum: (DMSO}_d_6) \ 1.4 \text{ (s, 9H), 2.4 \text{ (s, 3H), 2.90 \text{ (s, 3H), 3.65 \text{ (t, 2H), 4.0 \text{ (s, 3H), 4.35 \text{ (t, 2H), 6.15 \text{ (s, 1H), 6.8 \text{ (dd, 1H), 7.28 \text{ (s, 1H), 7.35 \text{ (d, 1H), 7.42 \text{ (s, 1H), 7.6 \text{ (s, 1H), 8.5 \text{ (s, 1H)}}})}}}}}}
\]
MS-ESI : 479 [MH]^+

Elemental analysis

\[ C_{26}H_{30}N_4O_5S \text{ Requires: C 65.3 H 6.3 N 11.7}\]
Example 150

A solution of 6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(N-methyl-N-tert-butoxycarbonylamino)ethoxy)quinazoline (550 mg, 1.15 mmol), (prepared as described in Example 149), in methylene chloride (10 ml) containing TFA (12 ml) was stirred for 3 hours at ambient temperature. After removal of the volatiles under vacuum, the residue was partitioned between methylene chloride and sodium hydrogen carbonate. The pH of the aqueous layer was adjusted to 11 with 2N sodium hydroxide. The organic layer was separated, washed with water, brine, dried (MgSO₄) and evaporated. The residue was triturated with ether, filtered and dried under vacuum to give 6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(N-methylamino)ethoxy)quinazoline (356 mg, 82 %).

1H NMR Spectrum: (DMSO-d₆) 2.4 (s, 3H), 2.5 (s, 3H), 2.9 (t, 2H), 4.0 (s, 3H), 4.25 (t, 2H), 6.25 (s, 1H), 6.9 (dd, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H), 11.0 (s, 1H)

MS-ESI : 379 [MH]+

Elemental analysis

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Example 151

A mixture of 6-methoxy-4-(2-methylindol-5-yloxy)-7-(piperidin-4-ylmethoxy)quinazoline (419 mg, 1 mmol), (prepared as described in Example 70), in DMF (6 ml) containing chloroacetonitrile (114 mg, 1.5 mmol), potassium carbonate (346 mg, 2.5 mmol) and potassium iodide (50 mg, 0.3 mmol) was stirred at ambient temperature overnight. The mixture was poured into water and the precipitate was filtered, washed with water and dried under vacuum. The residue was purified by column chromatography, eluting with methylene chloride, followed by methylene chloride/methanol (98/2 and 95/5). After removal of the solvent under vacuum, the residue was triturated with ether, filtered, washed with ether and dried under vacuum to give 7-((1-cyanomethyl)piperidin-4-ylmethoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (304 mg, 66 %).

1H NMR Spectrum: (DMSO-d₆, CF₃COOD) 1.6-1.8 (m, 2H), 2.05-2.2 (d, 2H), 2.2-2.3 (m, 1H), 2.45 (s, 3H), 3.2 (t, 2H), 3.65 (d, 2H), 4.1 (s, 3H), 4.22 (d, 2H), 4.6 (s, 2H), 6.2 (s, 0.5H, partially exchanged), 6.9 (dd, 1H), 7.35 (s, 1H), 7.4 (d, 1H), 7.55 (s, 1H), 7.8 (s, 1H), 9.1 (s,
Example 152

A mixture of 4-chloro-6-methoxy-7-(3-(N-methyl-N-methylsulphonylamino)propoxy)quinazoline (360 mg, 1.00 mmol), potassium carbonate (215 mg, 1.56 mmol) and 5-hydroxyindole (147 mg, 1.10 mmol) in DMF (8.0 ml) was stirred at 100 ºC for 5 hours and allowed to cool to ambient temperature. The solvent was removed by evaporation and the residue purified by silica column chromatography eluting with methanol (2.5 to 5%) in dichloromethane. The resulting solid was recrystallised from ethyl acetate, filtered and washed with diethyl ether to give 4-(indol-5-yloxy)-6-methoxy-7-(3-(N-methyl-N-methylsulphonylamino)propoxy)quinazoline (77mg, 17%).

1H NMR Spectrum: (DMSO$_d_6$) 2.07 (m, 2H), 2.78 (s, 3H), 2.87 (s, 3H), 3.25 (t, 2H), 3.97 (s, 3H), 4.23 (t, 2H), 6.43 (br s, 1H), 6.96 (dd, 1H), 7.32 (s, 1H), 7.41 (m, 3H), 7.59 (d, 1H), 8.48 (s, 1H) and 11.17 (s, 1H)

MS (ESI) : 457 (MH$^+$)

Elemental analysis  Found  C 57.5  H 5.3  N 12.0

C$_{22}$H$_{24}$N$_4$O$_5$S  Requires  C 57.9  H 5.3  N 12.3%

The starting material was prepared as follows:

Using an analogous procedure to that described for the synthesis of the starting material in Example 5, 4-(4-bromo-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline was made in a similar way to 4-(4-chloro-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline using 4-bromo-2-fluorophenol instead of 4-chloro-2-fluorophenol.

A mixture of 4-(4-bromo-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline (9.64g, 26.4 mmol) and triphenylphosphine (20.9g, 79.8 mmol) in dichloromethane (240ml) was stirred under nitrogen, at ambient temperature for 30 minutes. 3-(N-tertButoxycarbonyl)-propanolamine (6.26g, 35.8 mmol) was added followed by diethyl azodicarboxylate (12.4ml, 13.7g, 78.7 mmol). The reaction mixture was stirred for 2 hours. The solvent was then removed by evaporation and the residue taken up in acetonitrile (250ml). The solution was
concentrated to half the original volume and cooled. The resulting crystalline solid was filtered, washed with ether and dried to give 4-(4-bromo-2-fluorophenoxy)-7-(3-(N-tertbutoxy carbonylamino)propoxy)-6-methoxyquinoxaline (10.0g, 73%).

$^1$H NMR Spectrum: (DMSO$_d_6$) 1.37 (s, 9H), 1.94 (t, 2H), 3.13 (q, 2H), 3.97 (s, 3H), 4.21 (t, 2H), 6.89 (br s, 1H), 7.38 (s, 1H), 7.43 - 7.53 (m, 2H), 7.57 (s, 1H), 7.78 (dd, 1H) and 8.55 (s, 1H)

MS (ESI) : 522 (MH)$^+$

Elemental analysis

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C$_{23}$H$_{25}$N$_3$BrFO$_5$

4-(4-Bromo-2-fluorophenoxy)-7-(3-(N-tertbutoxy carbonylamino)propoxy)-6-methoxyquinoxaline (5.46g, 10.5mmol) was taken up in trifluoroacetic acid (75ml) and heated at 85°C for 1.5 hours. The solution was allowed to cool and the excess trifluoroacetic acid removed by evaporation. The residue was then treated with aqueous ammonia (0.88%) solution, extracted with dichloromethane (3x150ml) and filtered through phase separating paper. The solvent was removed by evaporation to give 7-(3-aminopropoxy)-4-(4-bromo-2-fluorophenoxy)-6-methoxyquinoxaline (4.42g, 100%).

$^1$H NMR Spectrum: (DMSO$_d_6$) 2.87 (m, 2H), 2.73 (t, 2H), 3.98 (s, 3H), 4.26 (t, 2H), 7.40 (s, 1H), 7.50 (m, 2H), 7.55 (s, 1H), 7.78 (dd, 1H) and 8.55 (s, 1H)

MS (ESI) : 422 (MH)$^+$

A solution of 7-(3-aminopropoxy)-4-(4-bromo-2-fluorophenoxy)-6-methoxyquinoxaline (2.71g, 6.4mmol) and triethylamine (1.1ml, 0.80g, 7.9mmol) in dichloromethane (15ml) was treated with a solution of methanesulphonyl chloride (0.53ml, 0.79g, 6.9mmol) in dichloromethane (10ml) and stirred at ambient temperature, under nitrogen for 18 hours. The dichloromethane was then removed by evaporation and THF (4ml) added. The resulting solution was treated with saturated aqueous sodium hydrogen carbonate solution (to pH 8), stirred vigorously for 30 minutes and the precipitate filtered, washed with water and dried to give 4-(4-bromo-2-fluorophenoxy)-6-methoxy-7-(3-(N-methylsulphonylamino)propoxy)quinoxaline (2.98g, 93%).

$^1$H NMR Spectrum: (DMSO$_d_6$) 2.01 (m, 2H), 2.90 (s, 3H), 3.15 (t, 2H), 3.96 (s, 3H), 4.25 (t, 2H), 7.06 (s, 1H), 7.40 (s, 1H), 7.49 (m, 2H), 7.56 (s, 1H), 7.78 (dd, 1H) and 8.54 (s, 1H)

MS (ESI) : 500/502 (MH)$^+$

4-(4-Bromo-2-fluorophenoxy)-6-methoxy-7-(3-(N-
methylsulphonylamino)propoxy)quinazoline (1.0g, 2mmol) was taken up in DMF (10ml), treated with sodium hydride (60% dispersion in mineral oil, 0.11g, 2.7mmol) and stirred, under nitrogen for 30 minutes. Methyl iodide (0.16ml, 2.6mmol) was added and the mixture stirred for 18 hours. The solvent was removed by evaporation and the residue taken up in water and extracted with dichloromethane (3x 30ml). The organic solution was then washed with water, brine, dried (MgSO₄) and evaporated to dryness. The crude product was purified by silica column chromatography eluting with methanol (2.5 to 5 %) in dichloromethane to give 4-(4-bromo-2-fluorophenoxy)-6-methoxy-7-(3-(N-methyl N-methylsulphonylamino)propoxy)quinazoline (0.86g, 83%).

1H NMR Spectrum: (DMSO-d₆) 2.06 (m, 2H), 2.78 (s, 3H), 2.87 (s, 3H), 3.24 (t, 2H), 3.97 (s, 3H), 4.23 (t, 2H), 7.39 (s, 1H), 7.48 (m, 2H), 7.55 (s, 1H), 7.78 (dd, 1H) and 8.54 (s, 1H)
MS (ESI) : 514/516 (MH)⁺

4-(4-Bromo-2-fluorophenoxy)-6-methoxy-7-(3-(N-methyl N-methylsulphonylamino)propoxy)quinazoline (4.70g, 9.1mmol) was dissolved in 2N aqueous hydrochloric acid solution (85ml) and heated at reflux for 1 hour. After cooling, the solution was carefully poured into saturated aqueous sodium hydrogen carbonate solution (to pH8) and stirred vigorously for 30 minutes. The resulting precipitate was filtered and dried. The filter cake was then taken up as a suspension in acetone, filtered, washed with diethyl ether and dried to give 6-methoxy-7-(3-(N-methyl-N-methylsulphonylamino)propoxy)quinazolin-4-one (3.23g, 88%).

1H NMR Spectrum: (DMSO-d₆) 2.02 (m, 2H), 2.77 (s, 3H), 2.86 (s, 3H), 3.22 (t, 2H), 3.86 (s, 3H), 4.13 (t, 2H), 7.09 (s, 1H), 7.42 (s, 1H), 7.95 (s, 1H) and 12.02 (s, 1H)
MS (ESI) : 342 (MH)⁺

6-Methoxy-7-(3-(N-methyl-N-methylsulphonylamino)propoxy)quinazolin-4-one (2.24g, 6.6mmol) was taken up in thionyl chloride (25ml) and treated with DMF (5 drops). The resulting solution was then heated at reflux for 1 hour followed by cooling to ambient temperature. The excess thionyl chloride was removed by evaporation followed by azeotroping with toluene (3x). The residue was basified with saturated aqueous sodium hydrogen carbonate solution (to pH8) and extracted twice with ethyl acetate. The organic solution was washed with water, brine, dried (MgSO₄) and evaporated to dryness to give 4-chloro-6-methoxy-7-(3-(N-methyl-N-methylsulphonylamino)propoxy)quinazoline (1.90g, 80%).
\textbf{Example 153}

A mixture of 4-chloro-6-methoxy-7-(3-(N-methyl-N-methylsulphonylamino)propoxy)quinazoline (360 mg, 1.00 mmol), (prepared as described for the starting material in Example 152), potassium carbonate (215 mg, 1.56 mmol) and 5-hydroxy-2-methyindole (162 mg, 1.10 mmol) in DMF (8.0 ml) was stirred at 100 °C for 5 hours and allowed to cool to ambient temperature. The solvent was removed by evaporation and the residue was purified by silica column chromatography eluting with methanol (2.5 to 5%) in dichloromethane. The resulting solid was recrystallised from ethyl acetate, filtered and washed with diethyl ether to give 6-methoxy-4-(2-methyindol-5-yloxy)-7-(3-(N-methyl-N-methylsulphonylamino)propoxy)quinazoline (166mg, 35%).

\textsuperscript{1}H NMR Spectrum: (DMSO\textsubscript{d}\textsubscript{6}) 2.06 (m, 2H), 2.38 (s, 3H), 2.79 (s, 3H), 2.89 (s, 3H), 3.24 (t, 2H), 3.96 (s, 3H), 4.21 (t, 2H), 6.11 (br s, 1H), 6.87 (dd, 1H), 7.23 (d, 1H), 7.30 (d, 1H), 7.35 (s, 1H), 7.57 (s, 1H), 8.46 (s, 1H) and 10.98 (s, 1H)

MS (ESI) : 471 (MH\textsuperscript{+})

Elemental analysis

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\textbf{Example 154}

A mixture of 4-chloro-6-methoxy-7-(3-(N-methyl-N-methylsulphonylamino)propoxy)quinazoline (150 mg, 0.42 mmol), (prepared as described for the starting material in Example 152), potassium carbonate (90 mg, 0.63 mmol) and 7-hydroxyquinoline (67 mg, 0.46 mmol) in DMF (5.0 ml) was stirred at 100 °C for 2 hours and allowed to cool to ambient temperature. The solvent was removed by evaporation and the residue taken up in 2N aqueous sodium hydroxide solution. The precipitate was filtered off, dried, taken up in dichloromethane and the solution filtered through phase separating paper. The filtrate was then evaporated to dryness. The resulting solid was recrystallised from acetonitrile, filtered and washed with diethyl ether to give 6-methoxy-7-(3-(N-methyl-N-methylsulphonylamino)propoxy)-4-(quinolin-7-yloxy)quinazoline (122mg, 63%).
Example 155

A mixture of 4-chloro-6-methoxy-7-(3-(N-methyl-N-methylsulphonylamino)propoxy)quinazoline (150 mg, 0.42 mmol), (prepared as described for the starting material in Example 152), potassium carbonate (90 mg, 0.63 mmol) and 7-hydroxy-4-methylquinoline (71 mg, 0.46 mmol), (Chem. Berich. 1967, 100, 2077), in DMF (5.0 ml) was stirred at 100 °C for 2 hours and allowed to cool to ambient temperature. The DMF solvent was removed by evaporation and the residue was taken up in 2N aqueous sodium hydroxide solution. The precipitate was filtered off, dried, taken up in dichloromethane and then filtered through phase separating paper. The solution was then evaporated to dryness. The resulting solid was recrystallised from acetonitrile, filtered and washed with diethyl ether to give 6-methoxy-7-(3-(N-methyl-N-methylsulphonylamino)propoxy)-4-(4-methylquinolin-7-yloxy)quinazoline (84mg, 42%).

Example 156

A mixture of (R,S)-4-chloro-6-methoxy-7-((1-methylpiperidin-3-yl)methoxy)quinazoline (90 mg, 0.28 mmol), (prepared as described for the starting material in Example 7), potassium carbonate (60 mg, 0.44 mmol) and 7-hydroxy-4-trifluoromethylquinoline (65 mg, 0.31 mmol), (prepared as in Ukr. Khim. Zh. (Russ. Ed) Vol. 59, No. 4, pp. 408-411, 1993), in DMF (2 ml) was stirred at 100 °C for 6 hours and then
allowed to cool to ambient temperature. The DMF solvent was removed by evaporation, the
residue was taken up in methanol/dichloromethane (1/1) and pre-absorbed onto silica. The
crude mixture was purified by silica column chromatography eluting with
dichloromethane/methanol/0.880 aqueous ammonia (95/5/1) and the product recrystallised
from acetonitrile to give (R,S)-6-methoxy-7-(((1-methylpiperidin-3-yl)methoxy)-4-(4-
trifluoromethylquinolinol-7-ylmethoxy)quinazoline (58mg, 42%).

1H NMR Spectrum: (DMSO-d₆ 100°C) 1.24 (m, 1H), 1.59 (m, 1H), 1.70 (m, 1H), 1.83 (m,
1H), 2.05 (m, 2H), 2.17 (m, 1H), 2.24 (dt, 1H), 2.64 (dd, 1H), 2.84 (dd, 1H), 4.05 (s, 3H), 4.18
(d, 2H), 7.43 (s, 1H), 7.69 (s, 1H), 7.87 (dd, 1H), 7.96 (d, 1H), 8.18 (s, 1H), 8.25 (dd, 1H),
8.59 (s, 1H) and 9.16 (d, 1H)

MS (ESI) : 499 (MH)+

Elemental analysis Found C 62.2 H 5.1 N 11.0
C₂₆H₂₃N₄F₂O₃ Requires C 62.6 H 5.1 N 11.2%

Example 157

A mixture of (R,S)-4-chloro-6-methoxy-7-(((1-methylpiperidin-3-
yl)methoxy)quinazoline (150 mg, 0.46 mmol), (prepared as described for the starting material
in Example 7), potassium carbonate (106 mg, 0.77 mmol) and 3-fluoro-7-hydroxyquinoline
(119 mg, 0.73 mmol) in DMF (5 ml) was stirred at 100 °C for 2 hours and then allowed to
cool to ambient temperature. The solvent was removed by evaporation and the residue treated
with 1.0 N aqueous sodium hydroxide solution (30 ml) then allowed to stir for 30 minutes.
The crude solid was collected by filtration and washed with water. The resultant solid was
dissolved in dichloromethane and filtered through phase separating paper. The solvent was
removed by evaporation and the solid residue was recrystallised from acetonitrile to give

(R,S)-4-(3-fluoroquinolinol-7-ylmethoxy)-6-methoxy-7-(((1-methylpiperidin-3-
yl)methoxy)quinazoline (83mg, 40%).

1H NMR Spectrum: (DMSO-d₆) 1.11 (m, 1H), 1.50 (m, 1H), 1.64 (m, 1H), 1.84 (m, 3H), 2.10
(m, 1H), 2.15 (s, 3H), 2.62 (d, 1H), 2.83 (d, 1H), 4.00 (s, 3H), 4.08 (d, 2H), 7.38 (s, 1H), 7.62
(s, 1H), 7.68 (dd, 1H), 7.97 (d, 1H), 8.10 (d, 1H), 8.34 (dd, 1H), 8.54 (s, 1H) and 8.97 (d, 1H)

MS (ESI) : 449 (MH)+

Elemental analysis Found C 66.2 H 5.6 N 12.3
C₂₅H₂₅N₄FO₃ 0.2 H₂O Requires C 66.4 H 5.7 N 12.4%
The starting material, 3-fluoro-7-hydroxyquinoline was prepared as follows:

3-Fluoro-7-methoxyquinol-2(1H)-one (300mg, 1.55mmol), (prepared as in Tetrahedron, Vol. 52, No. 9, pp. 3223-3228, 1996), was dissolved in thionyl chloride (3ml), treated with DMF (1 drop) and heated at reflux for 1 hour. The excess thionyl chloride was removed by evaporation and the residue azeotroped with toluene (3x). The residue was basified to pH8 with saturated aqueous sodium hydrogen carbonate solution and extracted with ethyl acetate (3x 20ml). The organic solution was washed with water and brine then dried (MgSO₄) and evaporated to dryness to give 2-chloro-3-fluoro-7-methoxyquinoline (320mg, 97%).

'1H NMR Spectrum: (CDCl₃) 3.95 (s, 3H), 7.25 (dd, 1H), 7.37 (d, 1H), 7.67 (d, 1H) and 7.78 (d, 1H)

MS (ESI) : 212 (MH)^+

A mixture of 2-chloro-3-fluoro-7-methoxyquinoline (310mg, 1.47mmol), triethylamine (310mg, 0.4ml, 3.07mmol) and 10% palladium on activated charcoal (50mg) in dry ethanol (5ml) was stirred under hydrogen gas at ambient temperature for 24 hours. The mixture was then filtered through celite. The celite was washed with methanol and the solvent was removed by evaporation from the combined filtrates. The crude material was purified by chromatography on silica, eluting with 10% ethyl acetate in isohexane to give 3-fluoro-7-methoxyquinoline (130mg, 54%).

'1H NMR Spectrum: (CDCl₃) 3.96 (s, 3H), 7.24 (dd, 1H), 7.44 (d, 1H), 7.66 (d, 1H) and 7.73 (dd, 1H) and 8.76 (d, 1H)

MS (ESI) : 178 (MH)^+

3-Fluoro-7-methoxyquinoline (130mg, 0.74mmol) was taken up in dichloromethane (2ml) under nitrogen and treated with boron tribromide (4ml of a 1.0M solution of in dichloromethane). The reaction mixture was stirred for 24 hours at ambient temperature followed by quenching the reaction by the slow addition of excess methanol. The solution was stirred for a further 2 hours and evaporated to dryness to give 3-fluoro-7-hydroxyquinoline which was used without further purification.

MS (ESI) : 164 (MH)^+

Example 158
A mixture of (R,S)-4-chloro-6-methoxy-7-[(1-methylpiperidin-3-yl)methoxy]quinazoline (240 mg, 0.75 mmol), (prepared as described for the starting material in Example 7), potassium carbonate (160 mg, 1.16 mmol) and 3-fluoro-7-hydroxy-2-methylquinoline (150 mg, 0.85 mmol) in DMF (6 ml) was stirred at 100 °C for 5 hours and then allowed to cool to ambient temperature. The solvent was removed by evaporation, then the residue was treated with water and 1.0 N aqueous sodium hydroxide solution (30 ml) then allowed to stir for 30 minutes. The crude solid was collected by filtration and washed with water. The resulting solid was dissolved in dichloromethane and filtered through phase separating paper. The solvent was removed by evaporation to give a solid residue which was recrystallised from acetonitrile to give 4-(3-fluoro-2-methylquinolin-7-yl)oxy)-6-methoxy-7-[(1-methylpiperidin-3-yl)methoxy]quinazoline (71 mg, 21%).

\(^1\text{H} \text{NMR Spectrum: (DMSO}_{d6}) \ 1.11 \text{ (m, 1H)}, \ 1.68 \text{ (m, 5H)}, \ 2.10 \text{ (m, 1H)}, \ 2.20 \text{ (s, 3H)}, \ 2.64 \text{ (m, 4H)}, \ 2.87 \text{ (d, 1H)}, \ 3.98 \text{ (s, 3H)}, \ 4.09 \text{ (d, 2H)}, \ 7.37 \text{ (s, 1H)}, \ 7.57 \text{ (dd, 1H)}, \ 7.60 \text{ (s, 1H)}, \ 7.86 \text{ (d, 1H)}, \ 8.02 \text{ (d, 1H)}, \ 8.20 \text{ (d, 1H)} \text{ and } 8.53 \text{ (s, 1H)}

MS (ESI) : 463 (MH)^+

Elemental analysis

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\[\text{C}_{26}\text{H}_{27}\text{N}_{4}\text{FO}_{3} \cdot 0.4 \text{H}_{2}\text{O}\]

The starting material was prepared as follows:

2-Chloro-3-fluoro-7-methoxyquinoline (210 mg, 1 mmol), (prepared as described for the starting material in Example 157), in anhydrous THF (1 ml) was added to a mixture of copper(I) bromide (570 mg, 4.0 mmol) and methylmagnesium bromide (3.0 M solution in diethyl ether, 2.7 ml, 8 mmol) in anhydrous THF (20 ml) at -78°C. The mixture was stirred for 1 hour at -78°C, allowed to warm to ambient temperature and then stirred for a further 18 hours. Saturated aqueous ammonium chloride solution and 5N aqueous sodium hydroxide solution (pH 12) were added and the product extracted with ethyl acetate (3x). The organic solution was washed with water, brine, dried (MgSO4) and evaporated to dryness to yield 3-fluoro-7-methoxy-2-methylquinoline (0.17 g, 91%).

\(^1\text{H} \text{NMR Spectrum: (CDCl}_{3}) \ 2.70 \text{ (d, 3H)}, \ 3.94 \text{ (s, 3H)}, \ 7.17 \text{ (dd, 1H)}, \ 7.37 \text{ (d, 1H)} \text{ and } 7.61 \text{ (m, 2H)}

MS (ESI) : 192 (MH)^+

3-Fluoro-7-methoxy-2-methylquinoline (0.16 g, 0.85 mmol) was taken up in
dichloromethane (4ml) under nitrogen and treated with boron tribromide solution (4ml of a 1.0M solution in dichloromethane, 4.0mmol). The reaction was stirred for 24 hours at ambient temperature followed by the slow addition of excess methanol. The solution was stirred for a further 2 hours and then evaporated to dryness to give 3-fluoro-7-hydroxy-2-methylquinoline which was used without further purification.

MS (ESI) : 178 (MH)+

**Example 159**

A mixture of 4-chloro-6-methoxy-7-(3-piperidinopropoxy)quinazoline (400mg, 1.19mmol), (prepared as described for the starting material in Example 67), potassium carbonate (255 mg, 1.84 mmol) and 7-hydroxyquinoline (180mg, 1.32 mmol) in DMF (10 ml) was stirred at 100 °C for 4 hours and then allowed to cool to ambient temperature. The resulting mixture was treated with 1.0 N aqueous sodium hydroxide solution (30 ml) and allowed to stir for 1 hour. The crude solid was collected by filtration and washed with water. The resulting solid was dissolved in dichloromethane and filtered through phase separating paper. The solvent was removed by evaporation to give a solid residue which was recrystallised from acetonitrile to give 6-methoxy-7-(3-piperidinopropoxy)-4-(quinolin-7-yloxy)quinazoline (0.27 g, 52%).

$^1$H NMR Spectrum: (DMSO$_d_6$) 1.37 (m, 2H), 1.51 (m, 4H), 1.95 (m, 2H), 2.32 (m, 4H), 2.42 (t, 2H), 3.98 (s, 3H), 4.23 (t, 2H), 7.38 (s, 1H), 7.56 (m, 2H), 7.62 (s, 1H), 7.91 (d, 1H), 8.09 (d, 1H), 8.44 (d, 1H), 8.54 (s, 1H) and 8.91 (dd, 1H)

MS (ESI) : 445 (MH)+

Elemental analysis

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**Example 160**

A mixture of 4-chloro-6-methoxy-7-(3-(N-methyl-N-methylsulphonylamino)propoxy)quinazoline (360 mg, 1.00 mmol), (prepared as described for the starting material in Example 152), potassium carbonate (215 mg, 1.56 mmol) and 2,3-dimethyl-5-hydroxyindole (177 mg, 1.10 mmol), (Arch. Pharm. 1972, 305, 159), in DMF (8.0 ml) was stirred at 100 °C for 5 hours and allowed to cool to ambient temperature. The solvent was removed by evaporation and the residue purified by silica column chromatography
eluting with methanol (2.5%) in dichloromethane. The resulting solid was recrystallised from tertbutyl methyl ether/acetonitrile, filtered and washed with diethyl ether to give 4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(3-(N-methyl-N-methylsulphonylamino)propoxy)quinazoline (201 mg, 42%).

$^1$H NMR Spectrum: (DMSO$_d_6$) 2.07 (m, 2H), 2.12 (s, 3H), 2.31 (s, 3H), 2.79 (s, 3H), 2.89 (s, 3H), 3.25 (t, 2H), 3.97 (s, 3H), 4.23 (t, 2H), 6.86 (dd, 1H), 7.20 (d, 1H), 7.25 (d, 1H), 7.35 (s, 1H), 7.58 (s, 1H), 8.46 (s, 1H) and 11.17 (s, 1H)

MS (ESI) : 485 (MH)$^+$

Elemental analysis

Found

C 59.5  H 5.8  N 11.4

Requires

C$_{24}$H$_{28}$N$_5$O$_5$S

Example 161

A mixture of 7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (322 mg, 1.00 mmol), (prepared as described in Example 49), potassium carbonate (414 mg, 3.00 mmol) and epibromohydrin (274 mg, 2.00 mmol) in DMF (7.0 ml) was stirred at 60 °C for 2 hours and allowed to cool to ambient temperature. The solvent was removed by evaporation and the residue taken up in dichloromethane (10ml). An aliquot (5ml) of this solution was treated with morpholine (48ul, 0.6 mmol) and stirred for 24 hours at ambient temperature. The solvent was removed by evaporation, treated with water and stirred vigorously for 30 minutes. The precipitate was filtered, washed with water and dried. The resultant solid was stirred as a suspension in acetone, filtered, washed with diethyl ether and dried to give 7-(2-hydroxy-3-morpholinopropoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (127 mg, 27%).

$^1$H NMR Spectrum: (DMSO$_d_6$) 2.38 (s, 3H), 2.45 (m, 6H), 3.57 (t, 4H), 3.95 (s, 3H), 4.03-4.14 (m, 2H), 4.23 (m, 1H), 4.95 (s, 1H), 6.12 (s, 1H), 6.86 (dd, 1H), 7.23 (d, 1H), 7.29 (d, 1H), 7.37 (s, 1H), 7.57 (s, 1H), 8.47 (s, 1H) and 10.98 (s, 1H)

MS (ESI) : 465 (MH)$^+$

Elemental analysis

Found

C 62.7  H 5.9  N 11.5

Requires

C$_{25}$H$_{33}$N$_5$O$_5$0.7H$_2$O

Example 162

A mixture of 7-(2,3-epoxypropoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (100 mg, 0.27 mmol) and piperidine (79ul, 0.8 mmol) in DMF (4ml) was heated at 70°C for 24
hours. The solvent was removed by evaporation and the residue was recrystallised from acetonitrile. The solid was filtered, washed with diethyl ether and dried to give **7-(2-hydroxy-3-piperidinopropoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline** (80mg, 65%).

1H NMR Spectrum: (DMSO-d$_6$) 1.35 (m, 2H), 1.51 (m, 4H), 2.39 (m, 9H), 3.96 (s, 3H), 4.08 (m, 2H), 4.21 (dd, 1H), 4.86 (br s, 1H), 6.11 (s, 1H), 6.87 (dd, 1H), 7.23 (d, 1H), 7.29 (d, 1H), 7.37 (s, 1H), 7.56 (s, 1H), 8.45 (s, 1H) and 10.98 (s, 1H)

MS (ESI) : 464 (MH)$^+$

Elemental analysis

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C$_{26}$H$_{30}$N$_4$O$_6$0.4H$_2$O

The starting material was prepared as follows:

A mixture of 7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (1.89 g, 5.90 mmol), (prepared as described in Example 49), potassium carbonate (2.43 g, 17.6 mmol) and epibromohydrin (1.61 g, 11.7 mmol) in DMF (40 ml) was stirred at 60 °C for 2 hours and allowed to cool to ambient temperature. The insoluble inorganic material was removed by filtration and the solvent was removed by evaporation. The residue was triturated with diethyl ether, filtered, washed with further diethyl ether and dried to give 7-(2,3-epoxypropoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (1.97g, 89%).

1H NMR Spectrum: (DMSO-d$_6$) 2.38 (s, 3H), 2.76 (m, 1H), 2.90 (t, 1H), 3.43 (m,1H), 3.97 (s, 3H), 4.04 (m, 1H), 4.57 (dd, 1H), 6.11 (s, 1H), 6.86 (dd, 1H), 7.27 (m, 2H), 7.38 (s, 1H), 7.59 (s, 1H), 8.46 (s, 1H) and 10.92 (s, 1H)

MS (ESI) : 378 (MH)$^+$

**Example 163**

A mixture of 7-(2,3-epoxypropoxy)-6-methoxy-4-(2-methylindol-5-yloxy) quinazoline (100mg, 0.27 mmol), (prepared as described for the starting material in Example 162), and pyrrolidine (67µl, 0.8mmol) in DMF (4ml) was heated at 70°C for 24 hours. The solvent was removed by evaporation and the residue purified by silica column chromatography eluting with dichloromethane/methanol/0.880 aqueous ammonia (100/8/1). The relevant fractions were evaporated to dryness then the residue treated with a little dichloromethane and dried under high vacuum to give **7-(2-hydroxy-3-pyrrolidin-1-ylpropoxy)-6-methoxy-4-(2-**
methyldindol-5-yloxy)quinazoline (44mg, 37%) as a white foam.

\(^1\)H NMR Spectrum: (DMSO\(_d_6\)) 1.69 (br s, 4H), 2.38 (s, 3H), 2.50 (m, 6H), 3.97 (s, 3H), 4.07 (m, 2H), 4.21 (dd, 1H), 4.96 (br s, 1H), 6.11 (s, 1H), 6.86 (dd, 1H), 7.23 (d, 1H), 7.29 (d, 1H), 7.35 (s, 1H), 7.56 (s, 1H), 8.46 (s, 1H) and 10.98 (s, 1H)

MS (ESI): 450 (MH)^+

Elemental analysis  Found   C 65.5  H 6.3  N 11.8  
C\(_{25}\)H\(_{30}\)N\(_4\)O\(_4\)0.4H\(_2\)O  Requires    C 65.9  H 6.4  N 12.3%

**Example 164**

A mixture of 7-(2,3-epoxypropoxy)-6-methoxy-4-(2-methyldindol-5-yloxy) quinazoline (100mg, 0.27 mmol), (prepared as described for the starting material in Example 162), and diethylamine (100ul, 0.8mmol) in DMF (4ml) was heated at 70°C for 24 hours. The solvent was removed by evaporation and the residue was purified by silica column chromatography eluting with dichloromethane/methanol/0.880 aqueous ammonia (100/8/1). The relevant fractions were evaporated to dryness then the residue treated with a little dichloromethane and dried under high vacuum to give 7-(3-(N,N-diethylamino)-2-hydroxypropoxy)-6-methoxy-4-(2-methyldindol-5-yloxy)quinazoline (55mg, 46%) as a white foam.

\(^1\)H NMR Spectrum: (DMSO\(_d_6\)) 0.96 (t, 6H), 2.38 (s, 3H), 2.52 (m, 6H), 3.96 (s, 3H), 3.97 (m, 1H), 4.09 (m, 1H), 4.23 (dd, 1H), 4.84 (br s, 1H), 6.12 (s, 1H), 6.88 (dd, 1H), 7.24 (d, 1H), 7.29 (d, 1H), 7.36 (s, 1H), 7.56 (s, 1H), 8.45 (s, 1H) and 10.98 (s, 1H)

MS (ESI): 452 (MH)^+

Elemental analysis  Found   C 66.2  H 6.7  N 12.4  
C\(_{25}\)H\(_{30}\)N\(_4\)O\(_4\)  Requires    C 66.6  H 6.7  N 12.4%

**Example 165**

A mixture of 7-(2,3-epoxypropoxy)-6-methoxy-4-(2-methyldindol-5-yloxy) quinazoline (100mg, 0.27 mmol), (prepared as described for the starting material in Example 162), and N-methylpiperazine (200ul, 1.8mmol) in DMF (4ml) was heated at 70°C for 24 hours. The solvent was removed by evaporation and the residue was recrystallised from acetonitrile. The solid was filtered, washed with diethyl ether and dried to give 7-(2-hydroxy-3-(4-methylpiperazin-1-yl)propoxy)-6-methoxy-4-(2-methyldindol-5-yloxy)quinazoline (41mg, 32%).
- 194 -

1H NMR Spectrum: (DMSO_d6) : 2.11 (s, 3H), 2.29 (m, 4H), 2.40 (s, 3H), 2.47 (m, 6H), 3.96 (s, 3H), 4.07 (m, 2H), 4.20 (dd, 1H), 4.89 (d, 1H), 6.11 (s, 1H), 6.87 (dd, 1H), 7.23 (d, 1H), 7.29 (d, 1H), 7.35 (s, 1H), 7.58 (s, 1H), 8.46 (s, 1H) and 10.98 (s, 1H)
MS (ESI) : 479 (MH)+
5

Elemental analysis Found C 64.4 H 6.5 N 14.4
C_{26}H_{31}N_{3}O_{4}0.3H_{2}O Requires C 64.7 H 6.6 N 14.5%

Example 166
A mixture of 7-(2,3-epoxypropoxy)-6-methoxy-4-(2-methylindol-5-yloxy) quinazoline (100mg, 0.27 mmol), (prepared as described for the starting material in Example 162), and isopropylamine (100ul, 0.8mmol) in DMF (4ml) was heated at 70°C for 24 hours. The solvent was removed by evaporation and the residue was purified by silica column chromatography eluting with dichloromethane/methanol/0.880 aqueous ammonia (100/8/1) to give 7-(2-hydroxy-3-(isopropylamino)propoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (18mg, 16%).
1H NMR Spectrum: (DMSO_d6) 1.00 (d, 6H), 2.40 (s, 3H), 2.56 - 2.78 (m, 3H), 3.97 (m, 4H), 4.07 - 4.28 (m, 2H), 5.04 (m, 1H), 6.12 (s, 1H), 6.88 (dd, 1H), 7.22 - 7.33 (m, 2H), 7.38 (s, 1H), 7.58 (s, 1H), 8.48 (s, 1H) and 10.98 (s, 1H)
MS (ESI) : 437 (MH)+

Example 167
A mixture of 4-chloro-6-methoxy-7-(3-piperidinopropoxy)quinazoline (168 mg, 0.5 mmol), (prepared as described for the starting material in Example 67), potassium carbonate (276 mg, 2.0 mmol) and 5-hydroxy-6-trifluoromethylindole (110 mg, 0.55 mmol) and DMA (4.0 ml) were stirred at 95°C for 1.5 hours and allowed to cool to ambient temperature. The reaction mixture was filtered and the filtrate evaporated under vacuum. The residue was purified by silica column chromatography eluting with dichloromethane/methanol/0.880 aqueous ammonia (89/10/1) to give a partially purified oil. This oil was further purified by high performance column chromatography on octadecysilane reverse phase silica eluting with acetonitrile/water/trifluoroacetic acid (60/39.8/0.2) to give an oil which was dissolved in dichloromethane and washed with saturated aqueous sodium hydrogen carbonate solution. The dichloromethane layer was evaporated to give 6-methoxy-7-(3-piperidinopropoxy)-4-
(6-trifluoromethylindol-5-yloxy)quinazoline (62 mg, 25%).

$^1$H NMR Spectrum: (DMSO$_d_6$) 1.45 (m, 2H), 1.60 (m, 4H), 2.13 (m, 2H), 2.44 (m, 4H), 2.56 (m, 2H), 4.04 (s, 3H), 4.27 (t, 2H), 6.63 (br s, 1H), 7.33 (s, 1H), 7.40 (t, 1H), 7.61 (s, 1H), 7.67 (s, 1H), 7.75 (s, 1H) and 8.60 (m, 2H).

5

MS (ESI) : 501 (MH)$^+$

Elemental analysis Found C 62.0 H 5.6 N 10.6

C$_{26}$H$_{22}$F$_3$N$_4$O$_3$ 0.35 H$_2$O, Requires C 61.6 H 5.5 N 11.0%

The starting material was prepared as follows:

Sodium hydride (1.8g, of a 60% dispersion in oil, 45 mmol) was added in portions to a stirred solution of benzyl alcohol (10.8g, 100 mmol) in DMA (100ml) with vigorous stirring under an atmosphere of nitrogen at ambient temperature. After warming to 45°C for 30 minutes the mixture was cooled to ambient temperature and added dropwise to a stirred solution of 2-chloro-5-nitro-trifluoromethylbenzene (11.3g, 50 mmol) in DMA (30ml), keeping the temperature below 10°C. The mixture was stirred at 25°C for 1 hour, then acidified with acetic acid and evaporated to give a yellow solid. The residue was dissolved in dichloromethane, washed with water then dried (MgSO$_4$), and evaporated. The residue was suspended in a mixture of hexane (70 ml) and diethyl ether (10 ml) and the resulting solid filtered off to give 2-benzyloxy-5-nitro-trifluoromethylbenzene (6.6g, 49%).

$^1$H NMR Spectrum: (CDCl$_3$) 5.33 (s, 2H), 7.13 (d, 1H), 7.31-7.43 (m, 5H), 8.35 (dd, 1H), 8.52 (d, 1H)

Potassium tert-butoxide (3.94g, 35.4mmol) was dissolved in anhydrous DMF (15ml) and a mixture of 2-benzyloxy-5-nitro-trifluoromethylbenzene (3.5g, 16.1 mmol) and 4-chlorophenylacetonitrile (2.96g, 17.7 mmol) in DMF (20 ml) was added over 30 minutes keeping the temperature at -15°C. The mixture was stirred at -10°C for 1 hour, then poured into 1M hydrochloric acid (150ml) and the product extracted with dichloromethane (2x100ml). The organic extracts were dried (MgSO$_4$) and purified by silica column chromatography eluting with dichloromethane/hexane (1/1) to give 5-benzyloxy-2-nitro-4-(trifluoromethyl)phenylacetonitrile (5.2g, 77%).

$^1$H NMR Spectrum: (CDCl$_3$) 4.30 (s, 2H), 5.38 (s, 2H), 7.25 (s, 1H), 7.33-7.50 (m, 5H) and 8.51 (s, 1H)

MS (ESI) : 335 (M-H)$^+$
5-Benzyloxy-2-nitro-4-(trifluoromethyl)phenylacetonitrile (2.22g, 6.6mmol) was dissolved in ethanol (45 ml), water (5ml) and acetic acid (0.32 ml) then hydrogenated with 10% palladium on carbon at 1 atmosphere pressure for 2 hours. The catalyst was filtered off and filtrate evaporated to give 5-hydroxy-6-trifluoromethylindole (1.12g, 84%).

1H NMR Spectrum: (CDCl₃) 4.48 (s, 1H), 6.48 (m, 1H), 7.14 (s, 1H), 7.32 (t, 1H), 7.57 (s, 1H) and 8.20 (br s, 1H)

MS (ESI) : 200 (M-H)

**Example 168**

A mixture of 4-chloro-6-methoxy-7-(3-piperidinopropoxy)quinazoline (200mg, 0.6 mmol), (prepared as described for the starting material in Example 67), potassium carbonate (248 mg, 1.8 mmol) and 5-hydroxy-6-methoxyindole (127 mg, 0.78 mmol) in DMA (4.0 ml) was stirred at 95°C for 2.5 hours. The reaction mixture was allowed to cool to ambient temperature, filtered and the filtrate evaporated under vacuum. The residue was purified by silica column chromatography eluting with dichloromethane/methanol/0.880 aqueous ammonia (89/10/1) and the resulting oil triturated with diethyl ether to give 4-(6-methoxyindol-5-yl)oxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline (106 mg, 38%).

1H NMR Spectrum: (DMSO-d₆) 1.38 (m, 2H), 1.47 (m, 4H), 1.95 (m, 2H), 2.32 (m, 4H), 2.40 (m, 2H), 3.66 (3H, s), 3.97 (3H, s), 4.28 (t, 2H), 6.35 (br s, 1H), 7.06 (s, 1H), 7.24 (t, 1H), 7.34 (s, 1H), 7.36 (s, 1H), 7.55 (s, 1H) and 8.41 (s, 1H)

MS (ESI) : 463 (MH+)

Elemental analysis

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The 5-hydroxy-6-methoxyindole starting material was made as follows:

5-Benzyllox-6-methoxyindole (253mg, 1.0mmol) was hydrogenated at 1 atmosphere pressure in methanol (10 ml) with 10% palladium on carbon (50 mg) for 2 hours at 25°C. The catalyst was filtered off and the filtrate evaporated to give 5-hydroxy-6-methoxyindole (141mg, 87%).

1H NMR Spectrum: (CDCl₃) 3.92 (s, 3H), 5.40 (s, 1H), 6.42 (br s, 1H), 6.87 (s, 1H), 7.07 (m, 1H), 7.13 (s, 1H), 7.93 (br s, 1H)
Example 169

A mixture of 4-chloro-6-methoxy-7-(3-piperidinopropoxy)quinazoline (200mg, 0.595 mmol), (prepared as described for the starting material in Example 67), potassium carbonate (411 mg, 2.98 mmol) and 4-hydroxyindole (103 mg, 0.774 mmol) in DMA (2.0 ml) was stirred at 85 °C for 3 hours and allowed to cool to ambient temperature. The reaction mixture was filtered and the filtrate evaporated to give a solid residue. The residue was purified by silica column chromatography, with gradient elution using dichloromethane with 0%, 2%, 4%, 10% methanolic ammonia to give 4-(indol-4-yl oxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline (131 mg, 51%).

\(^1\)H NMR Spectrum: (DMSO\(_d_6\)) 1.39 (m, 2H), 1.50 (m, 4H), 1.98 (t, 2H), 2.35 (m, 4H), 2.40 (t, 2H), 3.98 (s, 3H), 4.25 (t, 2H), 6.10 (t, 1H), 6.90 (d, 1H), 7.15 (t, 1H), 7.30 (t, 1H), 7.35 (d, 1H), 7.38 (s, 1H), 7.62 (s, 1H), 8.45 (s, 1H) and 11.29 (s, 1H)

MS (ESI) : 433 (MH)\(^+\)
m.p. 80 - 82 °C

Example 170

A mixture of 4-chloro-6-methoxy-7-(3-piperidinopropoxy)quinazoline (200mg, 0.595 mmol), (prepared as described for the starting material in Example 67), potassium carbonate (411 mg, 2.98 mmol) and 3-hydroxycarbazole (142 mg, 0.774 mmol) in DMA (2.0 ml) was stirred at 85 °C for 3 hours then allowed to cool to ambient temperature. The reaction mixture was filtered and the filtrate evaporated to give a solid residue. The residue was purified by silica column chromatography with gradient elution using dichloromethane with 0%, 2%, 4%, 10% methanolic ammonia to give 4-(9H-carbazol-3-yl oxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline (212 mg, 74%).

\(^1\)H NMR Spectrum: (DMSO\(_d_6\)) 1.39 (m, 2H), 1.50 (m, 4H), 2.35 (m, 4H), 2.40 (t, 2H), 3.98 (s, 3H), 4.25 (t, 2H), 7.05 (dd, 1H), 7.15 (t, 1H), 7.35 (t, 1H), 7.38 (s, 1H), 7.40 (s, 1H), 7.50 (d, 1H), 7.60 (s, 1H), 8.10 (d, 1H), 8.15 (d, 1H), 8.55 (s, 1H) and 11.33 (s, 1H)

MS (ESI) : 483 (MH)\(^+\)

Example 171
A mixture of 4-chloro-6-methoxy-7-(3-piperidinopropoxy)quinazoline (84 mg, 0.24 mmol), (prepared as described for the starting material in Example 67), potassium carbonate (162 mg, 1.18 mmol) and ethyl 7-chloro-5-hydroxyindole-2-carboxylate (62 mg, 0.26 mmol) in DMA (2.0 ml) was stirred at 100 °C for 2 hours and allowed to cool to ambient temperature. The reaction mixture was filtered and the filtrate evaporated. The residue was purified by silica column chromatography using gradient elution dichloromethane with 2.5%, 5%, 10% methanol, then dichloromethane with 2% ammonia to give 4-(7-chloro-2-(ethoxycarbonyl)indol-5-yl)-6-methoxy-7-(3-piperidinopropoxy)quinazoline (78 mg, 63%).

\[ {^1}H \text{ NMR Spectrum: (DMSO-d_6)} \]
1.30 (t, 3H), 1.40 (m, 2H), 1.50 (m, 4H), 1.98 (t, 2H), 2.35 (m, 4H), 2.40 (t, 2H), 3.98 (s, 3H), 4.25 (t, 2H), 4.30 (q, 2H), 7.15 (m, 1H), 7.18 (s, 1H), 7.60 (s, 1H), 8.40 (s, 1H) and 12.60 (s, 1H)

MS (ESI) : 539 (MH+)

Elemental analysis

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C_{29}H_{31}CIN_{6}O_{7} \text{ 0.5 H_2O}  

Requires

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The starting material was prepared as follows:

2-Chloro-4-methoxyaniline (2.719g, 14 mmol) was added to 8.0M aqueous hydrochloric acid (15 ml) and the suspension cooled to -5 °C. Sodium nitrite (1.063g, 15.4 mmol) was added as a solution in water (3 ml). After addition the pH was brought to pH 4-5 by addition of sodium acetate. In a separate flask, ethyl-α-ethyl acetoacetate (2.18 ml, 15.4 mmol) in ethanol (15 ml) at -5 °C was treated with potassium hydroxide (864 mg, 15.4 mmol) in water (3 ml) followed by ice (4 g). The diazonium salt prepared initially was then added rapidly to the second solution and stirred at -5 °C for 4 hours then allowed to warm to ambient temperature overnight. The mixture was extracted with ethyl acetate (3 x 100 ml) and the organic solutions dried (MgSO_4), filtered and solvent removed in *vacuo* to give an orange oil. This oil was dissolved in ethanol (35 ml) and the flask fitted with a reflux condenser. Concentrated sulphuric acid (35 ml) was then added dropwise, this caused the reaction to reflux with no external heating. The solution was stirred for 1 hour then the solvent removed by evaporation. The residue was taken up in water then extracted with ethyl acetate (3 x 100 ml). The organic solution was washed with brine, dried (MgSO_4), filtered and evaporated to give a brown oil. The crude oil was purified by silica column chromatography, eluting with
dichloromethane to give ethyl 7-chloro-5-methoxyindole-2-carboxylate (125 mg, 4%).

\(^1\)H NMR Spectrum: (CDCl\(_3\)) 1.40 (t, 3H), 3.98 (s, 3H), 4.40 (q, 2H), 6.60 (d, 1H), 7.05 (d, 1H), 7.15 (s, 1H) and 9.10 (s, 1H)

MS (ESI) : 254 (MH)^+

To a solution of ethyl 7-chloro-5-methoxyindole-2-carboxylate (82 mg, 0.323 mmol) in dichloromethane (5 ml) at -78 °C was added boron tribromide (1.07 ml of a 1.0M solution in DCM, 1.07 mmol) and the reaction stirred at -78 °C for 30 minutes then allowed to warm to ambient temperature overnight. Water was carefully added and the pH adjusted to pH 6-7 by addition of 2M sodium hydroxide. The mixture was extracted with ethyl acetate (2 x 50 ml), and the organic solution washed with brine, dried (MgSO\(_4\)), filtered and evaporated to give ethyl 7-chloro-5-hydroxyindole-2-carboxylate (55 mg, 71%) as an orange solid.

\(^1\)H NMR Spectrum: (DMSO\(_d_6\)) 1.38 (t, 3H), 4.35 (q, 2H), 6.60 (d, 1H), 6.95 (d, 1H), 7.10 (d, 1H), 9.80 (s, 1H) and 11.80 (s, 1H)

MS (ESI) : 238 (MH)^+

**Example 172**

A mixture of 7-benzylxoy-4-chloro-6-methoxyquinazoline (1.5 g, 4.99 mmol), (prepared as described for the starting material in Example 1), potassium carbonate (2.07 g, 15 mmol) and 2,3-dimethyl-5-hydroxyindole (1.21 g, 7.5 mmol), (Arch. Pharm. 1972, 305, 159), in DMF (75 ml) was stirred at 100 °C for 2 hours and allowed to cool to ambient temperature. The reaction mixture was filtered and the filtrate evaporated. The solid residue was purified by silica column chromatography, eluting with 2.5% methanol in dichloromethane to give 7-benzylxoy-4-(2,3-dimethylindol-5-xyloxy)-6-methoxyquinazoline (976 mg, 46%).

\(^1\)H NMR Spectrum: (CDCl\(_3\)) 2.10 (s, 3H), 2.30 (s, 3H), 3.98 (s, 3H), 5.30 (s, 2H), 6.85 (dd, 1H), 7.20 (d, 1H), 7.25 (d, 1H), 7.40 (m, 6H), 7.60 (s, 1H), 8.40 (s, 1H) and 10.74 (s, 1H)

MS (ESI) : 426 (MH)^+

**Example 173**

A mixture of 7-benzylxoy-4-(2,3-dimethylindol-5-xyloxy)-6-methoxyquinazoline (912 mg, 2.14 mmol), (prepared as described in Example 172), di-tert-butyl dicarbonate (1.871 g, 8.56 mmol) and 4-dimethylaminopyridine (70 mg, 0.5 mol%) in acetonitrile (40 ml ) was stirred at ambient temperature overnight. The solvent was then evaporated and the residue dissolved
in ethyl acetate. The organic solution was washed with 2N hydrochloric acid twice and then with brine. The organic layer was then dried (MgSO₄), filtered and evaporated to give 7-benzyloxy-4-(1-tert-butoxy carbonyl-2,3-dimethylindolin-5-yloxy)-6-methoxyquinazoline (1.108 g, 99%) as a yellow solid.

1H NMR Spectrum: (CDCl₃) 1.70 (s, 9H), 2.08 (s, 3H), 2.50 (s, 3H), 4.10 (s, 3H), 5.35 (s, 2H), 7.15 (dd, 1H), 7.38 (m, 6H), 7.60 (s, 1H), 8.20 (d, 1H) and 8.60 (s, 1H)

MS (ESI) : 526 (MH)+

Example 174

A mixture of 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (225 mg, 0.67 mmol), (prepared as described for the starting material in Example 1), potassium carbonate (106 mg, 0.77 mmol) and 2-hydroxyquinoline (111 mg, 0.76 mmol) in DMF (7.5 ml) was stirred at 100 °C for 5 hours and allowed to cool to ambient temperature. The reaction mixture was treated with 1.0 N aqueous sodium hydroxide solution (40 ml) and allowed to stir at ambient temperature for a few minutes. The reaction mixture was extracted 3 times with ethyl acetate and the extracts washed with water and brine. The organic extracts were dried over magnesium sulphate, filtered and the solvent removed by evaporation. The residue was purified by silica column chromatography eluting with dichloromethane/methanol (95/5) to give a solid which was triturated with ether, filtered and dried to give 6-methoxy-7-(3-morpholinopropoxy)-4-(quinolin-2-yloxy)-quinazoline (33 mg, 11%).

1H NMR Spectrum: (DMSO-d₆) 1.98 (m, 2H), 2.38 (m, 4H), 2.48 (t, 2H), 3.58 (m, 4H), 3.98 (s, 3H), 4.26 (t, 2H), 7.41 (s, 1H), 7.52 (d, 1H), 7.58 (s, 1H), 7.64 (t, 1H), 7.78 (m, 1H), 7.88 (d, 1H), 8.06 (d, 1H), 8.56 (d, 1H) and 8.57 (s, 1H)

MS (ESI) : 447 (MH)+

Elemental analysis

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Example 175

A mixture of 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (225 mg, 0.67 mmol), (prepared as described for the starting material in Example 1), potassium carbonate (106 mg, 0.77 mmol) and 5-hydroxyquinoline (111 mg, 0.77 mmol) in DMF (7.5 ml) was stirred at 100 °C for 5 hours and allowed to cool to ambient temperature. The reaction
mixture was treated with 1.0 N aqueous sodium hydroxide solution (40 ml) and allowed to stir at ambient temperature for a few minutes. The resulting precipitate was filtered off, washed with water and air dried for a short while. The damp solid was dissolved in dichloromethane, filtered through phase separating paper and the filtrate evaporated under vacuum. The residue was triturated with ether, filtered and dried to give 6-methoxy-7-(3-morpholinopropoxy)-4-(quinolin-5-yloxy)-quinazoline (178 mg, 59%).

$^1$H NMR Spectrum: (DMSO$_d_6$) 1.98 (m, 2H), 2.39 (m, 4H), 2.48 (t, 2H), 3.59 (t, 4H), 4.01 (s, 3H), 4.28 (t, 2H), 7.42, (s, 1H), 7.50 (m, 1H), 7.59 (d, 1H), 7.74 (s, 1H), 7.87 (t, 1H), 8.02 (d, 1H), 8.20 (m, 1H), 8.44 (s, 1H) and 8.96 (m, 1H)

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

Elemental analysis

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Example 176

A mixture of 4-chloro-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline (200 mg, 0.57 mmol), potassium carbonate (106 mg, 0.77 mmol) and 7-hydroxyquinoline (111 mg, 0.76 mmol) in DMF (7 ml) was stirred at 100 °C for 5 hours and allowed to cool to ambient temperature. The reaction mixture was treated with 1.0 N aqueous sodium hydroxide solution (40 ml) and allowed to stir at ambient temperature for a few minutes. The reaction mixture was extracted 4 times with ethyl acetate and the organic extracts washed with water and brine. The organic extracts were dried over magnesium sulphate, filtered and the solvent removed by evaporation. The residue was triturated with ether/isohexane, filtered and dried to give 6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)-4-(quinolin-7-yloxy)quinazoline (102 mg, 39%).

$^1$H NMR Spectrum: (DMSO$_d_6$) 1.96 (m, 2H), 2.15 (s, 3H), 2.35 (m, 8H), 2.46 (t, 2H), 3.99 (s, 3H), 4.24 (t, 2H), 7.39 (s, 1H), 7.56 (m, 1H), 7.61 (m, 1H), 7.62 (s, 1H), 7.92 (d, 1H), 8.10 (d, 1H), 8.44 (d, 1H), 8.54 (s, 1H) and 8.92 (m, 1H)

MS (ESI) : 460 (MH$^+$)

Elemental analysis

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C$_{36}$H$_{33}$N$_7$O$_7$, 0.3 H$_2$O

The starting material was prepared as follows:

A solution of 1-(3-hydroxypropyl)-4-methylpiperazine (2.4 g, 15 mmol), (prepared as described for the starting material in Example 133), in dichloromethane (60 ml) was treated with triethylamine (4.6 ml, 33 mmol) and p-toluenesulphonyl chloride (3.2 g, 17 mmol) and stirred at ambient temperature for 2 hours. The solution was washed with saturated aqueous sodium hydrogen carbonate solution followed by water and filtered through phase separating paper. The filtrate was evaporated under vacuum to give 3-(4-methyl-piperazin-1-yl)propyl-4-toluene sulphonate as an oil which crystallised on standing (3.7 g, 78%).

MS (ESI) : 313 (MH$^+$)

A mixture of 2-amino-4-benzyloxy-5-methoxybenzamide (J. Med. Chem. 1977, vol 20, 146-149, 10g, 0.04mol) 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 mixture was evaporated, water was added to the residue, the solid was filtered off, washed
with water and dried. Recrystallisation from acetic acid gave 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (8.7g, 84%).

A mixture of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (2.82g, 0.01mol), thionyl chloride (40ml) and DMF (0.28ml) was stirred and heated at reflux for 1 hour. The mixture was evaporated and azeotroped with toluene to give 7-benzyloxy-4-chloro-6-methoxyquinazoline hydrochloride (3.45g).

4-Chloro-2-fluoro-phenol (264mg, 1.8mmol) was added to a solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline hydrochloride (506mg, 1.5mmol) in pyridine (8ml) and the mixture heated at reflux for 45 minutes. The solvent was removed by evaporation and the residue partitioned between ethyl acetate and water. The organic layer was washed with 0.1M HCl, water and brine, dried (MgSO₄) and the solvent removed by evaporation. The solid residue was triturated with petroleum ether and the crude product collected by filtration and purified by flash chromatography eluting with methylene chloride/ether (9/1) to give 7-benzyloxy-4-(4-chloro-2-fluorophenoxy)-6-methoxyquinazoline (474mg, 77%) as a cream solid.

m.p. 179-180°C

¹H NMR Spectrum: (DMSO-d₆) 3.99(s, 3H); 5.36(s, 2H); 7.35-7.5(m, 4H); 7.55-7.65(m, 5H); 7.72(d, 1H); 8.6(s, 1H)

MS - ESI: 411 [MH]⁺

Elemental analysis:

Found C 63.38 H 4.07 N 6.78

C₂₂H₁₆ClFN₂O₃ 0.06H₂O 0.05CH₂Cl₂

Requires C 63.64 H 3.93 N 6.73%

A solution of 7-benzyloxy-4-(4-chloro-2-fluorophenoxy)-6-methoxyquinazoline (451mg, 1.1mmol) in TFA (4.5ml) was heated at reflux for 3 hours. The mixture was diluted with toluene and the volatiles removed by evaporation. The residue was triturated with methylene chloride, collected by filtration, washed with ether and dried under vacuum to give 4-(4-chloro-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline (320mg, 90%).

¹H NMR Spectrum: (DMSO-d₆) 4.0(s, 3H); 7.27(s, 1H); 7.43(dd, 1H); 7.56(t, 1H); 7.57(s, 1H); 7.72(dd, 1H); 8.5(s, 1H)

MS - ESI: 321 [MH]⁺

A mixture of the trifluoroacetic acid salt of 4-(4-chloro-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline (3.2 g, 7.4 mmol), potassium carbonate (6.1 g, 44.2 mmol) and 3-(4-methyl-1-piperazinyl)propyl-4-toluene sulphonate (3.0 g, 9.6 mmol) in DMF (60 ml) was
stirred at 90 °C for 5 hours and allowed to cool to ambient temperature. The reaction mixture was poured into water (700 ml) and extracted 5 times with ethyl acetate. The combined extracts were washed with water, saturated aqueous sodium hydrogen carbonate, water and saturated brine. The ethyl acetate solution was dried over magnesium sulphate, filtered and the solvent removed under vacuum to give a residue which was purified by silica column chromatography, eluting with dichloromethane/methanol/0.880 aqueous ammonia (100/8/1). The relevant fractions were combined and evaporated under vacuum to give a residue which was triturated with ether, filtered and dried to give 4-(4-chloro-2-fluorophenoxy)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline (1.64 g, 48 %).

$^1$H NMR Spectrum: (DMSOd$_6$) 1.95 (m, 2H), 2.14 (s, 3H), 2.35 (m, 8H), 2.44 (t, 2H), 3.96 (s, 3H), 4.22 (t, 2H), 7.38 (s, 1H), 7.40 (m, 1H), 7.54 (m, 2H), 7.68 (m, 1H) and 8.55 (s, 1H)

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

Elemental analysis

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C$_{23}$H$_{26}$ClFN$_4$O$_3$

4-(4-Chloro-2-fluorophenoxy)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline (2.6 g, 5.6 mmol) was treated with 2.0 N aqueous hydrochloric acid (45 ml) and the mixture stirred at 95 °C for 2 hours. The mixture was cooled, basified by the addition of solid sodium hydrogen carbonate and the water removed by azeotroping with toluene. The residue was purified by silica column chromatography eluting with dichloromethane/methanol/0.880 aqueous ammonia (50/8/1) to give 6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)-3,4-dihydroquinazolin-4-one (1.8 g, 96%).

MS (ESI) : 333 (MH)$^+$

6-Methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)-3,4-dihydroquinazolin-4-one (2.15 g, 6.48 mmol) was suspended in thionyl chloride (25 ml) and DMF (0.18 ml) and stirred under reflux for 2 hours. The thionyl chloride was evaporated under vacuum and the residue azeotroped twice with toluene. The residue was taken up in water, basified with saturated with aqueous sodium hydrogen carbonate solution and the aqueous solution extracted 4 times with dichloromethane. The combined extracts were washed with water and brine then filtered through phase separating paper. The filtrate was evaporated under vacuum and the residue purified by silica column chromatography eluting with dichloromethane/methanol/0.880 aqueous ammonia (100/8/1) to give a solid which was triturated with a little acetone, filtered
and dried to give 4-chloro-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propanoyl)quinazoline (1.2 g, 53%). This was used without further purification.

MS (ESI) : 351 (MH')

Example 177

A mixture of 4-chloro-6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)quinazoline (200 mg, 0.64 mmol), potassium carbonate (102 mg, 0.74 mmol) and 7-hydroxyquinoline (107 mg, 0.74 mmol) in DMSO (5 ml) was stirred at 100 °C for 5 hours and allowed to cool to ambient temperature. The mixture was poured into water, washed with dichloromethane and extracted twice with a 10/1 mixture of dichloromethane/methanol. The extracts were washed with water and brine, dried over magnesium sulphate, filtered and the filtrate evaporated under vacuum. The residue was purified by silica column chromatography, eluting with dichloromethane/methanol/0.880 aqueous ammonia (100/8/1) to give an oil which crystallised on trituration with ether to give 6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-4-(quinolin-7-yloxy)quinazoline (148 mg, 55%).

1H NMR Spectrum: (DMSOd₆) 3.25 (s, 3H), 3.50 (t, 2H), 3.60 (t, 2H), 3.80 (t, 2H), 4.00 (s, 3H), 4.30 (t, 2H), 7.40 (s, 1H), 7.55 (m, 1H), 7.60 (m, 1H), 7.65 (s, 1H), 7.90 (d, 1H), 8.10 (d, 1H), 8.40 (m, 1H), 8.50 (s, 1H) and 8.90 (m, 1H)

MS (ESI) : 422 (MH')

Elemental analysis  

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C₂₃H₂₃N₂O₅

The starting material was prepared as follows:

Diethyl azodicarboxylate (864µl, 5.5mmol) was added dropwise to a mixture of 7-hydroxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (1.2g, 3.9mmol) (prepared as described for the starting material in Example 12), triphenylphosphine (1.44g, 5.5mmol) and 2-(2-methoxyethoxy)ethanol (653µl, 5.5mmol) in methylene chloride (70ml) cooled at 0°C. The mixture was stirred for 1.5 hours at ambient temperature and the solvent was removed by evaporation. The residue was purified by column chromatography eluting with a mixture of ethyl acetate/methylene chloride (50/50 followed by 80/20). The purified solid was suspended in ether, collected by filtration and dried under vacuum to give 6-
methoxy-7-(2-(2-methoxyethoxy)ethoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (1.70g, 100%).

\(^1\)H NMR Spectrum: (DMSO\(_d_6\)) 1.13(s, 9 H); 3.26(s, 3H); 3.5(m, 2H); 3.65(m, 2H); 3.85(m, 2H); 3.91(s, 3H); 4.3(m, 2H); 5.9(s, 2H); 7.2(s, 1H); 7.5(s, 1H); 8.4(s, 1H)

Saturated methanolic ammonia (20ml) was added to a solution of 6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (2.26g, 5.5mmol) in a mixture of ethanol (40ml) and methylene chloride (15ml). The mixture was stirred for 24 hours at ambient temperature, and further methanolic ammonia (20ml) was added. The mixture was stirred for a further 24 hours at ambient temperature and the volatiles were removed by evaporation. The residue was triturated with ether, collected by filtration, dried under vacuum to give 6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-3,4-dihydroquinazolin-4-one (975mg, 78%).

\(^1\)H NMR Spectrum: (DMSO\(_d_6\)) 3.25(s, 3H); 3.45(t, 2H); 3.6(t, 2H); 3.8(t, 2H); 3.9(s, 3H); 4.2(t, 2H); 7.15(s, 1H); 7.45(s, 1H); 8.0(s, 1H)

MS - EI: 294 [M]⁺

A solution of 6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-3,4-dihydroquinazolin-4-one (930mg, 3.16mmol) in thionyl chloride (15ml) and DMF (150µl) was heated at 60°C for 1.5 hours. The mixture was allowed to cool and the volatiles were removed by evaporation and by azeotroping with toluene. The residue was dissolved in methylene chloride and 5% aqueous sodium hydrogen carbonate solution was added until the aqueous layer was at pH8. The organic layer was separated, washed with brine, dried (MgSO\(_4\)) and the solvent removed by evaporation. The residue was purified by flash chromatography eluting with ethyl acetate to give 4-chloro-6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)quinazoline (863mg, 87%).

\(^1\)H NMR Spectrum: (DMSO\(_d_6\)) 3.24(s, 3H); 3.47(m, 2H); 3.62(m, 2H); 3.84(t, 2H); 4.01(s, 3H); 4.25(t, 2H); 7.41(s, 1H); 7.49(s, 1H); 8.88(s, 1H)

**Example 178**

A mixture of 4-chloro-6-methoxy-7-(3-piperidinopropoxy)quinazoline (168 mg, 0.5 mmol), (prepared as described for the starting material in Example 67), potassium carbonate (207 mg, 1.5 mmol), 3-methyl-5-hydroxyindole (88mg, 0.6 mmol), (Can. J. Chem. 1964, 42, 514), and DMA (2.0 ml) was purged with nitrogen for 5 minutes at 25°C. This mixture was then stirred at 100°C for 3 hours then allowed to cool to ambient temperature, was filtered and
the filtrate evaporated under vacuum. The residue was purified by silica column 
chromatography eluting with dichloromethane/methanolic ammonia (7M) (90/10) to give 6-methoxy-4-(3-methylindol-5-yl)oxy)-7-(3-piperidinopropoxy)quinazoline (155 mg, 69%).

\(^1\)H NMR Spectrum: (DMSO-d\(_6\)) 1.37 (m, 2H), 1.50 (m, 4H), 1.95 (m, 2H), 2.21 (s, 3H), 2.34 (m, 4H), 2.42 (t, 2H), 3.96 (s, 3H), 4.22 (t, 2H), 6.95 (dd, 1H), 7.16 (s, 1H), 7.35 (m, 3H), 7.58 (s, 1H), 8.48 (s, 1H) and 10.82 (s, 1H)

MS (ESI) : 447 (MH)^+

Elemental analysis

\(\text{C}_{26}\text{H}_{30}\text{N}_{4}\text{O}_3\) 0.5 \(\text{H}_2\text{O}\),

Found

\(\text{C} 68.2\text{ H} 6.8\text{ N} 12.6\)

Requires

\(\text{C} 68.5\text{ H} 6.8\text{ N} 12.3\%\)

**Example 179**

Using an analogous procedure to that described in Example 178, 4-chloro-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline, (prepared as described for the starting material in Example 9), was used to give

6-methoxy-4-(3-methylindol-5-yl)oxy)-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline (154 mg, 79%).

\(^1\)H NMR Spectrum: (DMSO-d\(_6\)) 1.68 (m, 4H), 1.97 (m, 2H), 2.22 (s, 3H), 2.43 (m, 4H), 2.55 (t, 2H), 3.96 (s, 3H), 4.22 (t, 2H), 6.93 (dd, 1H), 7.16 (s, 1H), 7.35 (m, 3H), 7.58 (s, 1H), 8.48 (s, 1H) and 10.82 (br s, 1H)

MS (ESI) : 433 (MH)^+

m.p. 75-77°C

**Example 180**

Using an analogous procedure to that described in Example 178, 4-chloro-6-methoxy-7-(2-piperidinoethoxy)quinazoline was used to give 6-methoxy-4-(3-methylindol-5-yl)oxy)-7-(2-piperidinoethoxy)quinazoline (156 mg, 80%).

\(^1\)H NMR Spectrum: (DMSO-d\(_6\)) 1.38 (m, 2H), 1.50 (m, 4H), 2.24 (s, 3H), 2.73 (t, 2H), 3.96 (s, 3H), 4.28 (t, 2H), 6.93 (dd, 1H), 7.16 (s, 1H), 7.32 (d, 1H), 7.37 (m, 2H), 7.58 (s, 1H), 8.47 (s, 1H) and 10.82 (br s, 1H)

MS (ESI) : 433 (MH)^+

Elemental analysis

\(\text{C}_{25}\text{H}_{28}\text{N}_{4}\text{O}_3\) 0.75 \(\text{H}_2\text{O}\)

Found

\(\text{C} 67.0\text{ H} 6.5\text{ N} 13.0\)

Requires

\(\text{C} 67.3\text{ H} 6.6\text{ N} 12.6\%\)
The starting material was prepared as follows:

1-(2-Chloroethyl)piperidine hydrochloride (0.83g, 4.5mmol) was added to 7-hydroxy-6-methoxy-4-phenoxyquinazoline (1.0g, 3.73mmol), (prepared as described for the starting material in Example 1), and potassium carbonate (2.6g, 18.8mmol) in DMF (30ml), and the mixture heated at 110°C for 2.5 hours and allowed to cool. The insolubles were removed by filtration, and the volatiles were removed from the filtrate by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol (9/1) to give 6-methoxy-4-phenoxy-7-(2-piperidinoethoxy)quinazoline (1.2g, 85%).

^1H NMR Spectrum: (DMSO_d6) 1.38(m, 2H); 1.50(m, 4H); 2.4-2.5(m, 4H); 2.75(t, 2H); 3.95(s, 3H); 4.27(t, 2H); 7.30(m, 3H); 7.40(s, 1H); 7.46(m, 2H); 7.54(s, 1H); 8.52(s, 1H)
MS - ESI: 380 [MH]^+

A mixture of 6-methoxy-4-phenoxy-7-(2-piperidinoethoxy)quinazoline (1.15g, 3.0mmol) and 2M hydrochloric acid (20ml) was heated at 90°C for 2 hours and allowed to cool. The mixture was neutralised with solid sodium hydrogen carbonate and extracted with methylene chloride. The organic phase was separated, passed through phase separating paper and the volatiles removed by evaporation to give a solid product (230mg). The aqueous phase was adjusted to pH10, the resulting precipitate was collected by filtration, washed with water and dried to give a second crop of product (220mg). The products were combined to give 6-methoxy-7-(2-piperidinoethoxy)-3,4-dihydroquinazolin-4-one (450mg, 50%).

MS - ESI: 304 [MH]^+

A mixture of 6-methoxy-7-(2-piperidinoethoxy)-3,4-dihydroquinazolin-4-one (440mg, 1.45mmol), thionyl chloride (15ml) and DMF (3 drops) was heated at reflux for 3 hours then allowed to cool. The excess thionyl chloride was removed by evaporation and the residue was azeotroped with toluene to give a crude 4-chloro-6-methoxy-7-(2-piperidinoethoxy)quinazoline hydrochloride (640mg).

4-Chloro-6-methoxy-7-(2-piperidinoethoxy)quinazoline hydrochloride was suspended in methylene chloride (10ml) and saturated aqueous sodium hydrogen carbonate solution (5ml) then stirred vigorously for 10 minutes at ambient temperature. The layers were separated and the organic layer dried (MgSO_4) then evaporated to give a white solid. This solid was triturated with methanol (2.5ml), the resulting solid filtered off, washed with cold methanol and dried to give 4-chloro-6-methoxy-7-(2-piperidinoethoxy)quinazoline (0.36g).
Example 181

Using an analogous procedure to that described in Example 178, 4-chloro-6-methoxy-7-(3-(N-methyl-N-methylsulphonylamino)propoxy)quinazoline, (prepared as described for the starting material in Example 152), was used to give

6-methoxy-4-(3-methylindol-5-yloxy)-7-(3-(N-methyl-N-methylsulphonylamino)propoxy)quinazoline (104mg, 49%).

$^1$H NMR Spectrum: (DMSOd$_6$) 2.08 (m, 2H), 2.22 (s, 3H), 2.80 (s, 3H), 2.88 (s, 3H), 3.27 (t, 2H), 3.97 (s, 3H), 4.22 (t, 2H), 6.95 (dd, 1H), 7.17 (s, 1H), 7.35 (m, 3H), 7.59 (s, 1H), 8.48 (s, 1H) and 10.82 (br s, 1H)

MS (ESI) : 471 (MH)$^+$

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Example 182

A mixture of 4-chloro-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline (218 mg, 0.68 mmol), (prepared as described for the starting material in Example 9), 5-hydroxy-1H-pyrrolo[2,3-b]pyridine (100 mg, 0.75 mmol) and potassium carbonate (280 mg, 2.0mmol) in DMF (4 ml) was stirred at 95°C for 6 hours and allowed to cool to ambient temperature. The reaction mixture was treated with 1.0 N aqueous sodium hydroxide solution and allowed to stir at ambient temperature for a few minutes. The resulting precipitate was filtered off, washed with water and air dried to give a crude product which was purified by column chromatography, eluting with dichloromethane/methanol/880 ammonia (100/8/1). The relevant fractions were combined and evaporated ‘in vacuo’ to give a white solid. This was recolmmended using dichloromethane/methanol (4/1) solvent to give a white solid which was triturated with acetone, filtered and dried to give 6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)-4-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)quinazoline (50 mg, 18%).

m.p. 184.0 - 185.5°C

$^1$H NMR Spectrum: (DMSOd$_6$) 1.70 (m, 4H), 1.99 (m, 2H), 2.46 (m, 4H), 2.58 (t, 2H), 4.00 (s, 3H), 4.26 (t, 2H), 6.48 (t, 1H), 7.36 (s, 1H), 7.55 (t, 1H), 7.60 (s, 1H), 7.92 (d,1H), 8.19 (d, 1H), 8.50 (s,1H) and 11.78 (br s, 1H)

MS (ESI) : 420 (MH)$^+$
The starting material was prepared as follows:-

A suspension of 5-methoxy-1H-pyrrolo[2,3-b]pyridine (210 mg, 1.42 mmol), (Heterocycles 50, (2), 1065 - 1080, (1999)), in dichloromethane (10 ml) was stirred in an inert atmosphere, a 1.0M solution of boron tribromide in dichloromethane (4.3 ml, 4.3 mmol) added dropwise and the mixture stirred at ambient temperature overnight. The reaction mixture was taken to pH6 by the dropwise addition of 5N aqueous sodium hydroxide and further diluted with water. The aqueous solution was extracted several times with ethyl acetate, the extracts combined, washed with water followed by brine and dried over magnesium sulphate. The ethyl acetate solvent was removed ‘in vacuo’ and the residue purified by column chromatography, eluting with dichloromethane/methanol (95/5), to give a white solid. The solid was triturated with ether, filtered and dried to give 5-hydroxy-1H-pyrrolo[2,3-b]pyridine (108 mg, 57%).

m.p. 206-209°C

^1H NMR Spectrum: (DMSOd₆) 6.25 (s,1H), 7.27 (s,1H), 7.33 (s, 1H), 7.82 (s, 1H), 9.00 (s,1H) and 11.20 (s, 1H)

MS (ESI) : 135 (MH)^+

Example 183

A mixture of 4-chloro-6-methoxy-7-(3-piperidinopropoxy)quinazoline (168 mg, 0.5 mmol), (prepared as described for the starting material in Example 67), potassium carbonate (345 mg, 5.0 mmol), 5-hydroxy-2-indolecarboxylic acid (106mg, 0.6 mmol) and DMA (2.0 ml) was purged with nitrogen for 5 minutes at 25°C. This mixture was then stirred at 100°C for 3 hours, allowed to cool to ambient temperature, filtered and the filtrate evaporated under vacuum. The residue was purified on octadecylsilane reverse phase silica eluting with acetonitrile/water/trifluoroacetic acid (as a gradient from 30/69.8/0.2 to 50/49.8/0.2) and the product further purified by silica column chromatography eluting with dichloromethane/methanolic ammonia (7M) (90/10) to give 4-(2-carboxyindol-5-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline (85 mg 36%).
**Example 184**

4-Chloro-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline (0.15 g, 0.45 mmol), (prepared as described for the starting material in Example 50), potassium carbonate (94 mg, 0.68 mmol) and 7-hydroxyquinoline (79 mg, 0.54 mmol) were suspended in anhydrous DMF (1.5 ml) and heated to 90°C overnight. The compound was precipitated upon addition of water. The precipitate was collected by filtration, washed with water and dried under vacuum over phosphorus pentoxide to give 6-methoxy-7-(3-methylsulphonylpropoxy)-4-(quinolin-7-yloxy)quinazoline (161 mg, 81%).

\[^1\text{H} \text{NMR Spectrum: (DMSO}_d_6) 2.26 (m, 2H); 3.08 (s, 3H); 3.35 (m, 2H); 4.03 (s, 3H); 4.38 (m, 2H); 7.45 (s, 1H); 7.60 (m, 1H); 7.65 (m, 1H); 7.70 (s, 1H); 7.95 (d, 1H); 8.15 (d, 1H); 8.46 (d, 1H); 8.60 (s, 1H); 8.95 (d, 1H)\]

MS (ESI) : 440 [MH]^+

**Examples 185-188**

Using an analogous procedure to that described in Example 184, 4-chloro-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline (0.15 g, 0.45 mmol), (prepared as described for the starting material in Example 50), was reacted with the appropriate phenols to give the compounds in Table X.

**Table X**

<table>
<thead>
<tr>
<th>Example number</th>
<th>weight (mg)</th>
<th>yield %</th>
<th>MS-ESI [MH]^+</th>
<th>AR</th>
<th>note</th>
</tr>
</thead>
</table>


<p>| | | | | |</p>
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<tr>
<td>185</td>
<td>199</td>
<td>93</td>
<td>474</td>
<td>a</td>
</tr>
<tr>
<td>186</td>
<td>171</td>
<td>85</td>
<td>422</td>
<td>b</td>
</tr>
<tr>
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<td>183</td>
<td>88</td>
<td>460</td>
<td>c</td>
</tr>
<tr>
<td>188</td>
<td>83</td>
<td>40</td>
<td>455</td>
<td>d</td>
</tr>
</tbody>
</table>

a) Using 4-chloro-7-hydroxyquinoline (96 mg) gave 4-(4-chloroquinolin-7-yloxy)-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline.

\(^1\)H NMR Spectrum: (DMSO\(_d_6\)) 2.24 (m, 2H); 3.04 (s, 3H); 3.35 (m, 2H); 3.99 (s, 3H); 4.32 (m, 2H); 7.42 (s, 1H); 7.64 (s, 1H); 7.80 (d, 2H); 8.04 (d, 1H); 8.29 (d, 1H); 8.55 (s, 1H); 8.87 (d, 1H)

b) Using 5-hydroxy-2-methylindole (80 mg) gave 6-methoxy-4-(2-methylindol-5-yloxy)-7-(3-methylsulphonylpropoxy)quinazoline.

\(^1\)H NMR Spectrum: (DMSO\(_d_6\)) 2.24 (m, 2H); 2.40 (s, 3H); 3.05 (s, 3H); 3.35 (m, 2H); 4.0 (s, 3H); 4.32 (m, 2H); 6.13 (s, 1H); 6.88 (d, 1H); 7.25 (d, 1H); 7.32 (d, 1H); 7.39 (s, 1H); 7.60 (s, 1H); 8.50 (s, 1H)

c) Using 5-hydroxy-2-methylbenzothiazole (90 mg) gave 6-methoxy-4-(2-methyl-1,3-benzothiazol-5-yloxy)-7-(3-methylsulphonylpropoxy)quinazoline.

\(^1\)H NMR Spectrum: (DMSO\(_d_6\)) 2.24 (m, 2H); 2.28 (s, 3H); 3.05 (s, 3H); 3.35 (m, 2H); 4.0 (s, 3H); 4.32 (m, 2H); 7.36 (d, 1H); 7.41 (s, 1H); 7.65 (s, 1H); 7.87 (d, 1H); 8.11 (d, 1H); 8.53 (s, 1H)

d) Using 2,7-dihydroxynaphtalene (87 mg) gave 4-(7-hydroxy-2-naphthyl-oxy)-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline.
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$^1$H NMR Spectrum: (DMSO$_d_6$) 2.24 (m, 2H); 3.05 (s, 3H); 3.35 (m, 2H); 3.98 (s, 3H); 4.32 (m, 2H); 7.06 (d, 1H); 7.12 (s, 1H); 7.18 (d, 1H); 7.40 (d, 1H); 7.59 (m, 2H); 7.85 (m, 2H); 8.55 (d, 1H); 9.8 (br s, 1H)

**Example 189**

To a portion of 2-chloro-5-hydroxybenzimidazole (191 mg, 0.75 mmol) in DMF (3 ml) was added sodium hydride (60 mg, 1.5 mmol) under argon at ambient temperature. Ten minutes later 4-chloro-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (200 mg, 0.62 mmol), (prepared as described for the starting material in Example 10), was added and the mixture heated at 100 °C for 2 hours. More 2-chloro-5-hydroxybenzimidazole (30 mg, 0.12 mmol) and sodium hydride (11 mg, 0.28 mmol) were then added as the reaction was found to be incomplete. The heating was continued for an additional 1 hour. Work-up using ethyl acetate and a saturated aqueous solution of ammonium chloride followed by drying of the organic phase (MgSO$_4$) and evaporation of the solvent gave a crude product which was adsorbed on alumina using dichloromethane/methanol and purified by flash chromatography using neutral alumina and dichloromethane/methanol (98:2) as the eluent.

Evaporation of the solvent and trituration in ether gave 4-(2-chloro-1H-benzimidazol-6-yl)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (46 mg, 16%).

$^1$H NMR Spectrum: (DMSO$_d_6$ + TFA) 1.60 (m, 2H); 2.05 (d, 2H); 2.15 (m, 1H); 2.80 (s, 3H); 3.05 (m, 2H); 3.55 (m, 2H); 4.05 (s, 3H); 4.15 (d, 2H); 7.20 (dd, 1H); 7.50 (dd, 2H); 7.65 (d, 1H); 7.70 (s, 1H); 8.80 (s, 1H)

MS (ESI) : 454 [MH]$^+$

The starting material was synthesised as follows:

2-Chloro-5-methoxybenzimidazole (0.3 g, 1.64 mmol) was suspended in dichloromethane (20 ml) under argon followed by the addition of boron tribromide (233 ul, 2.46 mmol). The reaction mixture was stirred for 2 hours at ambient temperature. The solvent was evaporated and the resulting powder was added in portions to methanol (30 ml). Silica was added and the solvent was evaporated. The resulting powder was placed on the top of a silica column and the product was eluted off using dichloromethane/methanol (95/5).

Evaporation of the solvent and trituration in ether gave 2-chloro-5-hydroxybenzimidazole (440 mg, 99%).
Example 190

Using an analogous procedure to that described in Example 189, 4-chloro-6-methoxy-7-(1-methylpiperidin-4-yl)methoxyquinazoline, (prepared as described for the starting material in Example 10), was reacted with 5-hydroxy-2-methylbenzimidazole (200 mg, 0.62 mmol) and after work-up and purification on a 10 g silica ISOLUTE column using successively dichloromethane, dichloromethane/methanol (95/5) and dichloromethane/methanol saturated with ammonia (95/5), gave 6-methoxy-4-(2-methyl-1H-benzimidazol-6-yloxy)-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (68 mg, 25%).

1H NMR Spectrum: (DMSO$_d_6$ + TFA) 1.60 (m, 2H); 2.10 (m, 2H); 2.20 (m, 1H); 2.80 (s, 3H); 2.85 (s, 3H); 3.05 (m, 2H); 3.50 (m, 2H); 4.05 (s, 3H); 4.15 (d, 2H); 7.50 (s, 1H); 7.55 (d, 1H); 7.70 (s, 1H); 7.85 (d, 1H); 7.90 (d, 1H); 8.65 (s, 1H)

MS (ESI) : 434 [MH]$^+$

The starting material was prepared as follows:

The free base of 4-methoxy-1,2-phenylenediamine dihydrochloride (10 g) was obtained by shaking it with a mixture of ethyl acetate and a saturated aqueous solution of sodium hydrogen carbonate. The organic phase was then washed with brine, dried (MgSO$_4$) and the solvent evaporated. The obtained dark oil (6.08 g, 50 mmol) was solubilised in toluene (60 ml) and p-toluene sulfonic acid (60 mg) and triethyl orthoacetate (9.15 ml, 50 mmol) were added in turn. The mixture was heated to 110 °C until no more ethanol distilled off. The remaining toluene was removed by rotary evaporation and the residue purified by flash chromatography using dichloromethane/methanol (95/5) as the eluent. The obtained dark oil was triturated in ether and the solid collected by filtration to give 5-methoxy-2-methylbenzimidazole (4.15 g, 51%).

1H NMR Spectrum (DMSO$_d_6$ + TFA) 2.75 (s, 3H); 3.85 (s, 3H); 7.15 (dd, 1H); 7.25 (s, 1H); 7.70 (d, 1H)

Using an analogous procedure to that described for the synthesis of 2-chloro-5-hydroxybenzimidazole in Example 189, 5-methoxy-2-methylbenzimidazole (4.0 g, 25 mmol) was reacted with boron tribromide (7 ml, 74 mmol) in dichloromethane (150 ml) to give, after work-up and purification by flash chromatography using dichloromethane/methanol (90/10), 5-hydroxy-2-methylbenzimidazole (4.4 g, 76%).
Example 191

4-Chloro-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (200 mg, 0.62 mmol), (prepared as described for the starting material in Example 10), was suspended in DMF (3 ml) under argon. 3-Cyano-7-hydroxyquinoline (116 mg, 0.68 mmol) and potassium carbonate (129 mg, 0.93 mmol) were added and the reaction mixture was heated at 95 °C for 90 minutes. Upon cooling to ambient temperature the mixture was diluted with dichloromethane and poured on the top of an ISOLUTE silica column. Elution was done using successively dichloromethane, dichloromethane/methanol (95/5) and dichloromethane/methanol saturated with ammonia (95/5). Evaporation of the solvent and trituration of the solid in ether gave 4-(3-cyanoquinolin-7-yloxy)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (244 mg, 86%).

1H NMR Spectrum: (DMSO_d6 + TFA) 1.60 (m, 2H); 2.10 (m, 3H); 2.85 (s, 3H); 3.05 (m, 2H); 3.55 (m, 2H); 4.05 (s, 3H); 4.20 (d, 2H); 7.55 (s, 1H); 7.80 (s, 1H); 7.85 (dd, 1H); 8.15 (s, 1H); 8.3 (d, 1H); 8.85 (s, 1H); 9.20 (s, 1H); 9.25 (s, 1H)

MS (ESI) : 456 [MH]+ 456

The starting material was prepared as follows:

m-Anisidine (50 g, 407 mmol) and diethyl ethoxymethylene malonate (102 g, 407 mmol) were heated at 60 °C for 20 minutes. Diphenyl ether (270 ml) was then added and the temperature was raised to 240 °C over 30 minutes. The ethanol formed distilled off. Heating was maintained at this temperature for 1 hour then the reaction mixture was allowed to cool to 120 °C at which point the reaction mixture was diluted with heptane and allowed to stand overnight at ambient temperature. The brown solid was collected by filtration and washed with methanol and ether to give ethyl 7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (45 g, 45%). This reaction was repeated twice.

1H NMR Spectrum: (DMSO_d6) 1.25 (t, 3H); 3.85 (s, 3H); 4.20 (q, 2H); 6.95 (d, 1H); 7.00 (s, 1H); 8.05 (d, 1H); 8.50 (s, 1H)

Phosphorus oxychloride (88 ml) was added to ethyl 7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (58 g, 235 mmol) and the mixture was heated at reflux for 45 minutes under anhydrous conditions. Upon cooling to ambient temperature, phosphorus
oxychloride was evaporated and the solid residue was added in portions to a mixture of ammonia (150 ml) and ice (200g). External cooling as well as further addition of ammonia to maintain the pH around 8 was needed during this hydrolysis step. The aqueous phase was extracted with dichloromethane and the organic phase was washed with water and brine, dried (MgSO₄) and concentrated to about 300 ml. Pentane (400 ml) was added and the precipitate formed collected by filtration. Drying under vacuum gave 4-chloro-3-ethoxycarbonyl-7-methoxyquinoline (45.5 g, 73%).

\(^1\)H NMR Spectrum: (DMSO\(_d_6\)) 1.40 (t, 3H); 4.00 (s, 3H); 4.45 (q, 2H); 7.45 (dd, 1H); 7.55 (d, 1H); 8.30 (d, 1H); 9.10 (s, 1H)

4-Chloro-3-ethoxycarbonyl-7-methoxyquinoline (43 g, 162 mmol) was dissolved in acetic acid (250 ml), with 10% palladium on charcoal (1.5 g) and hydrogenated at atmospheric pressure during 8 hours. The catalyst was removed by filtration over a pad of celite and the solvent evaporated. The residue was diluted with water and the pH adjusted to 7-8 with a saturated solution of sodium hydrogen carbonate. The solid was collected by filtration, washed with water and dried under vacuum over phosphorus pentoxide to give 3-ethoxycarbonyl-7-methoxyquinoline (33 g, 88%) as a beige powder.

\(^1\)H NMR Spectrum: (DMSO\(_d_6\)) 1.40 (t, 3H); 3.95 (s, 3H); 4.40 (q, 2H); 7.35 (dd, 1H); 7.50 (d, 1H); 8.15 (d, 1H); 8.90 (d, 1H); 9.25 (d, 1H)

3-Ethoxycarbonyl-7-methoxyquinoline (28 g, 120 mmol) was added to a methanol solution saturated with ammonia. The suspension was stirred at ambient temperature in a glass pressure vessel for 2 weeks. The white solid was collected by filtration, washed with methanol and dried under vacuum to give 3-carbamoyl-7-methoxyquinoline (21 g, 86%).

\(^1\)H NMR Spectrum (DMSO\(_d_6\)) 3.95 (s, 3H); 7.35 (dd, 1H); 7.45 (d, 1H); 7.60 (br s, 1H); 8.00 (d, 1H); 8.20 (br s, 1H); 8.75 (s, 1H); 9.25 (s, 1H)

3-Carbamoyl-7-methoxyquinoline (4 g, 20 mmol) was suspended in anhydrous dichloromethane (60 ml) under argon. Anhydrous dimethyl sulphoxide (2.25 ml, 32 mmol) was added, the mixture was cooled to -78 °C and a solution of oxalyl chloride (2.08 ml, 24 mmol) in dichloromethane (20 ml) was added dropwise over the course of 1 hour. 15 Minutes after the end of the addition, triethylamine (8.3 ml, 60 mmol) was added dropwise and the heterogeneous reaction mixture stirred for an additional 1 hour at -78 °C then left to rise to ambient temperature. The unreacted starting material was removed by filtration and the filtrate was diluted with water and extracted with ethyl acetate. The organic phases were
combined, washed with brine, dried (MgSO₄) and the solvent evaporated. The residue was purified by flash chromatography using dichloromethane/methanol (97/3). The obtained solid was triturated with ether and gave, after drying under vacuum, 3-cyano-7-methoxyquinoline (1.47 g, 40%).

1H NMR Spectrum (DMSO-d₆) 4.00 (t, 3H); 7.40 (dd, 1H); 7.50 (d, 1H); 8.00 (d, 1H); 8.95 (s, 1H); 9.10 (d, 1H)

3-Cyano-7-methoxyquinoline (380 mg, 2.1 mmol) was suspended in benzene (10 ml), aluminium trichloride (826 mg, 6.2 mmol) was added and the mixture heated at reflux for 30 minutes. More aluminium trichloride (275 mg, 2.1 mmol) was added and the mixture refluxed for a further 2 hours. The solvent was evaporated, the dark green solid was added to ice and extracted with ethyl acetate. The organic phase was washed with brine, dried (MgSO₄) and evaporated. The solid was found to contain some aluminium salts which were removed as follows. The solid was dissolved in dichloromethane (200 ml) was stirred vigorously with a saturated sodium hydrogen carbonate solution for 1 hour. The product was collected by filtration of the aqueous phase and dried over phosphorus pentoxide under vacuum to give 3-cyano-7-hydroxyquinoline (238 mg, 68%).

1H NMR Spectrum (DMSO-d₆) 7.25 (d, 1H); 7.30(d, 1H); 7.95 (d, 1H); 8.85 (d, 1H); 9.00 (d, 1H)

Example 192

To 6-methoxy-7-(3-morpholinopropoxy)-4-((1-tertbutoxycarbonyl-1,2,3,4-tetrahydroquinolin-6-yl)oxy)quinazoline (110 mg, 0.2 mmol) in solution in dichloromethane (3 ml) was added TFA (0.3 ml) and the mixture stirred for 1 hour at ambient temperature. The solvents were evaporated and the remaining oil was diluted with dichloromethane and the pH adjusted to 9 with a saturated solution of sodium hydrogen carbonate. The organic phase was washed with, brine, dried (MgSO₄), filtered and the solvent evaporated to give 6-methoxy-7-(3-morpholinopropoxy)-4-(1,2,3,4-tetrahydroquinolin-6-yloxy)quinazoline (84 mg, 93%).

1H NMR Spectrum: (CDCl₃) 1.95 (m, 2H); 2.15 (m, 2H); 2.45 (m, 4H); 2.60 (t, 2H); 2.80 (t, 2H); 3.35 (t, 2H); 3.75 (m, 4H); 3.90 (br s, 1H); 4.05 (s, 3H); 4.30 (t, 2H); 6.55 (d, 1H); 6.85 (m, 2H); 7.30 (s, 1H); 7.55 (s, 1H); 8.65 (s, 1H)

MS (ESI) : 451 [MH]+
Elemental analysis:  

Found  C  66.4  H  6.9  N  12.4  

C$_{25}$H$_{30}$N$_{4}$O$_{4}$;  

Requires  C  66.7  H  6.7  N  12.4%

The starting material was prepared as follows:

6-Hydroxyquinoline (1 g, 6.9 mmol) was dissolved in methanol and hydrogenated at 3 atmospheres pressure with platinum(IV) oxide (276 mg) over 24 hours. The catalyst was removed by filtration over a pad of celite and the solvent was evaporated. The solid was washed with ether to give 6-hydroxy-(1,2,3,4)-tetrahydroquinoline (698 mg, 68%).

$^1$H NMR Spectrum (DMSO$_d_6$) 1.75 (m, 2H); 2.60 (m, 2H); 3.05 (m, 2H); 4.90 (br s, 1H); 6.30 (m, 3H); 8.25 (br s, 1H)

6-Hydroxy-(1,2,3,4)-tetrahydroquinoline (250 mg, 1.7 mmol) was suspended in acetone (1 ml) and trichloromethane (1 ml) under argon. Tert-Butyloxycarbonylanhydride (365 mg, 1.7 mmol) in solution in acetone was added dropwise followed by THF (2ml) to help the solubilisation. The reaction mixture was stirred overnight at ambient temperature, the solvent was evaporated, the residue was partitioned between ethyl acetate and water, the organic phase was washed with water, brine, dried (MgSO$_4$), filtered and the solvent evaporated. The resulting gum was purified by flash chromatography using dichloromethane/methanol (97/3) as solvent. Evaporation of the solvent gave 6-hydroxy-4-(1-tertbutoxycarbonyl-1,2,3,4-tetrahydroquinoline (344 mg, 82%) as a brown foam.

$^1$H NMR Spectrum: (DMSO$_d_6$) 1.50 (m, 9H); 1.90 (m, 2H); 2.70 (t, 2H); 3.65 (t, 2H); 4.75 (br s, 1H); 6.55 (d, 1H); 6.65 (dd, 1H); 7.45 (d, 1H)

6-Hydroxy-4-(1-tertbutoxycarbonyl-1,2,3,4-tetrahydroquinoline (82 mg, 0.32 mmol) was dissolved in anhydrous dimethylformamide under argon, with potassium carbonate (61 mg, 0.44 mmol) and 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (100 mg, 0.3 mmol), (prepared as described for the starting material in Example 1). No reaction occurred after 2 hours at 60 °C. Sodium hydride (12 mg, 0.3 mmol) was added and the reaction mixture was heated at 120 °C for 90 minutes. The cooled mixture was poured into water and ethyl acetate. The organic phase was washed with water, brine, dried (MgSO$_4$), filtered and the solvent evaporated. The residue was purified by flash chromatography using first dichloromethane/methanol (97/3) as solvent. Evaporation of the solvent gave 6-methoxy-7-(3-morpholinopropoxy)-4-((1-tertbutoxycarbonyl-1,2,3,4-tetrahydroquinolin-6-yl)oxy)quinazoline (115 mg, 71%) as a white solid.
1H NMR Spectrum: (DMSO$_d_6$) 1.55 (s, 9H); 1.95 (m, 2H); 2.15 (m, 2H); 2.50 (m, 4H); 2.60 (t, 2H); 2.85 (t, 2H); 3.75 (m, 6H); 4.05 (s, 3H); 4.30 (t, 2H); 7.00 (m, 2H); 7.35 (s, 1H); 7.55 (s, 1H); 7.80 (d, 1H); 8.65 (s, 1H)

Example 193

Using an analogous procedure to that described in Example 192, 4-((1-

tertbutoxycarbonyl-2,3-dihydro-indol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-
yl)propoxy) quinazoline (169 mg, 0.32 mmol) was reacted with TFA (1 ml) to give, after
work-up and purification, 4-((2,3-dihydro-1H-indol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-
yl)propoxy) quinazoline (124 mg, 91%).

1H NMR Spectrum: (CDCl$_3$) 1.90 (br, 4H); 2.30 (br, 2H); 2.70 (br d, 6H); 3.10 (t, 2H); 3.65 (t, 2H); 4.05 (s, 3H); 4.30 (t, 2H); 6.70 (d, 1H); 6.80 (dd, 1H); 7.00 (s, 1H); 7.30 (s, 1H); 7.55 (s, 1H); 8.65 (s, 1H)

MS (ESI) : 421 [MH]$^+$

The starting material was prepared as follows:

5-Hydroxyindole (2 g, 15 mmol) was dissolved in methanol (60 ml) under argon.
Sodium cyanoborohydride (1.89 g, 30 mmol) and trifluoroboron etherate (4.2 ml, 33 mmol)
were added and the mixture was heated at reflux for 3 hours then left to cool to ambient
temperature. The solvent was evaporated and the residue was partitioned between ethyl
acetate and water. Ammonia was added to adjust the pH to 10 and the aqueous phase was
extracted with more ethyl acetate. The combined organic phases were washed with water,
brine, dried (MgSO$_4$), filtered and the solvent evaporated. The residue was purified by flash
chromatography using dichloromethane/methanol (95/5) as solvent. Evaporation of the
solvent gave 5-hydroxy-2,3-dihydro-1H-indole (1.45 g, 73%) as an off white solid.

1H NMR Spectrum: (DMSO$_d_6$, TFA) 3.15 (t, 2H); 3.70 (t, 2H); 6.75 (dd, 1H); 6.85 (d, 1H);
7.30 (d, 1H)

5-Hydroxy-2,3-dihydro-1H-indole (1.5 g, 11.1 mmol) was suspended in a mixture of
acetone (7 ml) trichloromethane (7 ml) and THF (6 ml). tert-Butoxycarbonylanhydride (2.42
g, 11 mmol) in solution in THF (7 ml) was added dropwise. The reaction mixture was stirred
overnight at ambient temperature, the solvent was evaporated, the residue was partitioned
between ethyl acetate and water, the organic phase was washed with water, brine, dried
(MgSO₄), filtered and the solvent evaporated. The solid was purified by flash chromatography using dichloromethane/methanol (95/5) as solvent. Evaporation of the solvent gave 5-hydroxy-(1-tert-butoxycarbonyl)-2,3-dihydroindole (2.28 g, 87%) as an off white solid.

¹H NMR Spectrum: (CDCl₃) 3.05 (t, 2H); 3.95 (br s, 2H); 4.70 (br s, 1H); 6.60 (d, 1H); 6.65 (s, 1H); 7.70 (br s, 1H)

Sodium hydride (22 mg, 0.56 mmol) was suspended in anhydrous dimethylformamide under argon. 5-Hydroxy-(1-tert-butoxycarbonyl)-2,3-dihydroindole (131 mg, 0.56 mmol) was added followed 10 minutes later by 4-chloro-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline (150 mg, 0.47 mmol), (prepared as described for the starting material in Example 9). The reaction mixture was heated at 110 °C for 3 hours, cooled to ambient temperature and partitioned between ethyl acetate and water. The organic phase was washed with water, brine, dried (MgSO₄), filtered and the solvent evaporated. The residue was purified by flash chromatography using increasingly polar solvent mixtures starting with dichloromethane/methanol (90/10) and ending with dichloromethane/methanol saturated with ammonia (80/15/5). Evaporation of the solvent gave 4-(1-tert-butoxycarbonyl-2,3-dihydro-indol-5-yl-oxo)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline (178 mg, 73%) as a white solid.

¹H NMR Spectrum: (DMSO-d₆) 1.60 (s, 9H); 1.80 (m, 4H); 2.20 (m, 2H); 2.55 (m, 4H); 2.70 (t, 2H); 3.15 (t, 2H); 4.05 (br s, 5H); 4.30 (t, 2H); 7.00 (d, 1H); 7.05 (s, 1H); 7.30 (s, 1H); 7.55 (s, 1H); 7.90 (br s, 1H); 8.60 (s, 1H)

Example 194

Using an analogous procedure to that described in Example 192, 4-(1-tert-butoxycarbonyl-2,3-dihydro-indol-5-yl-oxo)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (191 mg, 0.37 mmol) was reacted with TFA (1 ml) to give, after work-up and purification, 4-(2,3-dihydro-indol-5-yl-oxo)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (103 mg, 67%).

¹H NMR Spectrum: (CDCl₃) 1.65 (m, 2H); 2.00 (m, 3H); 2.25 (m, 2H); 2.45 (s, 3H); 3.10 (m, 4H); 3.65 (t, 2H); 4.05 (s, 3H); 4.10 (d, 2H); 6.70 (d, 1H); 6.85 (dd, 1H); 7.0 (s, 1H); 7.25 (s, 1H); 7.55 (s, 1H); 8.60 (s, 1H)

MS (ESI) : 421 [MH⁺]
The starting material was prepared as follows:

Using an analogous procedure to that described in Example 193, 4-chloro-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (150 mg, 0.47 mmol), (prepared as described for the starting material in Example 10), was reacted with 5-hydroxy-(1-tertbutoxycarbonyl)-2,3-dihydroindole (132 mg, 0.56 mmol), (prepared as described for the starting material in Example 193), to give, after work-up and purification, 4-(1-tertbutoxycarbonyl-2,3-dihydroindol-5-yloxy)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (197 mg, 81%) as a white solid.

\[ ^1H\text{ NMR Spectrum: (CDCl}_3\text{)} \]
1.50 (br s, 1H); 2.00 (m, 5H); 2.30 (s, 3H); 2.90 (d, 2H); 3.15 (t, 2H); 4.05 (br s, 7H); 7.05 (br s, 2H); 7.30 (s, 1H); 7.55 (s, 1H); 7.95 (br s, 1H); 8.60 (s, 1H)

**Example 195**

To a suspension of 4-chloro-6-methoxy-7-(2-piperidinoethoxy)quinazoline (250mg, 0.78mmol), (prepared as described for the starting material in Example 180), in DMF (10ml) was added anhydrous potassium carbonate (320mg, 2.30mmol) and 7-hydroxyquinoline (135mg, 0.94mmol), and the reaction heated under reflux at 90C for 1 hour. The reaction was cooled to ambient temperature and 1N aqueous sodium hydroxide added. The resulting precipitate was filtered, washed with water and acetone, and dried under suction to give 6-methoxy-7-(2-piperidinoethoxy)-4-(quinolin-7-yloxy)quinazoline (248mg, 0.58mmol, 75%) as a white solid.

\[ ^1H\text{ NMR Spectrum: d}_4\text{ (300MHz, CDCl}_3\text{)} : 1.5 \text{ (2H, m; NCH}_2\text{CH}_2\text{CH}_2\text{)}, 1.6 \text{ (4H, m; 2 x NCH}_2\text{CH}_2\text{)}, 2.6 \text{ (4H, t; 2 x NCH}_3\text{), 2.9 \text{ (2H, t; NCH}_3\text{)}, 4.1 \text{ (3H, s; OCH}_3\text{), 4.3 \text{ (2H, t; OCH}_2\text{), 7.3 \text{ (1H, s; ArH), 7.4 \text{ (1H, dd; ArH), 7.5 \text{ (1H, dd; ArH), 7.6 \text{ (1H, s; ArH), 7.9 \text{ (1H, d; ArH), 8.0 \text{ (1H, d; ArH), 8.2 \text{ (1H, d; ArH), 8.6 \text{ (1H, s; ArH) and 8.9 \text{ (1H, dd; ArH)}}}}}}} \]

\[ m/z \text{ (ESP+)} \text{ 431 (MH}^+\text{, 100%)}} \]

**Example 196**

To a suspension of 7-benzylxoy-4-chloro-6-methoxyquinazoline (1.82g, 6.1mmol), (prepared as described for the starting material in Example 1), in DMF (50ml) was added potassium carbonate (2.50g, 18.1mmol) and 7-hydroxyquinoline (1.06g, 7.3mmol), and the reaction heated under reflux at 90C for 4 hours. The reaction was poured into 1N aqueous
sodium hydroxide and the resulting precipitate filtered, washed with water, and dried under suction. Further drying in a vacuum oven gave 7-benzyloxy-6-methoxy-4-(quinolin-7-yloxy)quinazoline (1.50g, 3.7mmol, 60%) as a cream solid.

1H NMR Spectrum: \(d_{\text{H}}\) (300MHz, DMSO-d6): 4.0 (3H, s; OCH3), 5.4 (2H, s; OCH2), 7.3-7.7 (9H, m; 9 x ArH), 7.9 (1H, br s; ArH), 8.1 (1H, d; ArH), 8.4 (1H, d; ArH), 8.5 (1H, s; ArH) and 8.9 (1H, d; ArH)

**Example 197**

A solution of 7-benzyloxy-6-methoxy-4-(quinolin-7-yloxy)quinazoline (1.50g, 3.70mmol), (prepared as described in Example 196), in trifluoroacetic acid (50ml) was heated at reflux for 150 minutes. The reaction was concentrated in vacuo and the reaction neutralised with saturated aqueous ammonium hydroxide. The resulting precipitate was filtered, washed with acetone and dried under suction to give 7-hydroxy-6-methoxy-4-(quinolin-7-yloxy)quinazoline (0.90g, 2.82mmol, 76%) as a white solid.

1H NMR Spectrum: \(d_{\text{H}}\) (300MHz, DMSO-d6): 4.0 (3H, s; OCH3), 7.1 (1H, s; ArH), 7.3-7.4 (3H, m; 3 x ArH), 7.9 (1H, br s; ArH), 8.1 (1H, d; ArH), 8.4-8.5 (2H, d; 2 x ArH) and 8.9 (1H, d; ArH)

\(m/z\) (ESP+) 320 (MH+, 100%)

**Example 198**

To a suspension of 7-hydroxy-6-methoxy-4-(quinolin-7-yloxy)quinazoline (450mg, 1.40mmol), (prepared as described in Example 197), in DMF (50ml) was added anhydrous potassium carbonate (773mg, 5.60mmol) and 4-(2-hydroxyethyl)morpholine (335mg, 1.80mmol), and the reaction heated under reflux for 2 hours. The DMF was evaporated in vacuo, and the residue partitioned between dichloromethane and 1N aqueous sodium hydroxide. The mixture was extracted with dichloromethane (3 x 200ml), dried (MgSO4) and concentrated in vacuo. The crude product was triturated with hexane/ether to afford a solid which was filtered and dried under suction to give 6-methoxy-7-(2-morpholinoethoxy)-4-(quinolin-7-yloxy)quinazoline (430mg, 1.00mmol, 71%) as a light brown solid.

1H NMR Spectrum: \(d_{\text{H}}\) (300MHz, CDCl3): 2.7 (4H, t; 2 x NCH2); 3.0 (2H, t; NCH2), 3.7 (4H, t; 2 x OCH2), 4.1 (3H, s; OCH3), 4.4 (2H, t; OCH2), 7.2 (1H, s; ArH), 7.4 (1H, dd; ArH), 7.5
(1H, dd; ArH), 7.6 (1H, s; ArH), 7.9 (1H, d; ArH), 8.0 (1H, br s; ArH), 8.2 (1H, d; ArH), 8.6 (1H, s; ArH) and 8.9 (1H, dd; ArH)

m/z (ESP+) 433 (MH⁺, 100%)

Elemental analysis

Found  C 65.0  H 5.6  N 12.6
Requires C 65.3  H 5.7  N 12.7%

C₂₄H₂₄N₄O₄ 0.5H₂O

---

**Example 199**

To a solution of 7-hydroxy-6-methoxy-4-(quinolin-7-yloxy)quinazoline (100mg, 0.31mmol), (prepared as described in Example 197), and (S)-(+) 5-(hydroxymethyl)-2-pyrrolidinone (101mg, 0.47mmol) in dichloromethane (10ml) was added triphenylphosphine (244mg, 0.93mmol) and DEAD (0.15ml, 162mg, 0.93mmol), and the reaction stirred at ambient temperature overnight. The reaction mixture was placed directly onto a 2g SCX ion-exchange column, and eluted with dichloromethane, then dichloromethane/methanol (4/1), then dichloromethane/methanol/ammonium hydroxide (20/5/1). The appropriate fractions were concentrated in vacuo, and the residue triturated with ether to give a solid which was filtered and dried under suction to give (**5S**)-6-methoxy-7-(5-oxo-pyrrolidin-2-ylmethoxy)-4-(quinolin-7-yloxy)quinazoline (55mg, 0.13mmol, 43%) as a yellow solid.

¹H NMR Spectrum: d₂ (300MHz, CDCl₃): 2.3-2.5 (4H, m; 2 x pyrrolidinone-CH₃), 4.0-4.1 (4H, m; pyrrolidinone-CH; OCH₃), 4.2-4.3 (2H, m; OCH₃), 6.1 (1H, br s; NH), 7.3 (1H, s; ArH), 7.4 (1H, dd; ArH), 7.5 (1H, dd; ArH), 7.9 (1H, d; ArH), 8.0 (1H, br s; ArH), 8.2 (1H, d; ArH), 8.6 (1H, s; ArH) and 8.9 (1H, dd; ArH)

m/z (ESP+) 417 (MH⁺, 100%)

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**Example 200**

To a solution of 4-chloro-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline (100mg, 0.31mmol), (prepared as described for the starting material in Example 9), in DMF (10ml) was added potassium carbonate (124mg, 0.9mmol, 3eq.) followed by 2-hydroxycarbazole (66mg, 0.36mmol, 1.2eq.) and the reaction heated at 100°C for 4 hours. The DMF was removed in vacuo, the residue dissolved in dichloromethane and placed onto a 2g SCX ion-exchange column. Elution with dichloromethane, followed by 20% methanol/dichloromethane then 20% methanol/dichloromethane + 3% ammonium hydroxide, gave the crude product as a brown solid. Further purification by silica bond elut
chromatography eluting with dichloromethane to 15% methanol/dichloromethane + 1% ammonium hydroxide, followed by trituration with ether gave 4-(9H-carbazol-2-yloxy)-6-methoxy-7-(3-pyrrolidin-1-yl)propoxyquinazoline (31mg, 22%) as a white solid.

$^1$H NMR Spectrum: $d_H$ (300MHz, DMSO-$d_6$) 1.7 (4H, m; 2 x pyrrolidine-CH$_2$), 2.0 (2H, t; OCH$_2$CH$_2$), 2.5 (4H, m; 2 x pyrrolidine-NCH$_2$), 2.6 (2H, t; NCH$_2$), 4.0 (3H, s; OCH$_3$), 4.2 (2H, t; OCH$_2$), 7.1 (1H, br d; ArH), 7.2 (1H, t; ArH), 7.3-7.4 (3H, m; 3 x ArH), 7.5 (1H, br d; ArH), 7.6 (1H, s; ArH), 8.1-8.2 (2H, m; 2 x ArH), 8.5 (1H, s; ArH), 11.3 (1H, s; carbazole NH)

$m/z$ (ESI+) 469 (MH$^+$, 100%)

**Example 201**

To a solution of 7-hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline (98 mg, 0.32 mmol), 2-((N-(3,6-dichloropyridazin-4-yl)-N-methyl)amino)ethanol (107 mg, 0.48 mmol), (prepared as described for the starting material in Example 142), triphenylphosphine (168 mg, 0.64 mmol) in methylene chloride (1 ml) and DMF (0.5 ml) cooled at 4°C was added a solution of diethyl azodicarboxylate (101 µl, 0.64 mmol) in methylene chloride (0.4 ml). The mixture was stirred for 12 hours at 4°C and overnight at ambient temperature. The precipitate was filtered, washed with ether and dried under vacuum to give 7-(2-((N-(3,6-dichloropyridazin-4-yl)-N-methyl)amino)ethoxy)-4-(indol-5-ylamino)-6-methoxyquinazoline (72 mg, 44%).

MS-ESI : 510-512 [MH]$^+$

$^1$H NMR Spectrum: (DMSO-$d_6$) 3.12 (s, 3H); 3.85 (s, 3H); 4.1 (t, 2H); 4.45 (t, 2H); 6.45 (s, 1H); 7.2 (s, 1H); 7.3 (s, 1H); 7.35 (m, 2H); 7.42 (d, 1H); 7.8 (s, 1H); 7.85 (s, 1H); 8.35 (s, 1H); 9.45 (s, 1H)

The starting material was prepared as follows:

A solution of 7-benzylxyloxy-4-chloro-6-methoxyquinazoline (5g, 16.6 mmol), (prepared as described for the starting material in Example 1), 5-aminoindole (2.4 g, 18.2 mmol) in isopropanol (60 ml) containing 5N hydrogen chloride in isopropanol (260 µl, 1.6 mmol) was refluxed for 90 minutes. After cooling the volatiles were removed under vacuum. The solid was triturated with isopropanol, filtered, washed with isopropanol followed by ether and dried
under vacuum to give 7-benzyloxy-4-(indol-5-ylamino)-6-methoxyquinazoline hydrochloride (6.9g, 96%).

H NMR Spectrum: (DMSO$_d_6$) 4.05 (s, 3H); 5.35 (s, 2H); 6.5 (s, 1H); 7.3 (d, 1H); 7.4-7.65 (m, 9H); 7.8 (s, 1H); 8.3 (s, 1H); 8.7 (s, 1H)

A solution of 7-benzyloxy-4-(indol-5-ylamino)-6-methoxyquinazoline hydrochloride (10g, 23.1 mmol) in methanol (300ml) and DMF (100ml) containing ammonium formate (22gr, 347 mmol) and 10% palladium on charcoal (1g) was stirred overnight at ambient temperature. The solution was filtered over celite and washed with DMF followed by methanol. The filtrate was evaporated. The residue was dissolved in aqueous ammonia 2mM (300ml) and stirred for 15 minutes. The solid was filtered, washed with water followed by ethyl acetate and ether and dried under vacuum at 50°C for 2 days. The solid was purified by column chromatography eluting with methanol/methylene chloride (1/9). The volatiles were removed under vacuum and the solid was left under vacuum at 70°C for 2 days to give 7-hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline (6.8 g, 97%)

MS-ESI: 307 [MH]+

H NMR Spectrum: (DMSO$_d_6$) 3.98 (s, 3H); 6.42 (s, 1H); 7.0 (s, 1H); 7.3-7.45 (m, 3H); 7.85 (s, 2H); 8.28 (s, 1H); 9.35 (s, 1H); 10.25 (br s, 1H); 11.05 (s, 1H)

**Examples 202–204**

Using an analogous procedure to that described in Example 201, 7-hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline, (prepared as described for the starting material in Example 201), was used in the synthesis of the compounds described in Table XI.

**Table XI**

<table>
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<th>Yield %</th>
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<th>R</th>
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<td>b</td>
<td>N _methyl-N _pyridyl</td>
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<td></td>
<td></td>
<td></td>
<td>c</td>
<td>N _methyl-N _pyridyl</td>
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a) 7-Hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline was reacted with 2-(N-methyl-N-(4-pyridyl)amino)ethanol (73mg), (EP 0359389), to give 4-(indol-5-ylamino)-6-methoxy-7-(2-(N-methyl-N-(4-pyridyl)amino)ethoxy)quinazoline.

1H NMR Spectrum: (DMSO\_d\_6) 3.08 (s, 3H); 3.9 (t, 2H); 3.95 (s, 3H); 4.35 (t, 2H); 6.45 (s, 1H); 6.75 (d, 2H); 7.15 (s, 1H); 7.35 (m, 2H); 7.4 (d, 1H); 7.85 (s, 1H); 7.9 (s, 1H); 8.15 (d, 2H); 8.38 (s, 1H); 9.45 (s, 1H)

b) 7-Hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline was reacted with 3-hydroxymethyl pyridine (53 mg) to give 4-(indol-5-ylamino)-6-methoxy-7-((3-pyridyl)methoxy)quinazoline.

1H NMR Spectrum: (DMSO\_d\_6) 4.0 (s, 3H); 5.35 (s, 2H); 6.42 (s, 1H); 7.3-7.55 (m, 5H); 7.8-8.0 (m, 3H); 8.4 (s, 1H); 8.6 (d, 1H); 8.75 (s, 1H); 9.5 (s, 1H)

c) 7-Hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline was reacted with 5-(2-hydroxyethyl)-4-methylthiazole (69 mg) to give 4-(indol-5-ylamino)-6-methoxy-7-(2-(4-methyl-1,3-thiazol-5-yl)ethoxy)quinazoline.

1H NMR Spectrum: (DMSO\_d\_6) 2.45 (s, 3H); 3.32 (t, 2H); 3.95 (s, 3H); 4.32 (t, 2H); 6.45 (s, 1H); 7.15 (s, 1H); 7.3-7.45 (m, 3H); 7.85 (s, 1H); 7.9 (s, 1H); 8.35 (s, 1H); 8.85 (s, 1H); 9.45 (s, 1H)

Example 205
To a solution of 7-hydroxy-6-methoxy-4-(2-methylindol-5-ylamino)quinazoline (102 mg, 0.32 mmol), 4-(3-hydroxypropyl)morpholine (70 mg, 0.48 mmol), (prepared as described for the starting material in Example 60), triphenylphosphine (168 mg, 0.64 mmol) in methylene chloride (1 ml) and DMF (0.5 ml) cooled at 4°C was added a solution of diethyl azodicarboxylate (101 μl, 0.64 mmol) in methylene chloride (0.4 ml). The mixture was stirred for 12 hours at 4°C and overnight at ambient temperature. The mixture was poured onto a column of silica (IST isolate ® 10 g of silica) and was eluted with methylene chloride (15 ml) followed by 5% methanol in methylene chloride (45 ml) followed by 5% methanol (saturated with ammonia) in methylene chloride (30 ml) followed by 10% methanol (saturated with ammonia) in methylene chloride (45 ml) followed by 15% methanol (saturated with ammonia) in methylene chloride (30 ml). The fractions containing the expected product were evaporated to give 6-methoxy-4-(2-methylindol-5-ylamino)-7-(3-morpholinopropoxy)quinazoline (63 mg, 44%).

MS-ESI : 448 [MH]^+

^1H NMR Spectrum: (DMSO_d_6) 2.0 (m, 2H); 2.4 (s, 3H); 2.3-2.6 (m, 6H); 3.6 (t, 4H); 3.95 (s, 3H); 4.2 (t, 2H); 6.12 (s, 1H); 7.12 (s, 1H); 7.3 (br s, 2H); 7.7 (s, 1H); 7.85 (s, 1H); 8.35 (s, 1H); 9.4 (s, 1H)

The starting material was prepared as follows:

A solution of 2-methyl-5-nitroindole (1 g, 5.7 mmol) in ethanol (25ml) and THF (25 ml) containing 10% palladium on charcoal (128mg) was hydrogenated until uptake of hydrogen ceased. The mixture was filtered and the filtrate was evaporated to give 5-amino-2-methylindole (830 mg, quant.).

^1H NMR Spectrum: (DMSO_d_6) 2.3 (s, 3H); 4.3 (br s, 2H); 5.8 (s, 1H); 6.35 (d, 1H); 6.55 (s, 1H); 6.95 (d, 1H); 10.35 (br s, 1H)

Using an analogous procedure to that described for the synthesis of the starting material in Example 201, 7-benzzyloxy-4-chloro-6-methoxyquinazoline (2 g, 6.6 mmol), (prepared as described for the starting material in Example 1), was reacted with 5-amino-2-methylindole (1.07g, 7.3 mmol) to give 7-benzzyloxy-6-methoxy-4-(2-methylindol-5-ylamino)quinazoline hydrochloride (2.9 g, quant.).

MS-ESI : 411 [MH]^+
- 228 -

1H NMR Spectrum: (DMSO_d6) 2.41 (s, 3H); 4.01 (s, 3H); 5.33 (s, 2H); 6.18 (s, 1H); 7.25 (d, 1H); 7.3-7.7 (m, 8H); 8.3 (s, 1H); 8.7 (s, 1H); 11.1 (s, 1H); 11.4 (s, 1H)

Using an analogous procedure to that described for the synthesis of the starting material in Example 201, 7-benzylloxy-6-methoxy-4-(2-methylindol-5-ylamino)quinazoline hydrochloride (2.87g, 6.4 mmol) was reacted with ammonium formate (6g, 9.6 mmol) to give 7-hydroxy-6-methoxy-4-(2-methylindol-5-ylamino)quinazoline (1.91g, 93%).

MS-ESI: 321 [MH]^+

1H NMR Spectrum: (DMSO_d6) 2.4 (s, 3H); 3.95 (s, 3H); 6.12 (s, 1H); 7.0 (s, 1H); 7.25 (s, 1H); 7.7 (s, 1H); 7.85 (s, 1H); 8.3 (s, 1H); 9.35 (s, 1H); 10.2 (br s, 1H); 10.9 (s, 1H)

Examples 206–207

Using an analogous procedure to that described for Example 205, 7-hydroxy-6-methoxy-4-(2-methylindol-5-ylamino)quinazoline, (prepared as described for the starting material in Example 205), was used in the synthesis of the compounds described in Table XII.

Table XII

<table>
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<th>Example Number</th>
<th>Weight (mg)</th>
<th>Yield %</th>
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a) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-ylamino)quinazoline (98 mg) was reacted with 3-(1,1-dioxothiomorpholino)-1-propanol (93 mg), (prepared as described for the starting
material in Example 5), to give 7-(3-(1,1-dioxothiomorpholino)propoxy)-6-methoxy-4-(2-methylindol-5-ylamino)quinazoline.

$^1$H NMR Spectrum: (DMSO$_d_6$) 2.0 (m, 2H); 2.4 (s, 3H); 2.7 (t, 2H); 2.95 (m, 4H); 3.15 (m, 4H); 3.95 (s, 3H); 4.2 (t, 2H); 6.15 (s, 1H); 7.18 (s, 1H); 7.28 (m, 2H); 7.7 (s, 1H); 7.85 (s, 1H); 8.35 (s, 1H); 9.4 (s, 1H)

b) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-ylamino)quinazoline (98 mg) was reacted with 1-(2-hydroxyethyl)piperidine (62 mg) to give 6-methoxy-4-(2-methylindol-5-ylamino)-7-(2-piperidinoethoxy)quinazoline.

$^1$H NMR Spectrum: (DMSO$_d_6$) 1.4 (m, 2H); 1.45-1.6 (m, 4H); 2.42 (s, 3H); 2.45 (br s, 4H); 2.75 (t, 2H); 3.95 (s, 3H); 4.25 (t, 2H); 6.15 (s, 1H); 7.15 (s, 1H); 7.25 (br s, 2H); 7.7 (s, 1H); 7.88 (s, 1H); 8.35 (s, 1H); 9.4 (s, 1H)

Example 208

Using an analogous procedure to that described in Example 205, 7-hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline (98 mg, 0.32 mmol), (prepared as described for the starting material in Example 201), was reacted with 3-(1,2,3-triazol-1-yl)propan-1-ol (61 mg, 0.48 mmol) to give 4-(indol-5-ylamino)-6-methoxy-7-(3-(1,2,3-triazol-1-yl)propoxy)quinazoline (56 mg, 42%).

MS-ESI : 416 [MH]$^+$

$^1$H NMR Spectrum: (DMSO$_d_6$) 2.4 (m, 2H); 4.0 (s, 3H); 4.2 (t, 2H); 4.65 (t, 2H); 6.45 (s, 1H); 7.15 (s, 1H); 7.35 (m, 2H); 7.42 (d, 1H); 7.75 (s, 1H); 7.88 (s, 1H); 7.9 (s, 1H); 8.2 (s, 1H); 8.38 (s, 1H); 9.42 (s, 1H)

The starting material was prepared as follows:

A mixture of 1,2,3-triazole (5g, 72.4 mmol) and ethyl acrylate (7.8 ml, 72.4 mmol) containing pyridine (50 drops) was heated at 90$^\circ$C for 4 hours. After cooling, the volatiles were removed under vacuum and the residue was purified by column chromatography eluting with methylene chloride/ether to give ethyl (1H-1,2,3-triazol-1-yl)propanoate (8.96g, 73%).

$^1$H NMR Spectrum: (CDCl$_3$) 1.25 (t, 3H); 2.95 (t, 2H); 4.15 (q, 2H); 4.7 (t, 2H); 7.65 (s, 1H); 7.7 (s, 1H)
A solution of ethyl (1H-1,2,3-triazol-1-yl)propanoate (8.96g, 53 mmol) in THF (50ml) was added dropwise to a suspension of lithium aluminium hydride (3 g, 79 mmol) in THF (250ml) cooled at 0°C. After stirring for 1 hour at 5°C, the mixture was stirred for 1 hour at ambient temperature. The mixture was cooled at 0°C and 4N sodium hydroxide (30ml) was added dropwise. The mixture was filtered and the solid was washed with THF followed by ethyl acetate. The filtrate was dried (MgSO₄) and evaporated. The residue was purified by column chromatography, eluting with methylene chloride/methanol (94/6) to give 3-(1,2,3-triazol-1-yl)propan-1-ol (6.2 g, 92%).

^1H NMR Spectrum: (CDCl₃) : 2.1-2.2 (m, 3H); 3.65 (m, 2H); 4.6 (t, 2H); 7.6 (s, 1H); 7.72 (s, 1H)

**Examples 209–216**

Using an analogous procedure to that described in Example 208, 7-hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline, (prepared as described for the starting material in Example 201), was used in the synthesis of the compounds described in Table XIII.

**Table XIII**

<table>
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<tr>
<th>Example Number</th>
<th>Weight (mg)</th>
<th>Yield %</th>
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</tbody>
</table>
a) 7-Hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 2-(N-(2-methoxethyl)-N-methylamino)ethanol (64 mg), (prepared as described for the starting material in Example 59), to give 4-(indol-5-ylamino)-6-methoxy-7-(2-(N-(2-methoxethyl)-N-methylamino)ethoxy)quinazoline.

1H NMR Spectrum: (DMSOD$_6$) 2.35 (s, 3H); 2.68 (t, 2H); 2.82 (t, 2H); 3.25 (s, 3H); 3.5 (t, 2H); 3.97 (s, 3H); 4.22 (t, 2H); 6.45 (s, 1H); 7.18 (s, 1H); 7.3-7.45 (m, 3H); 7.88 (m, 2H); 8.35 (s, 1H); 9.42 (s, 1H)

b) 7-Hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 1-(3-hydroxypropyl)pyrrolidin-2,5-dione (76 mg) to give 7-(3-(2,5-dioxopyrrolidin-1-yl)propoxy)-4-(indol-5-ylamino)-6-methoxyquinazoline.

1H NMR Spectrum: (DMSOD$_6$) 2.05 (m, 2H); 2.65 (s, 3H); 3.6 (t, 2H); 3.98 (s, 2H); 4.15 (t, 2H); 6.45 (s, 1H); 7.1 (s, 1H); 7.3-7.45 (m, 3H); 8.7 (s, 1H); 8.8 (s, 1H); 8.35 (s, 1H); 9.45 (s, 1H)
The starting material was prepared as follows:

A solution of pyrrolidine-2,5-dione (5g, 50.5 mmol) and 3-bromopropan-1-ol (6.85 ml, 76 mmol) in acetonitrile (80ml) containing potassium carbonate (14g, 100 mmol) was refluxed overnight. After cooling, the mixture was filtered and the filtrate was evaporated. The residue was dissolved in methylene chloride and purified by column chromatography, eluting with ethylacetate/petroleum ether (4/1). After evaporation of the volatiles, the residue was distilled at 100-125°C under about 0.1 mm Hg to give 1-(3-hydroxypropyl)pyrrolidin-2,5-dione (2.6 g, 34%).

1H NMR Spectrum: (CDCl₃) 1.8 (m, 2H); 2.52 (t, 1H); 2.78 (s, 4H); 3.58 (q, 2H); 3.7 (t, 2H)

c) 7-Hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 3-(1,1-dioxothiomorpholino)-1-propanol (93mg), (prepared as described for the starting material in Example 5), to give 7-(3-(1,1-dioxothiomorpholino)propoxy)-4-(indol-5-ylamino)-6-methoxyquinazoline.

1H NMR Spectrum: (DMSO_d₆) 2.0 (m, 2H); 2.7 (t, 2H); 2.95 (br s, 4H); 3.15 (br s, 4H); 3.97 (s, 3H); 4.2 (t, 2H); 6.45 (s, 1H); 7.2 (s, 1H); 7.3-7.5 (m, 3H); 7.9 (2s, 2H); 8.35 (s, 1H); 9.42 (s, 1H)

d) 7-Hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 3-((4-methyl-4H-1,2,4-triazol-3-yl)sulphanyl)propan-1-ol (83 mg) to give 4-(indol-5-ylamino)-6-methoxy-7-(3-((4-methyl-4H-1,2,4-triazol-3-yl)sulphanyl)propoxy)quinazoline.

1H NMR Spectrum: (DMSO_d₆) 2.22 (m, 2H); 3.3 (m, 2H); 3.65 (s, 3H); 3.95 (s, 3H); 4.25 (t, 2H); 6.45 (s, 1H); 7.15 (s, 1H); 7.3-7.45 (m, 3H); 7.88 (s, 1H); 8.0 (s, 1H); 8.35 (s, 1H); 8.58 (s, 1H); 9.45 (s, 1H)

The starting material was prepared as follows:

A solution of 4-methyl-4H-1,2,4-triazole-3-thiol (1.72g, 15 mmol) and 3-bromopropan-1-ol (1.39g, 10 mmol) in DMF (10ml) containing potassium carbonate (1.57g, 14 mmol) was heated at 40°C for 30 minutes. The mixture was then partitioned between saturated ammonium chloride and ethyl acetate. The aqueous layer was evaporated to dryness and the residue was triturated with ethyl acetate and methylene chloride. The suspension was
filtered and the filtrate was dried (MgSO₄) and evaporated. The residue was purified by column chromatography eluting with methylene chloride/methanol (9/1) to give 3-((4-methyl-4H-1,2,4-triazol-3-yl)sulphanyland)propan-1-ol (510mg, 30%).

1H NMR Spectrum: (CDCl₃) 2.02 (m, 2H); 3.45 (t, 2H); 3.55 (s, 3H); 3.75 (t, 2H); 8.15 (s, 1H)

e) 7-Hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 1-(3-hydroxypropyl)-4-methylpiperazine (76 mg), (prepared as described for the starting material in Example 133), to give 4-(indol-5-ylamino)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline.

1H NMR Spectrum: (DMSO-d₆) 2.0 (m, 2H); 2.2 (s, 3H); 2.25-2.55 (m, 10H); 4.0 (s, 3H); 4.2 (t, 2H); 6.45 (s, 1H); 7.15 (s, 1H); 7.35 (m, 2H); 7.42 (d, 1H); 7.88 (br s, 2H); 8.38 (s, 1H); 9.42 (s, 1H)

f) 7-Hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 2-methoxyethanol (37 mg) to give 4-(indol-5-ylamino)-6-methoxy-7-(2-methoxyethoxy)quinazoline.

1H NMR Spectrum: (DMSO-d₆) 3.4 (s, 3H); 3.75 (t, 2H); 3.98 (s, 3H); 4.38 (t, 2H); 6.45 (s, 1H); 7.18 (s, 1H); 7.35 (m, 2H); 7.42 (d, 1H); 7.85 (s, 1H); 7.9 (s, 1H); 8.38 (s, 1H); 9.5 (s, 1H)

g) 7-Hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 2-(2-methoxyethoxy)ethanol (58 mg) to give 4-(indol-5-ylamino)-6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)quinazoline.

1H NMR Spectrum: (DMSO-d₆) 3.3 (s, 3H); 3.5 (t, 2H); 3.65 (t, 2H); 3.85 (t, 2H); 4.0 (s, 3H); 4.28 (t, 2H); 6.45 (s, 1H); 7.18 (s, 1H); 7.35 (m, 2H); 7.45 (d, 1H); 7.88 (s, 1H); 7.9 (s, 1H); 8.35 (s, 1H); 9.45 (s, 1H)

h) 7-Hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 1-(2-hydroxyethyl)piperidine (62 mg) to give 4-(indol-5-ylamino)-6-methoxy-7-(2-piperidinoethoxy)quinazoline.
Example 217-223

Using an analogous procedure to that described in Example 205, 7-hydroxy-4-(indol-6-ylamino)-6-methoxyquinazoline was used in the synthesis of the compounds described in Table XIV.

The starting material was prepared as follows:

Using an analogous procedure to that described for the preparation of the starting material in Example 201, 6-nitroindole (500mg, 3 mmol) was hydrogenated to give 6-aminooindole (395mg, quant.).

\[ \text{\textsuperscript{1H} NMR Spectrum: (DMSO\textsubscript{d6}) 6.41 (s, 1H); 6.6 (dd, 1H); 6.63 (s, 1H); 7.0 (t, 1H); 7.4 (d, 1H); 7.87 (br s, 1H)} \]

Using an analogous procedure to that described for the preparation of the starting material in Example 201, 7-benzylxoy-4-chloro-6-methoxyquinazoline (2.5 g, 8.3 mmol), (prepared as described for the starting material in Example 1), was reacted with 6-aminooindole (1.5g, 11.4 mmol) to give 7-benzylxoy-4-(indol-6-ylamino)-6-methoxyquinazoline hydrochloride (3.18g, 89%).

MS-ESI: 397 [MH]+

\[ \text{\textsuperscript{1H} NMR Spectrum: (DMSO\textsubscript{d6}) 4.02 (s, 3H); 5.35 (s, 2H); 6.5 (s, 1H); 7.25 (dd, 1H); 7.35-7.6 (m, 5H); 7.63 (d, 1H); 7.72 (s, 1H); 8.3 (s, 1H); 8.75 (s, 1H); 11.3 (br s, 1H)} \]

Using an analogous procedure to that described for the preparation of the starting material in Example 201, 7-benzylxoy-4-(indol-6-ylamino)-6-methoxyquinazoline hydrochloride was treated with ammonium formate (655mg, 10.4 mmol) to give 7-hydroxy-4-(indol-6-ylamino)-6-methoxyquinazoline (162 mg, 76%).

MS-ESI: 307 [MH]+

\[ \text{\textsuperscript{1H} NMR Spectrum: (DMSO\textsubscript{d6}) 4.0 (s, 3H); 6.4 (s, 1H); 7.0 (s, 1H); 7.3 (m, 2H); 7.5 (d, 1H); 7.85 (s, 1H); 8.0 (s, 1H); 8.35 (s, 1H); 9.35 (s, 1H); 11.05 (s, 1H)} \]
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<th>Yield %</th>
<th>MS-ESI [MH]^+</th>
<th>Note</th>
<th>R</th>
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</tbody>
</table>
-236-

a) 7-Hydroxy-4-(indol-6-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 3-(1,2,3-triazol-1-yl)propan-1-ol (61 mg), (prepared as described for the starting material in Example 208), to give **4-(indol-6-ylamino)-6-methoxy-7-(3-(1,2,3-triazol-1-yl)propoxy)quinazoline**.

\[ \text{\textsuperscript{1}H NMR Spectrum: (DMSO)}_d_{6} 2.42 (t, 2H); 4.02 (s, 3H); 4.2 (t, 2H); 4.62 (t, 2H); 6.42 (s, 1H); 7.15 (s, 1H); 7.3 (m, 2H); 7.55 (d, 1H); 7.75 (s, 1H); 7.92 (s, 1H); 8.02 (s, 1H); 8.2 (s, 1H); 8.42 (s, 1H); 9.45 (s, 1H) \]

b) 7-Hydroxy-4-(indol-6-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 3-(1,1-dioxothiomorpholino)-1-propanol (93 mg), (prepared as described for the starting material in Example 5), to give **7-(3-(1,1-dioxothiomorpholino)propoxy)-4-(indol-6-ylamino)-6-methoxyquinazoline**.

\[ \text{\textsuperscript{1}H NMR Spectrum: (DMSO)}_d_{6} 2.0 (m, 2H); 2.7 (t, 2H); 2.95 (br s, 4H); 3.12 (br s, 4H); 4.0 (s, 3H); 4.2 (t, 2H); 6.42 (s, 1H); 7.2 (s, 1H); 7.3 (m, 2H); 7.55 (d, 1H); 7.9 (s, 1H); 8.02 (s, 1H); 8.42 (s, 1H); 9.48 (s, 1H) \]

c) 7-Hydroxy-4-(indol-6-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 3-((4-methyl-4H-1,2,4-triazol-3-yl)sulphanyl)propan-1-ol (83 mg), (prepared as described for the starting material in Example 212), to give **4-(indol-6-ylamino)-6-methoxy-7-(3-((4-methyl-4H-1,2,4-triazol-3-yl)sulphanyl)propoxy)quinazoline**.

\[ \text{\textsuperscript{1}H NMR Spectrum: (DMSO)}_d_{6} 2.22 (t, 2H); 3.3 (t, 2H); 3.6 (s, 3H); 4.0 (s, 3H); 4.28 (t, 2H); 6.4 (s, 1H); 7.18 (s, 1H); 7.3 (m, 2H); 7.53 (d, 1H); 7.9 (s, 1H); 8.02 (s, 1H); 8.42 (s, 1H); 8.58 (s, 1H); 9.45 (s, 1H) \]

d) 7-Hydroxy-4-(indol-6-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 1-(2-hydroxyethyl)piperidine (62 mg) to give **4-(indol-6-ylamino)-6-methoxy-7-(2-piperidinoethoxy)quinazoline**.

\[ \text{\textsuperscript{1}H NMR Spectrum: (DMSO)}_d_{6} 1.3-1.6 (m, 6H); 2.5 (br s, 4H); 2.75 (t, 2H); 4.0 (s, 3H); 4.25 (t, 2H); 6.42 (s, 1H); 7.2 (s, 1H); 7.3 (m, 2H); 7.55 (d, 1H); 7.9 (s, 1H); 8.02 (s, 1H); 8.42 (s, 1H); 9.45 (s, 1H) \]
e) 7-Hydroxy-4-(indol-6-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 1-(3-hydroxypropyl)pyrrolidine (62 mg) to give 4-(indol-6-ylamino)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline.

The starting material was prepared as follows:

A solution of pyrrolidine (50 g, 0.7 mol) and 3-chloropropan-1-ol (66.15 g, 0.7 mol) in acetonitrile (1 l) containing potassium carbonate (145 g, 1.05 mol) was refluxed for 20 hours. After cooling, the mixture was filtered, the solid was washed with acetonitrile and the filtrate was evaporated. The residue was distilled at about 130°C under about 70 mmHg to give 1-(3-hydroxypropyl)pyrrolidine (62.1 g, 69%).

MS-ESI : 130 [MH]+

1H NMR Spectrum: (CDCl₃) 1.6-1.8 (m, 6H); 2.55 (br s, 4H); 2.75 (t, 2H); 3.85 (t, 2H); 5.2-5.8 (br s, 1H)

f) 7-Hydroxy-4-(indol-6-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 3-((N-(2,6-dimethyl-4-pyridyl)-N-methyl)amino)propan-1-ol (93 mg) to give 7-(3-(N-(2,6-dimethyl-4-pyridyl)-N-methyl)amino)propoxy)-4-(indol-6-ylamino)-6-methoxyquinazoline.

1H NMR Spectrum: (DMSOd₆) 2.08 (m, 2H); 2.22 (s, 6H); 2.95 (s, 3H); 3.6 (t, 2H); 4.05 (s, 3H); 4.15 (t, 2H); 6.35 (s, 2H); 6.42 (s, 1H); 7.15 (s, 1H); 7.3 (m, 2H); 7.55 (d, 1H); 7.92 (s, 1H); 8.02 (s, 1H); 8.4 (s, 1H); 9.45 (s, 1H)

The starting material was prepared as follows:

A solution of 4-chloro-2,6-dimethylpyridine (2.12 g, 15 mmol) and 3-(N-methylamino)-propan-1-ol (4g, 45 mmol) containing 2N hydrogen chloride in ether (10 drops) was heated at 140°C for 1 hour. The mixture was diluted with water (10ml) and poured onto a suspension of MgSO₄ (125g) in ethyl acetate (200ml). The mixture was filtered. The filtrate was evaporated and the residue was triturated with ether. The solid was filtered and dried under vacuum to give 3-((N-(2,6-dimethyl-4-pyridyl)-N-methyl)amino)propan-1-ol (1.76 g, 61%).

MS-El : 194 [M.]+

1H NMR Spectrum: (CDCl₃) 1.75-1.95 (m, 2H); 2.4 (s, 6H); 3.0 (s, 3H); 3.48 (t, 2H); 3.7 (t, 2H); 6.25 (s, 2H)
g) 7-Hydroxy-4-(indol-6-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 3-hydroxymethyl pyridine (53 mg) to give 4-(indol-6-ylamino)-6-methoxy-7-(3-pyridyl)methoxy)quinazoline.

\[ 1^H \text{NMR Spectrum: } (\text{DMSO}_d_6) \begin{align*}
4.02 & (s, 3H) ; \\
5.35 & (s, 2H) ; \\
6.42 & (s, 1H) ; \\
7.22-7.4 & (m, 3H) ; \\
7.5 & (m, 1H) ; \\
7.55 & (d, 1H) ; \\
7.95 & (s, 1H) ; \\
7.97 & (d, 1H) ; \\
8.0 & (s, 1H) ; \\
8.42 & (s, 1H) ; \\
8.6 & (d, 1H) ; \\
8.78 & (s, 1H) ; \\
9.5 & (s, 1H)
\end{align*} \]

**Example 224**

Using an analogous procedure to that described in Example 208, 7-hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline (98 mg, 0.32 mmol), (prepared as described for the starting material in Example 201), was reacted with (E)-4-(pyrrolidin-1-yl)but-2-en-1-ol (68 mg, 0.48 mmol), (prepared as described for the starting material in Example 129). After evaporation of the fractions containing the expected product, the residue was triturated with isopropanol (1 ml) containing 6.2 N hydrogen chloride in isopropanol (100 μl). After stirring at ambient temperature for 10 minutes, ether (500 μl) was added. The precipitate was filtered and washed several times with ether to give 4-(indol-5-ylamino)-6-methoxy-7-(E)-4-(pyrrolidin-1-yl)but-2-en-1-yloxy)quinazoline hydrochloride (14 mg, 10 %).

\[ 1^H \text{NMR Spectrum: } (\text{DMSO}_d_6) \begin{align*}
1.85-2.7 & (br s, 4H) ; \\
2.95-3.1 & (br s, 2H) ; \\
3.0 & (m, 2H) ; \\
3.4-3.5 & (m, 2H) ; \\
3.8 & (d, 2H) ; \\
4.0 & (s, 3H) ; \\
4.8 & (d, 2H) ; \\
6.0-6.3 & (m, 2H) ; \\
6.5 & (s, 1H) ; \\
7.2-7.53 & (m, 4H) ; \\
7.75 & (s, 1H) ; \\
8.25 & (s, 1H) ; \\
8.8 & (br s, 1H)
\end{align*} \]

**Example 225**

7-Hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline, (prepared as described for the starting material in Example 201), was treated as follows. After purification by chromatography and evaporation of the solvent, the residue was triturated in a solution of isopropanol (1 ml) containing 6.2 N hydrogen chloride in isopropanol (100 μl). After stirring for 10 minutes at ambient temperature, ether (500 μl) was added. The solid was filtered and dried under vacuum to give 7-hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline hydrochloride.
Using an analogous procedure to that described in Example 224, 7-hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline hydrochloride was used in the synthesis of the compounds described in Table XV.

**Table XV**

<table>
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<th>Example Number</th>
<th>Weight (mg)</th>
<th>Yield %</th>
<th>MS-ESI [MH]⁺</th>
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</table>

a) 7-Hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline hydrochloride (98 mg) was reacted with 3-((N-(2,6-dimethyl-4-pyridyl)-N-methyl)amino)propan-1-ol (93mg), (prepared as described for the starting material in Example 222), to give 7-(3-((N-(2,6-dimethyl-4-pyridyl)-N-methyl)amino)propoxy)-4-(indol-5-ylamino)-6-methoxyquinazoline.

\(^1\)H NMR Spectrum: (DMSOd₆) 2.2 (m, 2H); 2.5 (2br s, 6H); 3.2 (s, 3H); 3.8 (t, 2H); 4.1 (s, 3H); 4.25 (t, 2H); 6.52 (s, 1H); 6.75 (br s, 1H); 6.9 (br s, 1H); 7.35 (dd, 1H); 7.45 (br s, 2H); 7.5 (d, 1H); 7.8 (s, 1H); 8.4 (s, 1H); 8.75 (s, 1H)

**Example 226**

Using an analogous procedure to that described in Example 224, 7-hydroxy-4-(indol-6-ylamino)-6-methoxyquinazoline, (prepared as described for the starting material in Example 217), (98 mg, 0.32 mmol) was reacted with 4-(3-hydroxypropyl)morpholine (70 mg, 0.48 mmol), (prepared as described for the starting material in Example 60), to give 4-(indol-6-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline hydrochloride (26 mg, 19%). MS-ESI : 434 [MH]⁺
\textbf{Examples 227–229}

Using an analogous procedure to that described in Example 226, 7-hydroxy-4-(indol-6-ylamino)-6-methoxyquinazoline, (prepared as described for the starting material in Example 217), was used in the synthesis of the compounds described in Table XVI.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
Example number & Weight (mg) & Yield % & MS-ESI [MH]\textsuperscript{+} & Note & R \\
\hline
227 & 24 & 17 & 441 & a & \includegraphics[width=1cm]{example227}
\hline
228 & 14 & 10 & 430 & b & \includegraphics[width=1cm]{example228}
\hline
229 & 15 & 10 & 447 & c & \includegraphics[width=1cm]{example229}
\hline
\end{tabular}
\end{table}

a) 7-Hydroxy-4-(indol-6-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 2-((N-methyl-N-(4-pyridyl))amino)ethanol (73 mg), (EP 0359389A1), to give \textbf{4-(indol-6-ylamino)-6-methoxy-7-(2-((N-methyl-N-(4-pyridyl))amino)ethoxy)quinazoline hydrochloride}. 
b) 7-Hydroxy-4-(indol-6-ylamino)-6-methoxyquinazoline (98 mg) was reacted with (E)-4-(pyrrolidin-1-yl)but-2-en-1-ol (68 mg, 0.48 mmol), (prepared as described for the starting material in Example 129) to give 4-(indol-6-ylamino)-6-methoxy-7-(E)-4-(pyrrolidin-1-yl)but-2-en-1-yl)oxo)quinazoline hydrochloride.

\[^1\text{H} \text{NMR Spectrum: (DMSO}_d_6) 1.8-2.1 (m, 4H); 2.9-3.1 (m, 2H); 3.4-3.5 (br s, 2H); 3.87 (d, 2H); 4.05 (s, 3H); 4.9 (d, 2H); 6.1 (m, 1H); 6.3 (m, 1H); 6.5 (s, 1H); 7.25 (d, 1H); 7.45 (m, 2H); 7.65 (d, 1H); 7.75 (s, 1H); 8.3 (s, 1H); 8.8 (s, 1H)\]

c) 7-Hydroxy-4-(indol-6-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 1-(3-hydroxypropyl)-4-methylpiperazine (76 mg), (prepared as described for the starting material in Example 133), to give 4-(indol-6-ylamino)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline hydrochloride.

**Example 230**

Using an analogous procedure to that described in Example 224, 7-hydroxy-6-methoxy-4-(2-methylindol-5-ylamino)quinazoline (102 mg, 0.32 mmol), (prepared as described for the starting material in Example 205), was reacted with 1-(3-hydroxypropyl)-2-methylimidazole (67 mg, 0.48 mmol), (EP 0060696 A1), to give 6-methoxy-7-(3-(2-methylimidazol-1-yl)propoxy)-4-(2-methylindol-5-ylamino)quinazoline (53 mg, 37%).

MS-ESI : 443 [MH]^+

\[^1\text{H} \text{NMR Spectrum: (DMSO}_d_6) 2.42 (s, 3H); 2.62 (s, 3H); 4.03 (s, 3H); 4.3 (t, 2H); 4.35 (t, 2H); 6.2 (s, 1H); 7.22 (d, 1H); 7.35 (d, 1H); 7.45 (s, 1H); 7.6 (dd, 1H); 7.65 (dd, 1H); 7.7 (s, 1H); 8.35 (s, 1H); 8.75 (s, 1H)\]

**Examples 231–235**

Using an analogous procedure to that described in Example 224, 7-hydroxy-6-methoxy-4-(2-methylindol-5-ylamino)quinazoline (102 mg, 0.32 mmol), (prepared as
described for the starting material in Example 205), was used in the synthesis of the compounds described in Table XVII.

**Table XVII**

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<th>Weight (mg)</th>
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<td>18</td>
<td>444</td>
<td>b</td>
<td></td>
</tr>
<tr>
<td>233</td>
<td>23</td>
<td>15</td>
<td>476</td>
<td>c</td>
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</tr>
<tr>
<td>234</td>
<td>33</td>
<td>22</td>
<td>461</td>
<td>d</td>
<td></td>
</tr>
<tr>
<td>235</td>
<td>26</td>
<td>19</td>
<td>423</td>
<td>e</td>
<td>MeO--O--Me</td>
</tr>
</tbody>
</table>

a) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-ylamino)quinazoline (102 mg) was reacted with 3-((N-(2,6-dimethyl-4-pyridyl)-N-methyl)amino)propan-1-ol (93 mg), (prepared as described for the starting material in Example 222), to give 7-(3-((N-(2,6-dimethyl-4-pyridyl)-N-methyl)amino)propoxy)-6-methoxy-4-(2-methylindol-5-ylamino)quinazoline.
b) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-ylamino)quinazoline (102 mg) was reacted with (E)-4-(pyrrolidin-1-yl)but-2-en-1-ol (68 mg, 0.48 mmol), (prepared as described for the starting material in Example 129) to give 6-methoxy-4-(2-methylindol-5-ylamino)-7-((E)-4-(pyrrolidin-1-yl)but-2-en-1-yl)oxy)quinazoline.

\[ \text{H NMR Spectrum: (DMSO$_d_6$) 2.2 (m, 2H); 2.4 (s, 6H); 2.45 (s, 3H); 3.15 (s, 3H); 3.75 (t, 2H); 4.02 (s, 3H); 4.25 (t, 2H); 6.2 (s, 1H); 6.72 (br s, 1H); 6.85 (br s, 1H); 7.2 (dd, 1H); 7.3-7.4 (m, 2H); 7.62 (s, 1H); 8.3 (s, 1H); 8.7 (s, 1H).} \]

c) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-ylamino)quinazoline (102 mg) was reacted with 3-((4-methyl-4H-1,2,4-triazol-3-yl)sulphanyl)propan-1-ol (83 mg), (prepared as described for the starting material in Example 212), to give 6-methoxy-4-(2-methylindol-5-ylamino)-7-((4-methyl-4H-1,2,4-triazol-3-yl)sulphanyl)propoxy)quinazoline.

\[ \text{H NMR Spectrum: (DMSO$_d_6$) 2.25 (m, 2H); 2.45 (s, 3H); 3.35 (t, 2H); 3.65 (s, 3H); 4.05 (s, 3H); 4.35 (t, 2H); 6.2 (s, 1H); 7.2 (d, 1H); 7.35 (s, 1H); 7.37 (d, 1H); 7.62 (s, 1H); 8.25 (s, 1H); 8.75 (s, 1H); 8.9 (s, 1H).} \]

d) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-ylamino)quinazoline (102 mg) was reacted with 1-(3-hydroxypropyl)-4-methylpiperazine (76 mg), (prepared as described for the starting material in Example 133), to give 6-methoxy-4-(2-methylindol-5-ylamino)-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline.

e) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-ylamino)quinazoline (102 mg) was reacted with 2-(2-methoxyethoxy)ethanol to give 6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-4-(2-methylindol-5-ylamino)quinazoline.

\[ \text{H NMR Spectrum: (DMSO$_d_6$) 2.45 (s, 3H); 3.28 (s, 3H); 3.5 (t, 2H); 3.65 (t, 2H); 3.9 (t, 2H); 4.02 (s, 3H); 4.33 (t, 2H); 6.2 (s, 1H); 7.2 (d, 1H); 7.4 (m, 2H); 7.63 (s, 1H); 8.28 (s, 1H); 8.73 (s, 1H).} \]
Example 236

A solution of 4-chloro-6-methoxy-7-((1-cyanomethyl)piperidin-4-yl)methoxy)quinazoline (200 mg, 0.58 mmol) and 5-hydroxyindole (85 mg, 0.63 mmol) in DMF (3 ml) containing cesium carbonate (282 mg, 0.86 mmol) was stirred at 90°C for 90 minutes. After cooling, the mixture was poured onto water (25 ml). The precipitate was filtered, dried under vacuum and purified by reverse phase column chromatography on silica (kromasil ® C18) eluting with methanol/water (1 % acetic acid) (1/1). The fractions containing the expected product were combined and evaporated to give 7-((1-cyanomethyl)piperidin-4-ylmethoxy)-4-(indol-5-yl oxy)-6-methoxyquinazoline (44 mg, 17 %).

MS-ESI : 444 [MH]+

1H NMR Spectrum: (DMSO-d6, CF3COOD) 1.7 (m, 2H); 2.15 (d, 2H); 2.2-2.35 (m, 1H); 3.20 (t, 2H); 3.65 (d, 2H); 4.1 (s, 3H); 4.25 (d, 2H); 4.62 (s, 2H); 6.5 (s, 0.5 H, partly exchanged); 7.1 (dd, 1H); 7.5 (s, 1H); 7.5-7.6 (m, 3H); 7.85 (s, 1H); 9.1 (s, 1H)

The starting material was prepared as follows:

To a suspension of 6-methoxy-7-(piperidin-4-ylmethoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one hydrochloride (34 g, 84 mmol), (prepared as described for the starting material in Example 12), in water cooled at 0°C was added 1N sodium hydroxide until the mixture was at pH8. The solution was extracted with trichloromethane and the organic layer was dried (MgSO4), filtered and evaporated to give 6-methoxy-7-(piperidin-4-ylmethoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (29g).

To a solution of 6-methoxy-7-(piperidin-4-ylmethoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (28.9 g, 72 mmol) and aqueous formaldehyde 12 M (11.95 ml, 141 mmol) in methanol/THF (1/1) (580 ml) was added sodium cyanoborohydride (5.7 g, 86 mmol) in portions. After stirring for 90 minutes at ambient temperature, the volatiles were removed under vacuum and the residue was partitioned between methylene chloride and water. The organic layer was separated, dried (MgSO4) and evaporated. The residue was dissolved in methanol saturated with ammonia (500 ml). The mixture was stirred for 36 hours at ambient temperature. The volatiles were removed under vacuum. The residue was triturated with a mixture ether/methylene chloride, filtered, washed with ether and dried under vacuum. The solid was dissolved in thionyl chloride (180 ml) and DMF (1.8 ml) was added.
After stirring at 80°C for 75 minutes the volatiles were removed under vacuum. The residue was azeotroped with toluene twice and the solid was partitioned between methylene chloride and water and the pH of the aqueous layer was adjusted to 9 with 2N sodium hydroxide. The organic layer was dried (MgSO₄) and evaporated. The residue was purified by column chromatography on aluminium oxide eluting with methylene chloride, followed by methylene chloride/ethyl acetate (70/30 followed by 50/50) followed by ethyl acetate and ethyl acetate/methanol (80/20) to give 4-chloro-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (11.2 g) (identical to the starting material prepared in Example 10) and 4-chloro-6-methoxy-7-((1-(cyanomethyl)piperidin-4-yl)methoxy)quinazoline (2.55 g).

MS-ESI : 347 [MH]+

¹H NMR Spectrum: (DMSO-d₆) 1.42 (m, 2H) ; 1.85 (d, 2H) ; 1.8-1.9 (m, 1H) ; 2.2 (t, 2H) ; 2.85 (d, 2H) ; 3.75 (s, 2H) ; 4.05 (s, 3H) ; 4.15 (d, 2H) ; 7.42 (s, 1H) ; 7.5 (s, 1H) ; 8.9 (s, 1H)

Example 237

A solution of 4-chloro-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (2 gr, 6.22 mmol), (prepared as described for the starting material in Example 10), and 4-fluoro-5-hydroxy-2-methylindole (1.23 g, 7.46 mmol) in DMF (30 ml) containing potassium carbonate (1.28 g, 9.33 mmol) was stirred at 95°C for 2 hours. After cooling, the volatiles were removed under vacuum and the residue was triturated with ether, filtered and dried under vacuum. The residue was purified by column chromatography eluting with methanol/methylene chloride (1/9) followed by methanol/methanol saturated with ammonia/methylene chloride (20/1/79 followed by 20/5/75). The fractions containing the expected product were combined and evaporated. The solid was triturated with methanol, filtered and dried under vacuum to give 4-(4-fluoro-2-methylindol-5-yl)oxy)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (1.95 g, 69 %).

MS-ESI : 451 [MH]+
The starting material was prepared as follows:

To a solution of 2-fluoro-4-nitroanisole (9.9 g, 58 mmol) and 4-chlorophenoxyacetonitrile (10.7 g, 64 mmol) in DMF (50 ml) cooled at -15°C was added potassium tert-butoxide (14.3 g, 127 mmol) in DMF (124 ml). After stirring for 30 minutes at -15°C, the mixture was poured onto cooled 1N hydrochloric acid. The mixture was extracted with ethyl acetate. The organic layer was washed with 1N sodium hydroxide, brine, dried (MgSO₄) and evaporated. The residue was purified by column chromatography eluting with methylene chloride. The fractions containing the expected product were combined and evaporated. The residue was dissolved in ethanol (180 ml) and acetic acid (24 ml) containing 10 % palladium on charcoal (600 mg) and the mixture was hydrogenated under 3 atmospheres pressure for 2 hours. The mixture was filtered, and the volatiles were removed under vacuum. The residue was partitioned between ethyl acetate and water. The organic layer was separated, and washed with saturated sodium hydrogen carbonate followed by brine, dried (MgSO₄) and evaporated. The residue was purified by column chromatography eluting with methylene chloride to give a mixture of 4-fluoro-5-methoxyindole and 6-fluoro-5-methoxyindole (5.64 g, 59 %) in a ratio 1/2.

1H NMR Spectrum: (DMSOd₆) 3.85 (s, 3H); 6.38 (s, 1H, 6-Fluoro); 6.45 (s, 1H; 4-Fluoro); 6.9-7.4 (m, 3H)

A solution of 4-fluoro-5-methoxyindole and 6-fluoro-5-methoxyindole in a ratio 1/2 (496 mg, 3 mmol), di-tertbutyl dicarbonate (720 mg, 3.3 mmol) in acetonitrile (12 ml) containing DMAP (18 mg, 0.15 mmol) was stirred at ambient temperature for 24 hours. The volatiles were removed under vacuum. The residue was dissolved in ethyl acetate, washed with 1N hydrochloric acid, followed by water, brine, dried (MgSO₄) and evaporated to give a mixture of 4-fluoro-5-methoxy-1-tert-butoxycarbonylindole and 6-fluoro-5-methoxy-1-tert-butoxycarbonylindole in a ratio 1/2 (702 mg, 88 %).
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1H NMR Spectrum: (DMSO$_d_6$) 1.65 (s, 9H); 3.9 (s, 3H); 6.6 (d, 1H, 6-fluoro); 6.72 (d, 1H, 4-fluoro); 7.2 (t, 1H, 6-fluoro); 7.4 (d, 1H, 4-fluoro); 7.62 (d, 1H, 6-fluoro); 7.68 (d, 1H, 4-fluoro); 7.78 (s, 1H, 4-fluoro); 7.85 (s, 1H, 6-fluoro)

To a solution of 4-fluoro-5-methoxy-1-tert-butoxycarbonylindole and 6-fluoro-5-methoxy-1-tert-butoxycarbonylindole in a ratio 1/2 (8.1 g, 30.5 mmol) in THF (100 ml) cooled at -65°C was added tert-butyllithium (1.7 M) (23 ml, 35.7 mmol). After stirring for 4 hours at -70°C, methyl iodide (8.66 g, 61 mmol) was added and the mixture was left to warm-up to ambient temperature. Water was added and the mixture was extracted with ether. The organic layer was washed with water, brine, dried (MgSO$_4$) and evaporated and was used directly in the next step.

The crude product was dissolved in methylene chloride (100 ml) and TFA (25 ml) was added. After stirring for 1 hour at ambient temperature, the volatiles were removed under vacuum. The residue was dissolved in ethyl acetate and the organic layer was washed with 1N sodium hydroxide, followed by water, brine, dried (MgSO$_4$) and evaporated. The residue was purified by column chromatography, eluting with ethyl acetate/petroleum ether (3/7) to give 6-fluoro-5-methoxy-2-methylindole (1.6 g) and 4-fluoro-5-methoxy-2-methylindole (0.8 g, 48%).

6-fluoro-5-methoxy-2-methylindole:
MS-ESI : 180 [MH]$^+$

1H NMR Spectrum: (DMSO$_d_6$) 2.35 (s, 3H); 3.8 (s, 3H); 6.05 (s, 1H); 7.1 (s, 1H); 7.12 (s, 1H); 10.8 (s, 1H)

4-fluoro-5-methoxy-2-methylindole:
MS-ESI : 180 [MH]$^+$

1H NMR Spectrum: (DMSO$_d_6$) 2.35 (s, 3H); 3.8 (s, 3H); 6.15 (s, 1H); 6.9 (t, 1H); 7.05 (d, 1H); 11.0 (s, 1H)

To a solution of 4-fluoro-5-methoxy-2-methylindole (709 mg, 3.95 mmol) in methylene chloride (9 ml) cooled at -30°C was added a solution of boron tribromide (2.18 g, 8.7 mmol) in methylene chloride (1 ml). After stirring for 1 hour at ambient temperature, the mixture was poured onto water and was diluted with methylene chloride. The pH of the aqueous layer was adjusted to 6. The organic layer was separated, washed with water, brine, dried (MgSO$_4$) and evaporated. The residue was purified by column chromatography, eluting
with ethyl acetate/petroleum ether (3/7) to give 4-fluoro-5-hydroxy-2-methylindole (461 mg, 70 %).

MS-ESI : 166 [MH]⁺

1H NMR Spectrum: (DMSO-d₆) 2.35 (s, 3H) ; 6.05 (s, 1H) ; 6.65 (dd, 1H) ; 6.9 (d, 1H) ; 8.75 (s, 1H) ; 10.9 (s, 1H)

13C NMR Spectrum: (DMSO-d₆) 13.5 ; 94.0 ; 106.0 ; 112 ; 118.5 (d) ; 132 (d) ; 136 (d) ; 136.5 ; 142.5 (d)

Alternatively the 4-fluoro-5-hydroxy-2-methylindole may be prepared as follows:

To a suspension of sodium hydride (5.42 g, 226 mmol) (prewashed with pentane) in THF (100 ml) cooled at 10°C was added ethyl acetoacetate (29.4 g, 226 mmol) while keeping the temperature below 15°C. After completion of addition, the mixture was further stirred for 15 minutes and cooled to 5°C. A solution of 1,2,3-trifluoro-4-nitrobenzene (20 g, 113 mmol) in THF (150 ml) was added while keeping the temperature below 5°C. The mixture was then left to warm up to ambient temperature and stirred for 24 hours. The volatiles were removed under vacuum and the residue was partitioned between ethyl acetate and 2N aqueous hydrochloric acid. The organic layer was washed with water, brine, dried (MgSO₄) and evaporated. The residue was dissolved in concentrated hydrochloric acid (650 ml) and acetic acid (600 ml) and the mixture was refluxed for 15 hours. After cooling, the volatiles were removed under vacuum and the residue was partitioned between aqueous sodium hydrogen carbonate (5 %) and ethyl acetate. The organic layer was washed with sodium hydrogen carbonate, water, brine, dried (MgSO₄) and evaporated. The residue was purified by column chromatography eluting with ethylacetate/petroleum ether (75/25) to give 3-acetilmethyl-1,2-difluoro-4-nitrobenzene (17.5 g, 72 %).

1H NMR Spectrum: (CDCl₃) 2.4 (s, 3H) ; 4.25 (s, 2H) ; 7.25 (dd, 1H) ; 8.0 (dd, 1H)

A solution of 3-acetilmethyl-1,2-difluoro-4-nitrobenzene (500 mg, 2.3 mmol) in methylene chloride (5 ml) containing montmorillonite K10 (1 g) and trimethyl orthofomate (5 ml) was stirred for 24 hours at ambient temperature. The solid was filtered, washed with methylene chloride and the filtrate was evaporated to give 1,2-difluoro-3-(2,2-dimethoxypropyl)-4-nitrobenzene (534 mg, 88 %).

1H NMR Spectrum: (CDCl₃) 1.2 (s, 3H) ; 3.2 (s, 6H) ; 3.52 (s, 2H) ; 7.18 (dd, 1H) ; 7.6 (m, 1H)
JUMBO APPLICATIONS / PATENTS

THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE THAN ONE VOLUME.

THIS IS VOLUME __1__ OF __2__

NOTE: For additional volumes please contact the Canadian Patent Office.
CLAIMS:

1. Use of a compound of the formula (I):

\[ \text{C} \quad (R^1)_n \]
\[ (R^2)_m \quad \text{H} \quad \text{N} \quad \text{Z} \quad \text{H} \]

(l)

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 which independently are O, N or S;
- \( Z \) is \(-\text{O}-, -\text{NH}- \) or \(-\text{S}-;\)
- \( n \) 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, \( C_{1-3} \) alkylsulphonyl, \(-\text{NR}^3\text{R}^4 \), wherein \( R^3 \) and \( R^4 \) which may be the same or different, each represents hydrogen or \( C_{1-3} \) alkyl, or \( R^5 X^1 \), wherein \( X^1 \)
- \( R^2 \) represents a direct bond, \(-\text{O}-, -\text{CH}_2-, -\text{OC(O)}-, -\text{C(O)}-, -\text{S}-, -\text{SO}_2- \), \(-\text{NR}^5\text{C(O)}-, -\text{C(O)}\text{NR}^7-, -\text{SO}_2\text{NR}^8-, -\text{NR}^9\text{SO}_2- \) or \(-\text{NR}^{10}-, \) wherein \( R^5, R^7, R^8, R^9 \) and \( R^{10} \) each independently represents hydrogen, \( C_{1-3} \) alkyl or \( C_{1-3} \) alkoxy\( C_{2-3} \) alkyl, and \( R^5 \) is 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 which are hydroxy, fluoro, chloro, bromo or amino;

(2) C_{1-5}alkylX^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, azetidinyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, which independently are O, S or N, which C_{1-3}alkyl group may bear 1 or 2 substituents which are oxo, hydroxy, halogeno or C_{1-4}alkoxy and which cyclic group may bear 1 or 2 substituents which are 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}alkoxy carbonyl, 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 or 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 an azetidinyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, which independently are O, S or N, which cyclic group may bear one or more C_{1-4}alkyl substituents;

(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 an azetidinyl or a 5-6-membered saturated heterocyclic group, linked via carbon or nitrogen, with 1-2 heteroatoms, which independently are O, S or N, which heterocyclic group may bear 1 or 2 substituents which are
oxo, hydroxy, halogeno, cyano, C₁₄cyanoalkyl, C₁₄alkyl, C₁₄hydroxyalkyl, C₁₄alkoxy, C₁₄alkoxyC₁₄alkyl, C₁₄alkylsulphonylC₁₄alkyl, C₁₄alkoxycarbonyl, C₁₄aminoalkyl, C₁₄alkylamino, di(C₁₄alkyl)amino, C₁₄alkylaminoC₁₄alkyl, di(C₁₄alkyl)aminoC₁₄alkyl, C₁₄alkylaminoC₁₄alkoxy, di(C₁₄alkyl)aminoC₁₄alkoxy or a group (-(O-))(C₁₄alkyl)_f ringD, wherein f is 0 or 1, g is 0 or 1 and ring D is an azetidinyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, which independently are O, S or N, which cyclic group may bear one or more C₁₄alkyl substituents;

(6) C₁₅alkylR²⁸, wherein R²⁸ is as defined herein;

(7) C₂₅alkenylR²⁸, wherein R²⁸ is as defined herein;

(8) C₂₅alkynylR²⁸, wherein R²⁸ is as defined herein;

(9) R²⁹, wherein R²⁹ represents a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group, linked via carbon or nitrogen, with 1-3 heteroatoms which are O, N or S, which pyridone, phenyl or aromatic heterocyclic group may carry up to 5 substituents which are hydroxy, halogeno, amino, C₁₄alkyl, C₁₄alkoxy, C₁₄hydroxyalkyl, C₁₄aminoalkyl, C₁₄alkylamino, C₁₄hydroxyalkoxy, carboxy, trifluoromethyl, cyano, -C(O)NR³⁰R³¹, -NR³²C(O)R³³, wherein R³⁰, R³¹, R³² and R³³, which may be the same or different, each represents hydrogen, C₁₄alkyl or C₁₃alkoxyC₂₃alkyl, or a group (-(O-))(C₁₄alkyl)_g ringD, wherein f is 0 or 1, g is 0 or 1 and ring D is an azetidinyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, which independently are O, S and N, which cyclic group may bear one or more C₁₄alkyl substituents;

(10) C₁₅alkylR²⁹, wherein R²⁹ is as defined herein;

(11) C₂₅alkenylR²⁹, wherein R²⁹ is as defined herein;

(12) C₂₅alkynylR²⁹, wherein R²⁹ is as defined herein;

(13) C₁₅alkylX⁶R²⁹, wherein X⁶ represents -O-, -S-, -SO₂-, -NR³⁴C(O)-, -C(O)NR³⁵-, -SO₂NR³⁶-, -NR³⁷SO₂- or -NR³⁸-, wherein R³⁴, R³⁵, R³⁶, R³⁷ and R³⁸
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each independently represents hydrogen, C$_{1-3}$alkyl or C$_{1-3}$alkoxyC$_{2-3}$alkyl, and R$^{29}$
is as defined herein;

(14) C$_{2-5}$alkenylX$^{7}$R$^{29}$, wherein X$^{7}$ represents -O-, -S-, -SO$_{2}$-, -NR$_{39}$C(O)-,
-C(O)NR$_{40}$-, -SO$_{2}$NR$_{41}$-, -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 herein;

(15) C$_{2-5}$alkynylX$^{8}$R$^{29}$, wherein X$^{8}$ represents -O-, -S-, -SO$_{2}$-, -NR$_{44}$C(O)-,
-C(O)NR$_{45}$-, -SO$_{2}$NR$_{46}$-, -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 herein;

(16) C$_{1-4}$alkylX$^{9}$C$_{1-4}$alkylR$^{29}$, wherein X$^{9}$ represents -O-, -S-, -SO$_{2}$-, 
-NR$_{49}$C(O)-, -C(O)NR$_{50}$-, -SO$_{2}$NR$_{51}$-, -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 herein;

(17) C$_{1-4}$alkylX$^{9}$C$_{1-4}$alkylR$^{28}$, wherein X$^{9}$ and R$^{28}$ are as defined herein;

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

(20) C$_{2-5}$alkenylX$^{9}$C$_{1-4}$alkylR$^{28}$, wherein X$^{9}$ and R$^{28}$ are as defined herein;

(21) C$_{2-5}$alkynylX$^{9}$C$_{1-4}$alkylR$^{28}$, wherein X$^{9}$ and R$^{28}$ are as defined herein; or

(22) C$_{1-4}$alkylR$^{54}$(C$_{1-4}$alkyl)$_{q}$(X$^{9}$)R$^{55}$, wherein X$^{9}$ is as defined herein, q is 0 or 1, r is 
0 or 1, and R$^{54}$ and R$^{55}$ are each independently hydrogen, C$_{1-3}$alkyl, 
cyclopentyl, cyclohexyl, azetidinyl or a 5-6-membered saturated heterocyclic group with 1-2
heteroatoms, which independently are O, S or N, which C_{1.5}alkyl group may bear
1 or 2 substituents which are oxo, hydroxy, halogeno or C_{1.4}alkoxy and which
cyclic group may bear 1 or 2 substituents which are 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 or 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 an azetidinyl or
a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, which
independently are O, S or N, which cyclic group may bear one or more C_{1.4}alkyl
substituents, 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 which are hydroxy, halogeno or amino; and

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}alkylsulphonyl, 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}_2C(O)-, -C(O)NR^{58}_2, -SO_2NR^{59}_2, -NR^{60}_2SO_2- or -NR^{61}_2, 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 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 which are hydroxy, fluoro, chloro,
bromo and amino;

(2) C_{1.5}alkylX^{11}C(O)R^{62}, wherein X^{11} represents -O- or -NR^{63}_2, 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,
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-NR<sup>64</sup>R<sup>65</sup> or -OR<sup>66</sup>, wherein R<sup>64</sup>, R<sup>65</sup> and R<sup>66</sup> which may be the same or different each represents hydrogen, C<sub>1-3</sub>alkyl or C<sub>1-3</sub>alkoxyC<sub>2-3</sub>alkyl;

(3) C<sub>1-3</sub>alkylX<sup>12</sup>R<sup>57</sup>, wherein X<sup>12</sup> represents -O-, -S-, -SO<sub>2</sub>-, -OC(O)-, -NR<sup>68</sup>C(O)-, -C(O)NR<sup>69</sup>-, -SO<sub>2</sub>NR<sup>70</sup>-, -NR<sup>71</sup>SO<sub>2</sub>- or -NR<sup>72</sup>- wherein R<sup>57</sup>, R<sup>68</sup>, R<sup>69</sup>, R<sup>70</sup>, R<sup>71</sup> and R<sup>72</sup> each independently represents hydrogen, C<sub>1-3</sub>alkyl or C<sub>1-3</sub>alkoxyC<sub>2-3</sub>alkyl, and R<sup>67</sup> represents hydrogen, C<sub>1-3</sub>alkyl, cyclopentyl, cyclohexyl, azetidinyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, which independently are O, S or N, which C<sub>1-3</sub>alkyl group may bear 1 or 2 substituents which are oxo, hydroxy, halogeno or C<sub>1-4</sub>alkoxy and which cyclic group may bear 1 or 2 substituents which are oxo, hydroxy, halogeno, cyano, C<sub>1-4</sub>cyanooalkyl, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>hydroxyalkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkylsulphonylC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxycarbonyl, C<sub>1-4</sub>aminoalkyl, C<sub>1-4</sub>alkylamino, di(C<sub>1-4</sub>alkyl)amino, C<sub>1-4</sub>alkylaminoC<sub>1-4</sub>alkyl, di(C<sub>1-4</sub>alkyl)aminoC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkylaminoC<sub>1-4</sub>alkoxy, di(C<sub>1-4</sub>alkyl)aminoC<sub>1-4</sub>alkoxy or a group

15 -(-O-)(C<sub>1-4</sub>alkyl)_{f}ringD, wherein f is 0 or 1, g is 0 or 1 and ring D is an azetidinyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, which independently are O, S and N, which cyclic group may bear one or more C<sub>1-4</sub>alkyl substituents;

(4) C<sub>1-3</sub>alkylX<sup>13</sup>C<sub>1-3</sub>alkylX<sup>14</sup>R<sup>73</sup>, wherein X<sup>13</sup> and X<sup>14</sup> which may be the same or different are each -O-, -S-, -SO<sub>2</sub>-, -NR<sup>74</sup>C(O)-, -C(O)NR<sup>75</sup>-, -SO<sub>2</sub>NR<sup>76</sup>-, -NR<sup>77</sup>SO<sub>2</sub>- or -NR<sup>78</sup>- wherein R<sup>74</sup>, R<sup>75</sup>, R<sup>76</sup>, R<sup>77</sup> and R<sup>78</sup> each independently represents hydrogen, C<sub>1-3</sub>alkyl or C<sub>1-3</sub>alkoxyC<sub>2-3</sub>alkyl, and R<sup>73</sup> represents hydrogen, C<sub>1-3</sub>alkyl or C<sub>1-3</sub>alkoxyC<sub>2-3</sub>alkyl;

(5) R<sup>73</sup>, wherein R<sup>73</sup> is an azetidinyl or a 5-6-membered saturated heterocyclic group, linked via carbon or nitrogen, with 1-2 heteroatoms, which independently are O, S or N, which heterocyclic group may bear 1 or 2 substituents which are oxo, hydroxy, halogeno, cyano, C<sub>1-4</sub>cyanooalkyl, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>hydroxyalkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkylsulphonylC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxycarbonyl, C<sub>1-4</sub>aminoalkyl, C<sub>1-4</sub>alkylamino, di(C<sub>1-4</sub>alkyl)amino, C<sub>1-4</sub>alkylaminoC<sub>1-4</sub>alkyl, di(C<sub>1-4</sub>alkyl)aminoC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkylaminoC<sub>1-4</sub>alkoxy, di(C<sub>1-4</sub>alkyl)aminoC<sub>1-4</sub>alkoxy or a group -(-O-)(C<sub>1-4</sub>alkyl)_{f}ringD, wherein f is 0 or 1, g is 0 or 1 and ring D is an azetidinyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms,
which independently are O, S and N, which cyclic group may bear one or more
C<sub>1-4</sub>alkyl substituents;

(6) C<sub>1-5</sub>alkylR<sup>79</sup>, wherein R<sup>79</sup> is as defined herein;

(7) C<sub>2-5</sub>alkenylR<sup>79</sup>, wherein R<sup>79</sup> is as defined herein;

(8) C<sub>2-5</sub>alkynylR<sup>79</sup>, wherein R<sup>79</sup> is as defined herein;

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

(10) C<sub>1-5</sub>alkylR<sup>80</sup>, wherein R<sup>80</sup> is as defined herein;

(11) C<sub>2-5</sub>alkenylR<sup>80</sup>, wherein R<sup>80</sup> is as defined herein;

(12) C<sub>2-5</sub>alkynylR<sup>80</sup>, wherein R<sup>80</sup> is as defined herein;

(13) C<sub>1-5</sub>alkylX<sup>15</sup>R<sup>80</sup>, wherein X<sup>15</sup> represents -O-, -S-, -SO-, -SO<sub>2</sub>-, -NR<sup>85</sup>C(O)-,
-C(O)NR<sup>86</sup>-, -SO<sub>2</sub>NR<sup>87</sup>-, -NR<sup>88</sup>SO<sub>2</sub>- or -NR<sup>89</sup>-, wherein R<sup>85</sup>, R<sup>86</sup>, R<sup>87</sup>, R<sup>88</sup> and R<sup>89</sup>
each independently represents hydrogen, C<sub>1-3</sub>alkyl or C<sub>1-3</sub>alkoxyC<sub>2-3</sub>alkyl, and R<sup>80</sup>
is as defined herein;

(14) C<sub>2-5</sub>alkenylX<sup>16</sup>R<sup>80</sup>, wherein X<sup>16</sup> represents -O-, -S-, -SO-, -SO<sub>2</sub>-, -NR<sup>90</sup>C(O)-,
-C(O)NR<sup>91</sup>-, -SO<sub>2</sub>NR<sup>92</sup>-, -NR<sup>93</sup>SO<sub>2</sub>- or -NR<sup>94</sup>-, wherein R<sup>90</sup>, R<sup>91</sup>, R<sup>92</sup>, R<sup>93</sup> and R<sup>94</sup>
each independently represents hydrogen, C<sub>1-3</sub>alkyl or C<sub>1-3</sub>alkoxyC<sub>2-3</sub>alkyl, and R<sup>80</sup>
is as defined herein;
(15) C_{2:5}alkynylX_{17}^{17}R_{80}^{80}, wherein X_{17} represents -O-, -S-, -SO-, -SO_{2}-, -NR_{96}^{96}C(O)-, -C(O)NR_{96}^{96}, -SO_{2}NR_{97}^{97}, -NR_{96}^{96}SO_{2}- or -NR_{99}^{99}, wherein R_{95}^{95}, R_{96}^{96}, R_{97}^{97}, R_{98}^{98} and R_{99}^{99} each independently represents hydrogen, C_{1:3}alkyl or C_{1:3}alkoxyC_{2:3}alkyl, and R_{80}^{80} is as defined herein;

(16) C_{1:4}alkylX_{18}^{18}C_{4:4}alkylR_{80}^{80}, wherein X_{18} represents -O-, -S-, -SO-, -SO_{2}-, -NR_{100}^{100}C(O)-, -C(O)NR_{101}^{101}, -SO_{2}NR_{102}^{102}, -NR_{103}^{103}SO_{2}- or -NR_{104}^{104}, wherein R_{100}^{100}, R_{101}^{101}, R_{102}^{102}, R_{103}^{103} and R_{104}^{104} each independently represents hydrogen, C_{1:3}alkyl or C_{1:3}alkoxyC_{2:3}alkyl, and R_{80}^{80} is as defined herein;

(17) C_{1:4}alkylX_{18}^{18}C_{1:4}alkylR_{79}^{79}, wherein X_{18} and R_{79}^{79} are as defined herein;

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

(20) C_{2:5}alkenylX_{18}^{18}C_{1:4}alkylR_{79}^{79}, wherein X_{18} and R_{79}^{79} are as defined herein;

(21) C_{2:5}alkynylX_{18}^{18}C_{1:4}alkylR_{79}^{79}, wherein X_{18} and R_{79}^{79} are as defined herein; or

(22) C_{1:4}alkylR_{105}^{105}(C_{1:4}alkyl)_{x}(X_{18}^{18})_{y}R_{106}^{106}, wherein X_{18} is as defined herein, x is 0 or 1, y is 0 or 1, and R_{105}^{105} and R_{106}^{106} are each independently hydrogen, C_{1:3}alkyl, cyclopentyl, cyclohexyl, azetidinyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, which independently are O, S or N, which C_{1:3}alkyl group may bear 1 or 2 substituents which are oxo, hydroxy, halogeno or C_{1:4}alkoxy and which cyclic group may bear 1 or 2 substituents which are 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}alkoxyxycarbonyl, C_{1:4}aminoalkyl, C_{1:4}alkylamino, di(C_{4:4}alkyl)amino, C_{1:4}alkylaminoc_{1:4}alkyl, di(C_{4:4}alkyl)aminoC_{1:4}alkyl, C_{1:4}alkylaminoc_{1:4}alkoxy, di(C_{4:4}alkyl)aminoC_{1:4}alkoxy
or a group \((-\text{O-})^f_{\text{C}_{1.4}\text{alkyl}}\)^g_{\text{ring D}},\) wherein \(f\) is 0 or 1, \(g\) is 0 or 1 and ring D is an azetidinyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, which independently are O, S or N, which cyclic group may bear one or more substituents which are \(\text{C}_{1.4}\text{alkyl},\) with the proviso that \(\text{R}^{105}\) cannot be hydrogen;

and additionally wherein any \(\text{C}_{1.5}\text{alkyl}, \text{C}_{2.5}\text{alkenyl}\) or \(\text{C}_{2.5}\text{alkynyl}\) group in \(\text{R}^{56}\chi^{10}\) may bear one or more substituents which are hydroxy, halogeno or amino;

or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal.

2. Use of a compound of the formula (I) or a pharmaceutically acceptable salt thereof as defined in claim 1, for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal.

3. The use according to claim 1 or 2, 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 which independently are O, N or S;

\(Z\) is \(-\text{O-}, \text{-NH-} \) or \(-\text{S-};;\)

\(\text{R}^{1}\) represents hydrogen, oxo, halogeno, hydroxy, \(\text{C}_{1.4}\text{alkoxy}, \text{C}_{1.4}\text{alkyl},\)
\(\text{C}_{1.4}\text{alkoxymethyl}, \text{C}_{1.4}\text{alkanoyl}, \text{C}_{1.4}\text{haloalkyl}, \text{cyano}, \text{amino}, \text{C}_{2.5}\text{alkenyl},\)
\(\text{C}_{2.5}\text{alkynyl}, \text{C}_{1.3}\text{alkanoyloxy}, \text{nitro}, \text{C}_{1.4}\text{alkanoylamino}, \text{C}_{1.4}\text{alkoxycarbonyl},\)
\(\text{C}_{1.4}\text{alkylsulphanyl}, \text{C}_{1.4}\text{alkylsulphinyl}, \text{C}_{1.4}\text{alkylsulphonyl}, \text{carbamoyl}, \text{N-}\text{C}_{1.4}\text{alkylcarbamoyl}, \text{N.N-di(C}_{1.4}\text{alkyl})\text{carbamoyl}, \text{aminosulphonyl}, \text{N-}\text{N-di(C}_{1.4}\text{alkyl})\text{aminosulphonyl}, \text{N-}\text{N-di(C}_{1.4}\text{alkyl})\text{aminosulphonyl}, \text{N-}\text{(C}_{1.4}\text{alkylsulphonyl})\text{amino, N-(C}_{1.4}\text{alkylsulphonyl})\text{-N-(C}_{1.4}\text{alkyl})\text{amino, N.N-di(C}_{1.4}\text{alkyl})\text{aminosulphonyl,}\)
\(\text{C}_{1.4}\text{alkylaminosulphonyl, N.N-di(C}_{1.4}\text{alkyl})\text{aminosulphonyl, N-}\text{(C}_{1.4}\text{alkylsulphonyl})\text{amino or a C}_{3.7}\text{alkylene chain joined to two ring C carbon atoms;\)

\(n\) 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}alkylsulphonyl, \(-NR^3R^4\), 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 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 which are hydroxy, fluoro or amino;

(2) C_{1-5}alkylX^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, which independently are O, S or N, which C_{1-3}alkyl group may bear 1 or 2 substituents which are oxo, hydroxy, halogeno or C_{1-4}alkoxy and which cyclic group may bear 1 or 2 substituents which are oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl or 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, which independently are O, S or N, which heterocyclic group may bear 1 or 2 substituents which are oxo, hydroxy,
halogeno, cyano, C<sub>1</sub>-C<sub>4</sub>cyanoalkyl, C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, C<sub>1</sub>-C<sub>4</sub>alkoxyC<sub>1</sub>-C<sub>4</sub>alkyl or C<sub>1</sub>-C<sub>4</sub>alkylsulphonylC<sub>1</sub>-C<sub>4</sub>alkyl;

(6) C<sub>1</sub>-C<sub>5</sub>alkylR<sup>28</sup>, wherein R<sup>28</sup> is as defined herein;

(7) C<sub>2</sub>-C<sub>5</sub>alkenylR<sup>28</sup>, wherein R<sup>28</sup> is as defined herein;

(8) C<sub>2</sub>-C<sub>5</sub>alkynylR<sup>28</sup>, wherein R<sup>28</sup> is as defined herein;

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

(10) C<sub>1</sub>-C<sub>5</sub>alkylR<sup>29</sup>, wherein R<sup>29</sup> is as defined herein;

(11) C<sub>2</sub>-C<sub>5</sub>alkenylR<sup>29</sup>, wherein R<sup>29</sup> is as defined herein;

(12) C<sub>2</sub>-C<sub>5</sub>alkynylR<sup>29</sup>, wherein R<sup>29</sup> is as defined herein;

(13) C<sub>1</sub>-C<sub>5</sub>alkylX<sup>6</sup>R<sup>29</sup>, wherein X<sup>6</sup> represents -O-, -S-, -SO-, -SO<sub>2</sub>-, -NR<sup>34</sup>C(O)-, -C(O)NR<sup>35</sup>-, -SO<sub>2</sub>NR<sup>36</sup>-, -NR<sup>37</sup>SO<sub>2</sub>- or -NR<sup>38</sup>-, wherein R<sup>34</sup>, R<sup>35</sup>, R<sup>36</sup>, R<sup>37</sup> and R<sup>38</sup> each independently represents hydrogen, C<sub>1</sub>-C<sub>3</sub>alkyl or C<sub>1</sub>-C<sub>3</sub>alkoxyC<sub>2</sub>-C<sub>3</sub>alkyl, and R<sup>29</sup> is as defined herein;

(14) C<sub>2</sub>-C<sub>5</sub>alkenylX<sup>7</sup>R<sup>29</sup>, wherein X<sup>7</sup> represents -O-, -S-, -SO-, -SO<sub>2</sub>-, -NR<sup>39</sup>C(O)-, -C(O)NR<sup>40</sup>-, -SO<sub>2</sub>NR<sup>41</sup>-, -NR<sup>42</sup>SO<sub>2</sub>- or -NR<sup>43</sup>-, wherein R<sup>39</sup>, R<sup>40</sup>, R<sup>41</sup>, R<sup>42</sup> and R<sup>43</sup> each independently represents hydrogen, C<sub>1</sub>-C<sub>3</sub>alkyl or C<sub>1</sub>-C<sub>3</sub>alkoxyC<sub>2</sub>-C<sub>3</sub>alkyl, and R<sup>29</sup> is as defined herein;

(15) C<sub>2</sub>-C<sub>5</sub>alkynylX<sup>8</sup>R<sup>29</sup>, wherein X<sup>8</sup> represents -O-, -S-, -SO-, -SO<sub>2</sub>-, -NR<sup>44</sup>C(O)-, -C(O)NR<sup>45</sup>-, -SO<sub>2</sub>NR<sup>46</sup>-, -NR<sup>47</sup>SO<sub>2</sub>- or -NR<sup>48</sup>-, wherein R<sup>44</sup>, R<sup>45</sup>, R<sup>46</sup>, R<sup>47</sup> and R<sup>48</sup> each independently represents hydrogen, C<sub>1</sub>-C<sub>3</sub>alkyl or C<sub>1</sub>-C<sub>3</sub>alkoxyC<sub>2</sub>-C<sub>3</sub>alkyl, and R<sup>29</sup> is as defined herein;
(16) \( C_{1-3}\text{alkyl}X^9C_{1-3}\text{alkyl}R^{29} \), wherein \( X^9 \) represents \(-\text{O}, -\text{S}, -\text{SO}_2, -\text{NR}^{49}\text{C(O)}\text{-}, -\text{C(O)}\text{NR}^{50}, -\text{SO}_2\text{NR}^{51}, -\text{NR}^{52}\text{SO}_2\text{-} \) or \(-\text{NR}^{53}\text{-} \), wherein \( R^{49}, R^{50}, R^{51}, R^{52} \) and \( R^{53} \) each independently represents hydrogen, \( C_{1-3}\text{alkyl} \) or \( C_{1-3}\text{alkoxyC}_{2-3}\text{alkyl} \), and \( R^{29} \) is as defined herein;

(17) \( C_{1-3}\text{alkyl}X^9C_{1-3}\text{alkyl}R^{28} \), wherein \( X^9 \) and \( R^{28} \) are as defined herein;

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

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

(20) \( C_{2-5}\text{alkenyl}X^9C_{1-4}\text{alkyl}R^{28} \), wherein \( X^9 \) and \( R^{28} \) are as defined herein; or

(21) \( C_{2-5}\text{alkynyl}X^9C_{1-4}\text{alkyl}R^{28} \), wherein \( X^9 \) and \( R^{28} \) are as defined herein.

4. The use according to claim 1 or 2, wherein \( R^2 \) represents hydroxy, halogeno, cyano, nitro, trifluoromethyl, \( C_{1-3}\text{alkyl} \), amino or \( R^5X^1 \text{-} \), wherein \( X^1 \) is as defined in claim 1 and \( R^5 \) is one of the following twenty-two groups:

(1) \( C_{1-4}\text{alkyl} \) which may be unsubstituted or which may be substituted with one or more groups which are fluoro, chloro or bromo, or \( C_{2-5}\text{alkyl} \) which may be unsubstituted or substituted with one or more groups which are hydroxy or amino;

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

(3) \( C_{2-4}\text{alkyII}X^3\text{R}^{16} \), wherein \( X^3 \) is as defined in claim 1 and \( R^{16} \) is a group which is \( C_{1-3}\text{alkyl} \), cyclopentyl, cyclohexyl, pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl or tetrahydropyranyl, which \( C_{1-3}\text{alkyl} \) group may bear 1 or 2 substituents which are oxo, hydroxy, halogeno or \( C_{1-2}\text{alkoxy} \) and which
cyclopentyl, cyclohexyl, pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl or tetrahydropyranyl group may bear 1 or 2 substituents which are oxo, hydroxy, halogeno, cyano, C₃-cyanoalkyl, C₃-hydroxyalkyl, C₃-alkoxy, C₃-alkoxycarbonyl, C₃-alkylamino, di(C₃-alkyl)amino, C₃-alkylaminoC₃-alkyl, di(C₃-alkyl)aminoC₃-alkyl, C₃-alkylaminoC₃-alkoxy, di(C₃-alkyl)aminoC₃-alkoxy or a group 

-(-O-)(C₃-alkyl)₉ringD, wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group which is pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino or thiomorpholino, which cyclic group may bear one or more C₃-alkyl substituents;

(4) C₂₃-alkylX⁴C₂₃-alkylX⁵R²², wherein X⁴ and X⁵ are as defined in claim 1 and R²² represents hydrogen or C₁₃-alkyl;

(5) R²⁸, wherein R²⁸ is as defined in claim 1;

(6) C₁₄-alkylR¹¹⁰, wherein R¹¹⁰ is a group: pyrrolidinyl, piperazinyl, piperidinyl, imidazolidin-1-yl, azetidinyl, 1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 1,3-dithiolan-2-yl or 1,3-dithian-2-yl, which group is linked to C₁₄-alkyl through a carbon atom and which group may bear 1 or 2 substituents which are oxo, hydroxy, halogeno, cyano, C₃-cyanoalkyl, C₃-alkyl, C₃-hydroxyalkyl, C₃-alkoxy, C₃-alkoxyC₃-alkyl, C₃-alkylsulphonylC₃-alkyl, C₃-alkoxycarbonyl, C₃-alkylamino, di(C₃-alkyl)amino, C₃-alkylaminoC₃-alkyl, di(C₃-alkyl)aminoC₃-alkyl, C₃-alkylaminoC₃-alkoxy, di(C₃-alkyl)aminoC₃-alkoxy or a group 

-(-O-)(C₃-alkyl)₉ringD, wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group which is pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino or thiomorpholino, which cyclic group may bear one or more substituents which are C₁₃-alkyl, or C₂₄-alkylR¹¹¹,

wherein R¹¹¹ is a group: morpholino, thiomorpholino, azetidin-1-yl, pyrrolidin-1-yl, piperazin-1-yl or piperidino which group may bear 1 or 2 substituents which are oxo, hydroxy, halogeno, cyano, C₃-cyanoalkyl, C₃-alkyl, C₃-hydroxyalkyl, C₃-alkoxy, C₃-alkoxyC₃-alkyl, C₃-alkylsulphonylC₃-alkyl, C₃-alkoxycarbonyl, C₃-alkylamino, di(C₃-alkyl)amino, C₃-alkylaminoC₃-alkyl, di(C₃-alkyl)aminoC₃-alkyl, C₃-alkylaminoC₃-alkoxy, di(C₃-alkyl)aminoC₃-alkoxy or a group 

-(-O-)(C₃-alkyl)₉ringD, wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group: pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl,
morpholino or thiomorpholino, which cyclic group may bear one or more C<sub>1-3</sub>-alkyl substituents;

(7) C<sub>3-4</sub>-alkenylR<sup>112</sup>, wherein R<sup>112</sup> represents R<sup>110</sup> or R<sup>111</sup> as defined herein;

(8) C<sub>3-4</sub>-alkynylR<sup>112</sup>, wherein R<sup>112</sup> represents R<sup>110</sup> or R<sup>111</sup> as defined herein;

(9) R<sup>29</sup>, wherein R<sup>29</sup> is as defined in claim 1;

(10) C<sub>1-4</sub>-alkylR<sup>29</sup>, wherein R<sup>29</sup> is as defined in claim 1;

(11) 1-R<sup>29</sup>-prop-1-en-3-yl or 1-R<sup>29</sup>-but-2-en-4-yl, wherein R<sup>29</sup> is as defined in claim 1 with the proviso that when R<sup>5</sup> is 1-R<sup>29</sup>-prop-1-en-3-yl, R<sup>29</sup> is linked to the alkenyl group via a carbon atom;

(12) 1-R<sup>29</sup>-prop-1-yn-3-yl or 1-R<sup>29</sup>-but-2-yn-4-yl, wherein R<sup>29</sup> is as defined in claim 1 with the proviso that when R<sup>5</sup> is 1-R<sup>29</sup>-prop-1-yn-3-yl, R<sup>29</sup> is linked to the alkynyl group via a carbon atom;

(13) C<sub>1-5</sub>-alkylX<sup>6</sup>R<sup>29</sup>, wherein X<sup>6</sup> and R<sup>29</sup> are as defined in claim 1;

(14) 1-(R<sup>29</sup>X<sup>7</sup>)but-2-en-4-yl, wherein X<sup>6</sup> and R<sup>29</sup> are as defined in claim 1;

(15) 1-(R<sup>29</sup>X<sup>8</sup>)but-2-yn-4-yl, wherein X<sup>6</sup> and R<sup>29</sup> are as defined in claim 1;

(16) C<sub>2-5</sub>-alkylX<sup>9</sup>C<sub>1-3</sub>-alkylR<sup>29</sup>, wherein X<sup>6</sup> and R<sup>29</sup> are as defined in claim 1;

(17) C<sub>2-5</sub>-alkylX<sup>9</sup>C<sub>1-3</sub>-alkylR<sup>28</sup>, wherein X<sup>6</sup> and R<sup>28</sup> are as defined in claim 1;

(18) C<sub>2-5</sub>-alkenyl which may be unsubstituted or which may be substituted with one or more fluorine atoms or with one or two groups which are hydroxy, fluoro, amino, C<sub>1-4</sub>-alkylamino, N,N-di(C<sub>1-4</sub>-alkyl)amino, aminosulphonyl, N-
C<sub>1-4</sub>-alkylaminosulphonyl or N,N-di(C<sub>1-4</sub>-alkyl)aminosulphonyl;

(19) C<sub>2-5</sub>-alkynyl which may be unsubstituted or which may be substituted with one or more fluorine atoms or with one or two groups which are hydroxy, fluoro, amino, C<sub>1-4</sub>-alkylamino, N,N-di(C<sub>1-4</sub>-alkyl)amino, aminosulphonyl, N-
C<sub>1-4</sub>-alkylaminosulphonyl or N,N-di(C<sub>1-4</sub>-alkyl)aminosulphonyl;
(20) C_{2-4}alkenylX^6C_{1-3}alkylR^{28}, wherein X^6 and R^{28} are as defined in claim 1;

(21) C_{2-4}alkynylX^6C_{1-3}alkylR^{28}, wherein X^6 and R^{28} are as defined in claim 1; or

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

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 which are hydroxy, halogeno or amino.

5.

The use according to any one of claims 1 to 4, wherein Z is -O- or -S-.

6.

The use according to any one of claims 1 to 5, wherein ring C is a 9-10-membered heteroaromatic bicyclic moiety which contains 1-3 heteroatoms which independently are O, N or S.

7.

The use according to any one of claims 1 to 6, wherein 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}alkylsulphinyl)-N-(C_{1-2}alkyl)amino or a C_{3-7}alkylene chain joined to two ring C carbon atoms.

8.

The use according to any one of claims 1 to 7, wherein n is 0, 1 or 2.

9.

The use according to any one of claims 1 to 8, wherein m is 1 or 2.

10. The use according to any one of claims 1 to 9, wherein the warm-blooded animal is a human.

11. A compound of the formula (I) as defined in any one of claims 1 and 3 to 9, for the use defined in claim 1, 2 or 10.
12. A commercial package comprising a compound of the formula (I) as defined in any one of claims 1 and 3 to 9, and associated therewith instructions for the use thereof as defined in claim 1, 2 or 10.

13. A compound of the formula (II):

\[
\begin{align*}
&\text{wherein:} \\
&\text{ring C is an 8, 9, 10, 12 or 13-membered bicyclic or tricyclic moiety which moieties may be saturated or unsaturated, which may be aromatic or non-aromatic, and which contains 1-3 heteroatoms which independently are O, N and S;} \\
&R^1, R^2 \text{ and } n \text{ are as defined in claim 1;} \\
&\text{Zb is } -\text{O- or } -\text{S-;} \text{ and} \\
&R^{2a} \text{ represents hydrogen, halogeno, } C_{1-3}\text{alkyl, trifluoromethyl, } C_{1-3}\text{alkoxy,} \\
&\text{C}_{1-3}\text{alkylsulphanyl, } -\text{NR}^3\text{R}^4, \text{ wherein } R^3 \text{ and } R^4, \text{ which may be the same or different, each represents hydrogen or } C_{1-3}\text{alkyl, or } R^{5a}(\text{CH}_2)_{2a}X^{1a}, \text{ wherein } R^{5a} \text{ is an azetidinyl or a 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, which independently are O, S or N, which heterocyclic group may bear 1 or 2 substituents which are oxo, hydroxy, halogeno, cyano, } C_{1-4}\text{cyanoalkyl,} \\
&\text{C}_{1-4}\text{alkyl, } C_{1-4}\text{hydroxyalkyl, } C_{1-4}\text{alkoxy, } C_{1-4}\text{alkoxyC}_{1-4}\text{alkyl,} \\
&C_{1-4}\text{alkylsulphonylC}_{1-4}\text{alkyl, } C_{1-4}\text{alkoxycarbonyl, } C_{1-4}\text{aminoalkyl, } C_{1-4}\text{alkylamino,} \\
&\text{di(}C_{1-4}\text{alkyl)amino, } C_{1-4}\text{alkylaminoC}_{1-4}\text{alkyl, di(}C_{1-4}\text{alkyl)aminoC}_{1-4}\text{alkyl,} \\
&\text{di(}C_{1-4}\text{alkyl)aminoC}_{1-4}\text{alkyl,} \text{ respectively.}
\end{align*}
\]
C_{1,4}alkylaminoC_{1,4}alkoxy, di(C_{1,4}alkyl)aminoC_{1,4}alkoxy or a group
\(-(-O-)(C_{1,4}alkyl)_{g}\)ringD, wherein f is 0 or 1, g is 0 or 1 and ring D is an azetidinyl or
a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, which
independently are O, S and N, which cyclic group may bear one or more C_{1,4}alkyl
substituents selected from, 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_{2}NR_{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;

with the proviso that R^{2} is not hydrogen;

or a salt thereof.

14. A compound of the formula (II) according to claim 13, wherein R^{2}
represents hydroxy, halogeno, cyano, nitro, trifluoromethyl, C_{1,3}alkyl, amino or
R^{5}X^{1}- wherein X^{1} is as defined in claim 1 and R^{5} is one of the following twenty-two
groups:

15 (1) C_{1,4}alkyl which may be unsubstituted or which may be substituted with one or
more groups which are fluoro, chloro or bromo, or C_{2,3}alkyl which may be
unsubstituted or substituted with one or more groups which are hydroxy or amino;

(2) C_{2,3}alkylX^{2}C(O)R^{11}, wherein X^{2} is as defined in claim 1 and R^{11} represents
-NR_{13}R^{14} or -OR_{15}, wherein R_{13}, R_{14} or 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^{3}R^{16}, wherein X^{3} is as defined in claim 1 and R^{16} is a group: C_{1,3}alkyl,
cyclopentyl, cyclohexyl, pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl,
azetidinyl or tetrahydropyranyl, which C_{1,3}alkyl group may bear 1 or 2 substituents
which are oxo, hydroxy, halogeno or C_{1,2}alkoxy and which cyclopentyl, cyclohexyl,
pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl or tetrahydropyranyl
group may bear 1 or 2 substituents which are 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,
30 di(C_{1,3}alkyl)aminoC_{1,3}alkoxy or a group -(-O-)(C_{1,3}alkyl)_{g}\)ringD, wherein f is 0 or 1,
g is 0 or 1 and ring D is a heterocyclic group which is pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino or thiomorpholino, which cyclic group may bear one or more C\textsubscript{1-3}alkyl substituents;

(4) C\textsubscript{2-3}alkylX\textsuperscript{4}C\textsubscript{2-3}alkylX\textsuperscript{5}R\textsuperscript{22}, wherein X\textsuperscript{4} and X\textsuperscript{5} are as defined in claim 1 and R\textsuperscript{22} represents hydrogen or C\textsubscript{1-3}alkyl;

(5) R\textsuperscript{28}, wherein R\textsuperscript{28} is as defined in claim 1;

(6) C\textsubscript{1,4}alkylR\textsuperscript{110}, wherein R\textsuperscript{110} is a group: pyrrolidinyl, piperazinyl, piperidinyl, imidazolidin-1-yl, azetidinyl, 1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 1,3-dithiolan-2-yl or 1,3-dithian-2-yl, which group is linked to C\textsubscript{1,4}alkyl through a carbon atom and which group may bear 1 or 2 substituents which are oxo, hydroxy, halogeno, cyano, C\textsubscript{1,3}cyanoalkyl, C\textsubscript{1-3}alkyl, C\textsubscript{1,3}hydroxyalkyl, C\textsubscript{1,3}alkoxy, C\textsubscript{1,2}alkoxyC\textsubscript{1-3}alkyl, C\textsubscript{1,2}alkylsulphonylC\textsubscript{1,3}alkyl, C\textsubscript{1,3}alkoxycarbonyl, C\textsubscript{1,3}alkylamino, di(C\textsubscript{1,3}alkyl)amino, C\textsubscript{1,3}alkylaminoC\textsubscript{1,3}alkyl, di(C\textsubscript{1,3}alkyl)aminoC\textsubscript{1,3}alkyl, C\textsubscript{1,3}alkylaminoC\textsubscript{1,3}alkoxy, di(C\textsubscript{1,3}alkyl)aminoC\textsubscript{1,3}alkoxy or a group -(O-)(C\textsubscript{1,3}alkyl)\textsubscript{f}ringD, wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group which is pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino or thiomorpholino, which cyclic group may bear one or more substituents which are C\textsubscript{1,3}alkyl or C\textsubscript{2-4}alkylR\textsuperscript{111}, wherein R\textsuperscript{111} is a group: morpholino, thiomorpholino, azetidin-1-yl, pyrrolidin-1-yl, piperazin-1-yl or piperidinyl which group may bear 1 or 2 substituents which are oxo, hydroxy, halogeno, cyano, C\textsubscript{1,3}cyanoalkyl, C\textsubscript{1-3}alkyl, C\textsubscript{1,3}hydroxyalkyl, C\textsubscript{1,3}alkoxy, C\textsubscript{1,2}alkoxyC\textsubscript{1,3}alkyl, C\textsubscript{1,2}alkylsulphonylC\textsubscript{1,3}alkyl, C\textsubscript{1,3}alkoxycarbonyl, C\textsubscript{1,3}alkylamino, di(C\textsubscript{1,3}alkyl)amino, C\textsubscript{1,3}alkylaminoC\textsubscript{1,3}alkyl, di(C\textsubscript{1,3}alkyl)aminoC\textsubscript{1,3}alkyl, C\textsubscript{1,3}alkylaminoC\textsubscript{1,3}alkoxy, di(C\textsubscript{1,3}alkyl)aminoC\textsubscript{1,3}alkoxy or a group -(O-)(C\textsubscript{1,3}alkyl)\textsubscript{f}ringD, wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group which is pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino or thiomorpholino, which cyclic group may bear one or more C\textsubscript{1,3}alkyl substituents;

(7) C\textsubscript{3-4}alkenylR\textsuperscript{112}, wherein R\textsuperscript{112} represents R\textsuperscript{110} or R\textsuperscript{111} as defined herein;

(8) C\textsubscript{3-4}alkynylR\textsuperscript{112}, wherein R\textsuperscript{112} represents R\textsuperscript{110} or R\textsuperscript{111} as defined herein;

(9) R\textsuperscript{29}, wherein R\textsuperscript{29} is as defined in claim 1;
(10) C_{14}alkylR^{29}, wherein R^{29} is as defined in claim 1;

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

(13) C_{15}alkylX^{6}R^{29}, wherein X^{6} and R^{29} are as defined in claim 1;

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

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

(16) C_{23}alkylX^{9}C_{13}alkylR^{29}, wherein X^{9} and R^{29} are as defined in claim 1;

(17) C_{23}alkylX^{9}C_{13}alkylR^{28}, wherein X^{9} and R^{28} are as defined in claim 1;

(18) C_{25}alkenyl which may be unsubstituted or which may be substituted with one or more fluorine atoms or with one or two groups which are hydroxy, fluoro, amino, C_{14}alkylamino, N,N-di(C_{14}alkyl)amino, aminosulphonyl, N-
C_{14}alkylaminosulphonyl or N,N-di(C_{14}alkyl)aminosulphonyl;

(19) C_{25}alkynyl which may be unsubstituted or which may be substituted with one or more fluorine atoms or with one or two groups which are hydroxy, fluoro, amino, C_{14}alkylamino, N,N-di(C_{14}alkyl)amino, aminosulphonyl, N-
C_{14}alkylaminosulphonyl or N,N-di(C_{14}alkyl)aminosulphonyl;

(20) C_{24}alkeny1X^{9}C_{13}alkylR^{28}, wherein X^{9} or R^{28} are as defined in claim 1;

(21) C_{24}alkeny1X^{9}C_{13}alkylR^{28}, wherein X^{9} and R^{28} are as defined in claim 1; or

(22) C_{13}alkylR^{54}(C_{13}alkyl)_{9}(X^{9})_{r}R^{55}, wherein X^{9}, q, r, R^{54} and R^{55} are as defined in claim 1;

and additionally wherein any C_{15}alkyl, C_{25}alkenyl or C_{25}alkynyl group in R^{5}X^{1-} may bear one or more substituents which are hydroxy, halogeno or amino.
15. A compound according to any one of claims 13 or 14, wherein Zb is -O-.

16. A compound according to any one of claims 13 to 15, wherein ring C is a 9-10-membered heteroaromatic bicyclic moiety which contains 1-3 heteroatoms which independently are O, N or S.

17. A compound according to any one of claims 13 to 16, wherein R¹ represents oxo, halogeno, hydroxy, C₁₋₂alkoxy, C₁₋₂alkyl, C₁₋₂alkoxymethyl, C₂₋₃alkanoyl, C₁₋₂haloalkyl, cyano, amino, C₂₋₄alkenyl, C₂₋₄alkynyl, C₂₋₃alkanoyloxy, nitro, C₂₋₃alkanoylamino, C₁₋₂alkoxycarbonyl, C₁₋₂alkylsulphany1, C₁₋₂alkylsulphinyl, C₁₋₂alkylsulphonyl, carbamoyl, N-C₁₋₂alkylcarbamoyl, N,N-di(C₁₋₂alkyl)carbamoyl, aminosulphonyl, N-C₁₋₂alkylaminosulphonyl, N,N-di(C₁₋₂alkyl)aminosulphonyl, N-(C₁₋₂alkylsulphonyl)amino, N-(C₁₋₂alkylsulphonyl)-N-(C₁₋₂alkyl)amino or a C₃₋₇alkylene chain joined to two ring C carbon atoms.

18. A compound according to any one of claims 13 to 17, wherein n is 0, 1 or 2.

19. A compound of the formula (IIb):

\[ \text{(IIb)} \]

wherein:

ring C, R¹, R² and n are as defined in claim 1;

25 Zb is -O-; and
R²a is as defined in claim 13, with the proviso that R² does not have any of the following values: hydrogen, substituted or unsubstituted C₁₅alkyl, halogeno, C₁₅alkoxy, C₂₅alkenyl, phenoxy or phenylC₁₅alkoxy;

or a salt thereof.

A compound according to claim 13 or 19, which is:

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-dioxothiomorpholinolopropoxy)-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-yl)methoxy)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-ylxyo)quinazoline,

(R,S)-4-(3-fluoroquinolin-7-ylxyo)-6-methoxy-7-((1-methylpiperidin-3-yl)methoxy)quinazoline,

5 4-(indol-5-ylxyo)-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline,

7-(3-N,N-dimethylaminopropoxy)-6-methoxy-4-(2-methylindol-5-ylxyo)quinazoline,

6-methoxy-4-(2-methylindol-5-ylxyo)-7-(2-(2-morpholinoethoxy)ethoxy)quinazoline,

7-(2-(N,N-diethylamino)ethoxy)-6-methoxy-4-(2-methylindol-5-ylxyo)quinazoline,

10 6-methoxy-7-(3-piperidinopropoxy)-4-(quinolin-7-ylxyo)quinazoline,

4-(2-methylindol-5-ylxyo)-7-(3-morpholinopropoxy)quinazoline,

4-(2-methylindol-5-ylxyo)-7-(2-(piperidin-1-yl)ethoxy)quinazoline,

4-(2-methylindol-5-ylxyo)-7-(2-(1H-1,2,4-triazol-1-yl)ethoxy)quinazoline,

6-methoxy-7-(3-piperidinopropoxy)-4-(6-trifluoromethylindol-5-ylxyo)quinazoline,

15 7-(3-(methylsulphonyl)propoxy)-4-(2-methylindol-5-ylxyo)quinazoline,

7-(3-(N,N-dimethylamino)propoxy)-4-(2,3-dimethylindol-5-ylxyo)-6-methoxyquinazoline,

4-(2,3-dimethylindol-5-ylxyo)-6-methoxy-7-(1-methylpiperidin-3-ylmethoxy)quinazoline,

20 7-(2-(N,N-diethylamino)ethoxy)-4-(indol-5-ylxyo)-6-methoxyquinazoline,

4-(indol-5-ylxyo)-6-methoxy-7-(2-(piperidin-2-yl)ethoxy)quinazoline,

4-(indol-5-ylxyo)-6-methoxy-7-(2-(piperidin-1-yl)ethoxy)quinazoline,

4-(indol-6-ylxyo)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
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7-(3-(ethlysulphonyl)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,

5 7-(2-hydroxy-3-(4-methylpiperazin-1-yl)propxoy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(N-methylamino)ethoxy)quinazoline, or
7-(2-hydroxy-3-(isopropylamino)propoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,

10 or a salt thereof.

21. A compound according to claim 13, which is:

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

15 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-4-(2-methylindol-5-yloxy)-7-(3-methylsulphonylpropoxy)quinazoline,
7-((1-cyanomethyl)piperidin-4-ylmethoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,

20 6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-morpholinoethoxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-pyrrolidin-1-ylmethoxy)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-(1H-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-yl)ethyl)carbamoyl)vinyl)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(3-(4-methylpiperazin-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-ylmethoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,
4-(2-methylindol-5-yloxy)-7-(3-(pyrrolidin-1-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,
5
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-yloxy)ethoxy)-4-(2-methylindol-5-yloxy)quinazoline,
10
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,
15
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,
20
6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(4-pyridyloxy)ethoxy)quinazoline,
4-(indol-5-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
(2R)-6-methoxy-(2-methyl-1H-indol-5-yloxy)-7-(2-hydroxy-3-piperidinopropoxy)quinazoline,
(5R)-6-methoxy-4-(2-methyl-1H-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,
(2R)-7-(2-hydroxy-3-(pyrrolidin-1-yl)propoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline,
(2R)-7-(2-hydroxy-3-morpholinopropoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline,
(2R)-7-(2-hydroxy-3-piperidinopropoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline,
(2S)-7-(2-hydroxy-3-((N,N-diisopropyl)amino)propoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline,
(2S)-7-(2-hydroxy-3-piperidinopropoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline,
(2R)-7-(2-hydroxy-3-piperidinopropoxy)-6-methoxy-4-(3-methylindol-5-yloxy)quinazoline,
(2R)-7-(2-hydroxy-3-(pyrrolidin-1-yl)propoxy)-6-methoxy-4-(3-methylindol-5-yloxy)quinazoline,
(2R)-7-(2-hydroxy-3-(pyrrolidin-1-yl)propoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,
(2R)-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-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)quinazoline,

(2S)-6-methoxy-(2-methyl-1H-indol-5-yloxy)-7-(2-hydroxy-3-piperidinopropoxy)quinazoline, or

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

or a salt thereof.

22. A compound according to claim 13, which is:

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

10 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,

15 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-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(2-(1-methylpiperidin-4-yl)ethoxy)quinazoline,
(2R)-7-(2-hydroxy-3-(pyrrolidin-1-yl)propoxy)-4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxyquinazoline, or

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

or a salt thereof.

23. 6-Methoxy-4-(2-methylindol-5-yloxy)-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline, or a salt thereof.

24. 4-(4-Fluoroindol-5-yloxy)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline, or a salt thereof.

25. 4-(4-Fluoroindol-5-yloxy)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline, or a salt thereof.

26. 4-(6-Fluoroindol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline, or a salt thereof.

27. 4-(4-Fluoroindol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline, or a salt thereof.

28. 4-(4-Fluoroindol-5-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline, or a salt thereof.

29. 4-(4-Fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline, or a salt thereof.

30. 4-(4-Fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline, or a salt thereof.

31. 4-(4-Fluoro-2-methylindol-5-yloxy)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline, or a salt thereof.

32. 4-(4-Fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline, or a salt thereof.
33. 4-(4-Fluoroindol-5-yloxy)-6-methoxy-7-(2-(1-methylpiperidin-4-yl)ethoxy)quinazoline, or a salt thereof.

34. (2R)-7-(2-hydroxy-3-(pyrrolidin-1-yl)propoxy)-4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxyquinazoline, or a salt thereof.

35. 4-(4-Fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(2-(1-methylpiperidin-4-yl)ethoxy)quinazoline, or a salt thereof.

36. A compound according to any one of claims 13 to 35, in the form of a pharmaceutically acceptable salt.

37. A pharmaceutical composition which comprises, as the active ingredient, a compound according to any one of claims 13 to 35, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient or carrier.

38. Use of a compound according to any one of claims 13 to 35, or a pharmaceutically acceptable salt thereof, or a composition according to claim 37, in the manufacture of a medicament for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal.

39. Use of a compound according to any one of claims 13 to 35, or a pharmaceutically acceptable salt thereof, or a composition according to claim 37, for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal.

40. Use of a compound according to any one of claims 13 to 35, or a pharmaceutically acceptable salt thereof, or a composition according to claim 37, in the manufacture of a medicament for the production of an anti-cancer effect in a warm-blooded animal.

41. Use of a compound according to any one of claims 13 to 35, or a pharmaceutically acceptable salt thereof, or a composition according to claim 37, for the production of an anti-cancer effect in a warm-blooded animal.
42. The use according to any one of claims 38 to 41, wherein the warm-blooded animal is a human.

43. A compound according to any one of claims 13 to 35, or a pharmaceutically acceptable salt thereof, or a composition according to claim 37, for the use defined in any one of claims 38 to 42.

44. A commercial package comprising a compound according to any one of claims 13 to 35, or a pharmaceutically acceptable salt thereof, or a composition according to claim 37, and associated therewith instructions for the use thereof as defined in any one of claims 38 to 42.

45. A process for the preparation of a compound of formula (II) according to claim 13, or of formula (IIb) according to claim 19, or a salt thereof, which comprises:

(a) the reaction of a compound of the formula (III):

\[
\begin{align*}
\text{(III)}
\end{align*}
\]

wherein \( R^2 \) and \( m \) are as defined for claim 13 or 19, and \( L^1 \) is a displaceable moiety, with a compound of the formula (IV):

\[
\begin{align*}
\text{(IV)}
\end{align*}
\]

wherein ring \( C \), \( R^1 \), \( Z \) and \( n \) are as defined for claim 13 or 19;
(b) a compound of formula (II) or (IIb) or a salt thereof, wherein at least one $R^2$ is $R^5X^1$, wherein $R^5$ is as defined for claim 13 or 19, 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, may be prepared by the reaction of a compound of the formula (V):

$$\begin{align*}
\text{(V)} \\
\text{wherein ring C, Z, R}^1, R^2 \text{ and } n \text{ are as defined for claim 13 or 19, and } X^1 \text{ is as herein defined in this section and } s \text{ is an integer from } 0 \text{ to } 2, \text{ with a compound of formula (VI)}:
\end{align*}$$

$$R^5\cdot L^1 \quad \text{(VI)}$$

wherein $R^5$ is as defined for claim 13 or 19, and $L^1$ is as herein defined;

(c) a compound of the formula (II) or (IIb) or a salt thereof, wherein at least one $R^2$ is $R^5X^1$, wherein $R^5$ is as defined for claim 13 or 19, 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):
with a compound of the formula (VIII):

\[ R^5-X^1-H \]  (VIII)

wherein \( R^1, R^2, R^5, \) ring \( C, Z \) and \( n \) are as defined for claim 13 or 19, and \( L^1, s \) and \( X^1 \) are as herein defined;

(d) a compound of the formula (II) or (IIb) or a salt thereof, wherein at least one \( R^2 \) is \( R^5X^1 \), wherein \( X^1 \) is as defined for claim 13 or 19, and \( R^5 \) is \( C_{1-6} \text{alkyl}R^{113} \), wherein \( R^{113} \) is one of the following nine groups:

15 (1) \( X^{19}C_{1-3} \text{alkyl} \), 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, \( C_{1-3} \text{alkyl} \) or \( C_{1-3} \text{alkoxyC}_{2-3} \text{alkyl} \);

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

20 (3) \( X^{20}C_{1-6} \text{alkyl}X^5R^{22} \), 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, \( C_{1-3} \text{alkyl} \) or \( C_{1-3} \text{alkoxyC}_{2-3} \text{alkyl} \), and \( X^5 \) and \( R^{22} \) are as defined for claim 13 or 19;

(4) \( R^{28} \), wherein \( R^{28} \) is as defined for claim 13 or 19;
(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 for claim 13 or 19;

(6) \( X^{22}C_{1-3}\)alkyl\(R^{29} \), 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 for claim 13 or 19;

(7) \( R^{29} \), wherein \( R^{29} \) is as defined for claim 13 or 19;

(8) \( X^{22}C_{1-4}\)alkyl\(R^{28} \), wherein \( X^{22} \) and \( R^{28} \) are as defined for claim 13 or 19; and

(9) \( R^{54}(C_{1-4}\)alkyl)\(_q(X^{22})_rR^{55} \), wherein \( q, r, X^{22}, R^{54} \) and \( R^{55} \) are as defined for claim 13 or 19;

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

(IX)

wherein \( X^1, R^1, R^2, \) ring C, Z and n are as defined for claim 13 or 19, and \( L^1 \) and s are as herein defined, with a compound of the formula (X):

(X)

wherein \( R^{113} \) is as defined herein;

(e) a compound of the formula (II) or (IIb) or a salt thereof, wherein one or more of the substituents (\( R^2 \))\(_m \) is represented by -NR\(^{127}\)R\(^{128}\), wherein 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 (II) or (IIb), wherein the substituent \((R^2)_m\) is an amino group, and an alkylating agent; or

(f) a compound of the formula (II) or (IIb) or a salt 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 \(-SO^-\);

and when a salt of a compound of formula (II) or (IIb) is required, reaction of the compound obtained with an acid or base whereby to obtain the desired salt.