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4-ANILINOQUINOLINE-3-CARBOXAMIDES AS CSF-1R KINASE INHIBITORS

BACKGROUND OF THE INVENTION

The invention relates to chemical compounds, or pharmaceutically acceptable salts thereof, which possess colony stimulating factor 1 receptor (CSF-1R) kinase inhibitory activity and are accordingly useful for their anti-cancer activity and thus in methods of treatment of the human or animal body. The invention also relates to processes for the manufacture of said chemical compounds, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments of use in the production of an anti-cancer effect in a warm-blooded animal such as man.

Receptor tyrosine kinases (RTK's) are a sub-family of protein kinases that play a critical role in cell signalling and are involved in a variety of cancer related processes including cell proliferation, survival, angiogenesis, invasion and metastasis. There are believed to be at least 96 different RTK's including CSF-1R.

CSF-1R or c-fms was originally identified as the oncogene v-fms from the feline sarcoma virus. CSF-1R is a member of the class III RTK's along with c-Kit, fms-related tyrosine kinase 3 (Flt3) and Platelet-derived growth factor receptor α and β (PDGFR α and PDGFR β). All of these kinases have been implicated in the process of tumorigenesis. CSF-1R is normally expressed as an immature 130 kDa transmembrane protein and ultimately results in a mature 145-160 kDa cell surface *N*-linked glycosylated protein. Macrophage colony stimulating factor (M-CSF or CSF-1), the ligand for CSF-1R, binds to the receptor resulting in dimerization, auto-phosphorylation of the receptor and subsequent activation of downstream signal transduction cascades (C.J. Sherr, Biochim Biophys Acta, 1988, 948: 225-243).

CSF-1R is normally expressed in myeloid cells of the mononuclear phagocytic lineage and their bone-marrow progenitors as well as the epithelial cells of the ducts and alveoli in the lactating, but not normal resting, breast tissue. CSF-1R activation stimulates the proliferation, survival, motility and differentiation of cells of the monocyte/macrophage lineage. The mature macrophage plays a key role in normal tissue development and immune defence (F.L. Pixley and E.R. Stanley, Trends in Cell Biology, 2004, 14(11): 628-638). For example, osteoblasts secrete CSF-1 and activate the receptor on osteoclastic progenitors resulting in differentiation into mature osteoclasts (S.L. Teitelbaum, Science, 2000, 289: 1504-1508). The CSF-1R axis plays an important role in placental development, embryonic implantation,

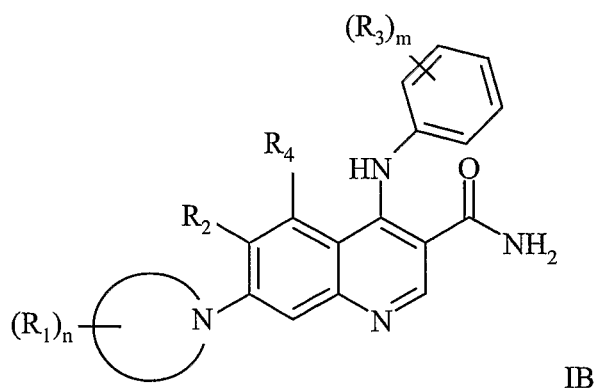
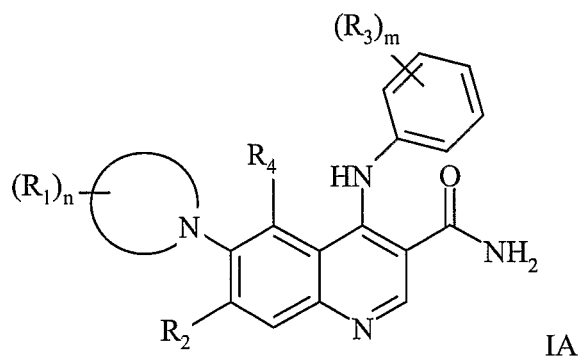
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mammary gland ductal and lobuloalveolar development and lactation (E. Sapi, Exp Biol Med, 2004, 229:1-11).

Transfection of CSF-1R with or without CSF-1 induces transformation and *in vivo* tumorigenicity of NIH3T3 (Rat2 and ovarian granulosa cells. Autocrine and/or paracrine
 5 signaling mechanisms have been implicated in the activation of CSF-1R in the tumour epithelium and tumour associated macrophage. Aberrant expression and activation of CSF-1R and/or its ligand have been found in human myeloid leukaemia, prostate, breast, ovarian, endometrial and a variety of other cancers. A number of studies have demonstrated that the overexpression of CSF-1R is associated with poor prognosis in several of these cancers. In
 10 addition, the CSF-1/CSF-1R axis plays a key role in the regulation of tumour-associated macrophage, which have been postulated to play a significant role in tumour angiogenesis, invasion and progression (E. Sapi, Exp Biol Med, 2004, 229:1-11).

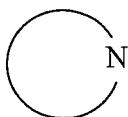
SUMMARY AND DETAILED DESCRIPTION OF THE INVENTION

15 Accordingly, the present invention provides a compound of formula IA or IB:



or a pharmaceutically acceptable salt thereof, wherein:

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is a 3-10 membered, nitrogen linked, heterocycle or heteroaryl; wherein if said heterocycle or heteroaryl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R₅;

- R₁ at each occurrence is independently halo, hydroxy, nitro, formyl, cyano, -CO₂H, -SH, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkoxy, -OC(O)-(C₁-C₆)alkyl, -C(O)-(C₁-C₆)alkyl, -CO₂(C₁-C₆)alkyl, -NR'R'', -NR'-C(O)-(C₁-C₆)alkyl, (C₁-C₆)alkylS(O)_a wherein a is 0 to 2, -NR'-C(O)-O(C₁-C₆)alkyl, -NR'-SO₂-(C₁-C₆)alkyl, -NR'-C(O)NR'R'', -SO₂-NR'R'', -C(O)-NR'R'', carbocyclyl, heterocyclo, heteroaryl or oxo;
- R₂ is hydrogen, halo, hydroxy, nitro, formyl, -CO₂H, -SH, cyano, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl, -O-(C₃-C₆)cycloalkyl, -OC(O)-(C₁-C₆)alkyl, -C(O)-(C₁-C₆)alkyl, -CO₂(C₁-C₆)alkyl, -NR'R'', -NR'-C(O)-(C₁-C₆)alkyl, (C₁-C₆)alkylS(O)_a wherein a is 0 to 2, -NR'-C(O)-O(C₁-C₆)alkyl, -NR'-SO₂-(C₁-C₆)alkyl, -NR'-C(O)NR'R'', -SO₂-NR'R'', -C(O)-NR'R'', -OC(O)-NR'R'', carbocyclyl, heterocyclo, heteroaryl or (C₁-C₆)alkoxy;
- R₃ at each occurrence is independently halo, nitro, formyl, cyano, hydroxy, -NR'R'', -CO₂H, -C(O)-(C₁-C₆)alkyl, -CO₂(C₁-C₆)alkyl, -C(O)-NR'R'', -NR'-C(O)-(C₁-C₆)alkyl, -NR'-C(O)NR'R'', -NR'-C(O)-O(C₁-C₆)alkyl, -O-C(O)-(C₁-C₆)alkyl, -SH, -SO₂-NR'R'', (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylS(O)_a wherein a is 0 to 2, -NR'-SO₂-(C₁-C₆)alkyl, carbocyclyl, heterocyclo, or heteroaryl, wherein if said heterocyclo or heteroaryl contains an -NH- moiety that nitrogen may be optionally substituted by (C₁-C₆)alkyl; or
- two R₃ groups on adjacent carbons may optionally form a 5- or 6-membered saturated, partially unsaturated, unsaturated and/or aromatic ring optionally containing 0, 1, or 2 heteroatoms selected from S, O, or NR_a wherein R_a is absent, H or (C₁-C₆)alkyl;
- R₄ is hydrogen or halo;
- m is 0-3; wherein the values of R₃ may be the same or different;
- n is 0-3; wherein the values of R₁ may be the same or different;
- p is independently 1 or 2 at each occurrence; and
- R₅ is selected from (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, -C(O)-(C₁-C₆)alkyl, -S(O)_p(C₁-C₆)alkyl, -CO₂(C₁-C₆)alkyl, -C(O)-NR'R'', benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

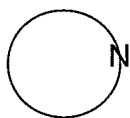
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R' and R'' independently at each occurrence are H, optionally substituted (C₁-C₆)alkyl, or optionally substituted aryl, or taken together with the nitrogen to which they are attached form an optionally substituted 3-6 membered ring saturated or partially unsaturated containing 0 or 1 additional heteroatom selected from NR_a; wherein said optional
 5 substituents may be selected from one or more R₆;

R₆ may be independently (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, halo, nitro, cyano, hydroxy, (C₁-C₆)alkoxy, -NR^xR^y, -COOR^x or -CONR^xR^y; and

R^x and R^y are independently of each other hydrogen or (C₁-C₆)alkyl; and wherein each R_a, R₁, R₂, R₃ and R₅ may be optionally substituted on carbon by one or more
 10 formyl, -SH, azido, halo, nitro, cyano, hydroxy, trifluoromethoxy, -OC(O)-(C₁-C₆)alkyl, -NR'R'', -CO₂H, -C(O)-(C₁-C₆)alkyl, -CO₂(C₁-C₆)alkyl, -C(O)-NR'R'', -S-(C₁-C₆)alkyl, -SO_p-(C₁-C₆)alkyl, -SO_pNR'R'', (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, -NR'-C(O)-(C₁-C₆)alkyl, -NR'-C(O)-O(C₁-C₆)alkyl, -NR'-SO₂-(C₁-C₆)alkyl, -NR'-C(O)NR'R'', (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, or (C₁-C₆)alkoxy.

15 According to a further aspect of the present invention there is provided a compound of formula IA or IB or a pharmaceutically acceptable salt thereof, wherein:



is a 3-8 membered heterocycle or heteroaryl;

R₁ at each occurrence is independently halo, hydroxyl, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkoxy, -OC(O)-(C₁-C₆)alkyl, -C(O)-(C₁-C₆)alkyl,
 20 -CO₂(C₁-C₆)alkyl, -C(O)-NR'R'', or oxo;

R₂ is hydrogen, halo, hydroxyl, cyano, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, or (C₁-C₆)alkoxy;

R₃ at each occurrence is independently halo, nitro, cyano, hydroxy, trifluoromethoxy, NR'R'', CO₂H, -C(O)-(C₁-C₆)alkyl, -CO₂(C₁-C₆)alkyl, -C(O)-NR'R'',
 25 -NR'-C(O)-(C₁-C₆)alkyl, -NR'-C(O)NR'R'', -NR'-C(O)-O(C₁-C₆)alkyl, -O-C(O)-(C₁-C₆)alkyl, SH, -SO₂-NR'R'', (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylS(O)_a wherein a is 0 to 2, -NR'-SO₂-(C₁-C₆)alkyl, -(C₃-C₆)cycloalkyl, heterocyclo, or heteroaryl, wherein if said heterocyclo or heteroaryl contains an -NH- moiety that nitrogen may be optionally substituted by (C₁-C₆)alkyl; and

30 wherein if two R₃ groups are on adjacent carbons, they may optionally form a 5- or 6-membered saturated, partially unsaturated or aromatic ring optionally containing 0, 1, or 2 heteroatoms selected from S, O, or NR_a wherein R_a is H or (C₁-C₆)alkyl, S, or O;

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R_4 is hydrogen or halo;

m is 0-3;

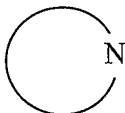
n is 0-3;

p is independently 1 or 2 at each occurrence; and

- 5 R' and R'' independently at each occurrence are H, (C₁-C₆)alkyl, or aryl, or taken together with the nitrogen to which they are attached form an optionally substituted 3-6 membered ring saturated or partially unsaturated containing 0 or 1 additional heteroatom selected from NR_a ; and

each R_a , R_1 , R_2 , and R_3 may be optionally substituted on carbon by azido, halo, nitro,
 10 cyano, hydroxy, trifluoromethoxy, -OC(O)-(C₁-C₆)alkyl, $NR'R''$, -CO₂H, C(O)-(C₁-C₆)alkyl, -CO₂(C₁-C₆)alkyl, -C(O)- $NR'R''$, S(C₁-C₆), SO_p(C₁-C₆)alkyl, SO_pNH(C₁-C₆)alkyl, SO_p $NR'R''$, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, or (C₁-C₆)alkoxy.

According to a further aspect of the present invention there is provided a compound of formula IA or IB or a pharmaceutically acceptable salt thereof, wherein:

- 15  is a 3-8 membered, nitrogen linked, heterocycle or heteroaryl; wherein if said heterocycle or heteroaryl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5 ;

R_1 at each occurrence is independently halo, hydroxy, nitro, formyl, cyano, -CO₂H, -SH, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkoxy,
 20 -OC(O)-(C₁-C₆)alkyl, -C(O)-(C₁-C₆)alkyl, -CO₂(C₁-C₆)alkyl, - $NR'R''$, - NR' -C(O)-(C₁-C₆)alkyl, (C₁-C₆)alkylS(O)_a wherein a is 0 to 2, - NR' -C(O)-O(C₁-C₆)alkyl, - NR' -SO₂-(C₁-C₆)alkyl, - NR' -C(O) $NR'R''$, -SO₂- $NR'R''$, -C(O)- $NR'R''$, carbocyclyl, heterocyclo, heteroaryl or oxo;

R_2 is hydrogen, halo, hydroxy, nitro, formyl, -CO₂H, -SH, cyano, (C₁-C₆)alkyl,
 25 (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl, -O-(C₃-C₆)cycloalkyl, -OC(O)-(C₁-C₆)alkyl, -C(O)-(C₁-C₆)alkyl, -CO₂(C₁-C₆)alkyl, - $NR'R''$, - NR' -C(O)-(C₁-C₆)alkyl, (C₁-C₆)alkylS(O)_a wherein a is 0 to 2, - NR' -C(O)-O(C₁-C₆)alkyl, - NR' -SO₂-(C₁-C₆)alkyl, - NR' -C(O) $NR'R''$, -SO₂- $NR'R''$, -C(O)- $NR'R''$, -OC(O)- $NR'R''$, carbocyclyl, heterocyclo, heteroaryl or (C₁-C₆)alkoxy;

30 R_3 at each occurrence is independently halo, nitro, formyl, cyano, hydroxy, - $NR'R''$, -CO₂H, -C(O)-(C₁-C₆)alkyl, -CO₂(C₁-C₆)alkyl, -C(O)- $NR'R''$, - NR' -C(O)-(C₁-C₆)alkyl, - NR' -C(O) $NR'R''$, - NR' -C(O)-O(C₁-C₆)alkyl, -O-C(O)-(C₁-C₆)alkyl, -SH, -SO₂- $NR'R''$,

- 6 -

(C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylS(O)_a- wherein a is 0 to 2, -NR'-SO₂-(C₁-C₆)alkyl, carbocyclyl, heterocyclo, or heteroaryl, wherein if said heterocyclo or heteroaryl contains an -NH- moiety that nitrogen may be optionally substituted by (C₁-C₆)alkyl; or

- 5 two R₃ groups on adjacent carbons may optionally form a 5- or 6-membered saturated, partially unsaturated, unsaturated and/or aromatic ring optionally containing 0, 1, or 2 heteroatoms selected from S, O, or NR_a wherein R_a is absent, H or (C₁-C₆)alkyl;

R₄ is hydrogen or halo;

m is 0-3; wherein the values of R₃ may be the same or different;

- 10 n is 0-3; wherein the values of R₁ may be the same or different;

p is independently 1 or 2 at each occurrence; and

R₅ is selected from (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, -C(O)-(C₁-C₆)alkyl, -S(O)_p(C₁-C₆)alkyl, -CO₂(C₁-C₆)alkyl, -C(O)-NR'R'', benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

- 15 R' and R'' independently at each occurrence are H, optionally substituted (C₁-C₆)alkyl, or optionally substituted aryl, or taken together with the nitrogen to which they are attached form an optionally substituted 3-6 membered ring saturated or partially unsaturated containing 0 or 1 additional heteroatom selected from NR_a; wherein said optional substituents may be selected from one or more R₆;

- 20 R₆ may be independently (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, halo, nitro, cyano, hydroxy, (C₁-C₆)alkoxy, -NR^xR^y, -COOR^x or -CONR^xR^y; and

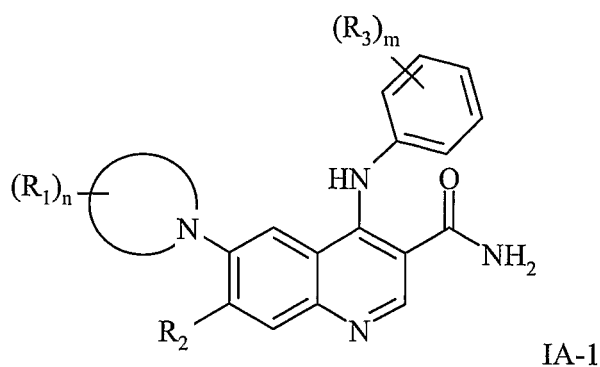
R^x and R^y are independently of each other hydrogen or (C₁-C₆)alkyl; and wherein

- each R_a, R₁, R₂, R₃ and R₅ may be optionally substituted on carbon by one or more formyl, -SH, azido, halo, nitro, cyano, hydroxy, trifluoromethoxy, -OC(O)-(C₁-C₆)alkyl, 25 -NR'R'', -CO₂H, -C(O)-(C₁-C₆)alkyl, -CO₂(C₁-C₆)alkyl, -C(O)-NR'R'', -S-(C₁-C₆)alkyl, -SO_p-(C₁-C₆)alkyl, -SO_pNR'R'', (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, -NR'-C(O)-(C₁-C₆)alkyl, -NR'-C(O)-O(C₁-C₆)alkyl, -NR'-SO₂-(C₁-C₆)alkyl, -NR'-C(O)NR'R'', (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, or (C₁-C₆)alkoxy.

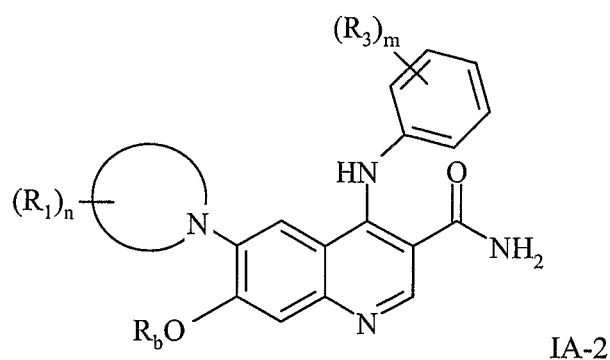
What is also provided is a compound of formula IA-1 or a pharmaceutically

- 30 acceptable salt thereof:

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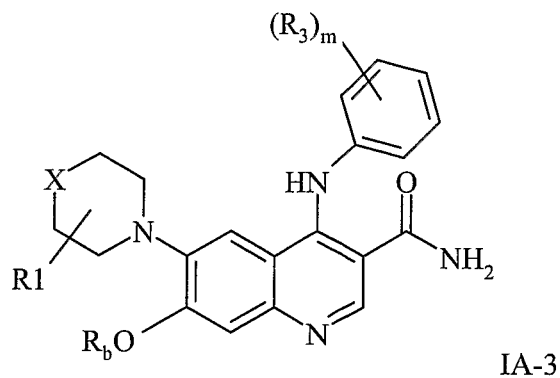


What is also provided is a compound of formula IA-2 or a pharmaceutically acceptable salt thereof:



- 5 wherein R_b at each occurrence is independently H, (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, $-C(O)-(C_1-C_6)$ alkyl, $-C(O)-NR'R''$, wherein each R_b may be optionally substituted on carbon by halo, cyano, hydroxy, trifluoromethoxy, $-OC(O)-(C_1-C_6)$ alkyl, $-NR'R''$, $-CO_2H$, $-C(O)-(C_1-C_6)$ alkyl, $-CO_2(C_1-C_6)$ alkyl, $-C(O)-NR'R''$, $-S(C_1-C_6)$ alkyl, $-SO_p(C_1-C_6)$ alkyl, $-SO_pNR'R''$, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, or (C_1-C_6) alkoxy, wherein R' , R'' , and p are as defined above.
- 10

What is also provided is a compound of formula IA-3 or a pharmaceutically acceptable salt thereof:



wherein

- 15 R_1 and R_b are as defined above; and

- 8 -

X is O, S, SO, SO₂, or N-R_c, wherein R_c is hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, -C(O)-(C₁-C₆)alkyl, -CO₂(C₁-C₆)alkyl, -C(O)-NR'R'', or -SO_pNH(C₁-C₆)alkyl,

wherein R_c may be optionally substituted on carbon by azido, halo, nitro, cyano, hydroxy, trifluoromethoxy, -OC(O)-(C₁-C₆)alkyl, -NR'R'', -CO₂H, -C(O)-(C₁-C₆)alkyl, -CO₂(C₁-C₆)alkyl, -C(O)-NR'R'', -S(C₁-C₆)alkyl, -SO_p(C₁-C₆)alkyl, -SO_pNR'R'', (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, or (C₁-C₆)alkoxy, wherein R', R'', and p are as defined above.

What is also provided is a compound of formula IA-3 or a pharmaceutically acceptable salt thereof wherein:

R₁ and R_b is as defined above; and

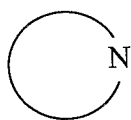
10 X is O, S, SO, SO₂, or N-R_c, wherein R_c is hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkoxy, -OC(O)-(C₁-C₆)alkyl, -C(O)-(C₁-C₆)alkyl, -CO₂(C₁-C₆)alkyl, -C(O)-NR'R'', or SO_pNH(C₁-C₆)alkyl,

wherein R_c may be optionally substituted on carbon by azido, halo, nitro, cyano, hydroxy, trifluoromethoxy, -OC(O)-(C₁-C₆)alkyl, NR'R'', -CO₂H, C(O)-(C₁-C₆)alkyl, -CO₂(C₁-C₆)alkyl, -C(O)-NR'R'', S(C₁-C₆), SO_p(C₁-C₆)alkyl, SO_pNH(C₁-C₆)alkyl, SO_pNR'R'', (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, or (C₁-C₆)alkoxy, wherein R', R'', and p are as defined above.

Particular values of variable groups are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

A compound of formula IA.

A compound of formula IB.

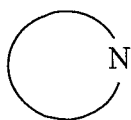


is a 5-7 membered, nitrogen linked, heterocycle; wherein if said heterocycle contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R₅; wherein

R₅ is selected from (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, -C(O)-(C₁-C₆)alkyl and -CO₂(C₁-C₆)alkyl; and

each R₅ may be optionally substituted on carbon by one or more cyano, hydroxy, -OC(O)-(C₁-C₆)alkyl, -NR'R'', (C₃-C₆)cycloalkyl or (C₁-C₆)alkoxy; wherein

30 R' and R'' independently at each occurrence are (C₁-C₆)alkyl.

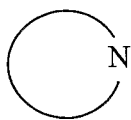


is piperazin-1-yl, piperidin-1-yl, morpholino, homopiperazin-1-yl and pyrrolidin-1-yl; wherein said piperazin-1-yl or homopiperazin-1-yl may be optionally substituted on nitrogen by a group selected from R₅; wherein

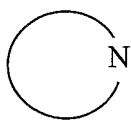
R₅ is selected from methyl, ethyl, isopropyl, cyclopropyl, acetyl, propionyl and
5 *t*-butoxycarbonyl; and

each R₅ may be optionally substituted on carbon by one or more cyano, hydroxy, acetoxy, -NR'R'', cyclopropyl or methoxy; wherein

R' and R'' are methyl.



is piperazin-1-yl, *N*-methylpiperazin-1-yl, *N*-ethylpiperazin-1-yl,
10 *N*-isopropylpiperazin-1-yl, *N*-acetyl piperazin-1-yl, *N*-(2-hydroxyacetyl)piperazin-1-yl,
N-(2-dimethylaminoethyl)piperazin-1-yl, *N*-(2-methoxyethyl)piperazin-1-yl,
N-(2-cyanoethyl)piperazin-1-yl, *N*-(2-hydroxyethyl)piperazin-1-yl,
N-(cyclopropylmethyl)piperazin-1-yl, *N*-(cyclopropyl)piperazin-1-yl,
N-((*R*)-2-hydroxypropionyl)piperazin-1-yl, *N*-((*S*)-2-hydroxypropionyl)piperazin-1-yl,
15 *N*-(*t*-butoxycarbonyl)piperazin-1-yl, *N*-(acetoxyacetyl)piperazin-1-yl, piperidin-1-yl,
morpholino, homopiperazin-1-yl, *N*-methylhomopiperazin-1-yl, *N*-ethylhomopiperazin-1-yl,
N-acetylhomopiperazin-1-yl, *N*-isopropylhomopiperazin-1-yl,
N-cyclopropylhomopiperazin-1-yl and pyrrolidin-1-yl.



is *N*-methylpiperazin-1-yl.
20 R₁ is hydroxy.

R₁ at each occurrence is hydroxy, -NR'R'' or oxo; wherein R' and R'' independently at each occurrence are (C₁-C₆)alkyl.

R₁ at each occurrence is hydroxy, -NMe₂ or oxo.

n is 0 or 1.

25 n is 0.

n is 1.

n is 0 or 1 and R₁ is hydroxy.

n is 0 or 1 and R₁ is hydroxy, -NMe₂ or oxo.

- 10 -

R₂ is hydrogen, halo or (C₁-C₆)alkoxy; wherein R₂ may be optionally substituted on carbon by one or more (C₁-C₆)alkoxy.

R₂ is hydrogen, halo or (C₁-C₆)alkoxy; wherein R₂ may be optionally substituted on carbon by one or more (C₁-C₆)alkoxy or hydroxy.

5 R₂ is hydrogen, halo or (C₁-C₆)alkoxy.

R₂ is hydrogen, fluoro, methoxy, ethoxy or isopropoxy; wherein R₂ may be optionally substituted on carbon by one or more methoxy.

R₂ is hydrogen, fluoro, methoxy, ethoxy or isopropoxy; wherein R₂ may be optionally substituted on carbon by one or more methoxy or hydroxy.

10 R₂ is hydrogen, fluoro, methoxy, ethoxy or isopropoxy.

R₂ is hydrogen, fluoro, methoxy, ethoxy, 2-(methoxy)ethoxy, 2-hydroxyethoxy or isopropoxy.

R₂ is hydrogen.

R₂ is fluoro.

15 R₂ is methoxy.

R₂ is ethoxy.

R₂ is isopropoxy.

R₂ is 2-(methoxy)ethoxy.

R₂ is 2-hydroxyethoxy.

20 R₃ at each occurrence is independently halo, (C₁-C₆)alkyl or (C₁-C₆)alkoxy; wherein R₃ may be optionally substituted on carbon by halo.

R₃ at each occurrence is independently fluoro, chloro, methyl, ethyl or methoxy; wherein R₃ may be optionally substituted on carbon by fluoro.

25 R₃ at each occurrence is independently fluoro, chloro, methyl, trifluoromethyl, ethyl, methoxy or trifluoromethoxy.

m is 1-3; wherein the values of R₃ may be the same or different.

m is 1.

m is 2; wherein the values of R₃ may be the same or different.

m is 3; wherein the values of R₃ may be the same or different.

30 (R₃)_m and the phenyl to which it is attached form 2,4-difluorophenyl, 2-fluoro-3-chlorophenyl or 2-fluoro-4-methylphenyl.

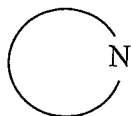
R₄ is hydrogen or fluoro.

R₄ is hydrogen.

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R₄ is fluoro.

Therefore in a further aspect of the invention there is provided a compound of formula IA or IB (as depicted above) wherein:



is a 5-7 membered, nitrogen linked, heterocycle; wherein if said

5 heterocycle contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R₅;

R₁ is hydroxy;

n is 0 or 1;

R₂ is hydrogen, halo or (C₁-C₆)alkoxy;

10 R₃ at each occurrence is independently halo, (C₁-C₆)alkyl or (C₁-C₆)alkoxy; wherein R₃ may be optionally substituted on carbon by halo;

m is 1-3; wherein the values of R₃ may be the same or different;

R₄ is hydrogen or fluoro;

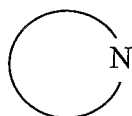
R₅ is selected from (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, -C(O)-(C₁-C₆)alkyl and

15 -CO₂(C₁-C₆)alkyl; wherein R₅ may be optionally substituted on carbon by one or more cyano, hydroxy, -OC(O)-(C₁-C₆)alkyl, -NR'R'', (C₃-C₆)cycloalkyl or (C₁-C₆)alkoxy; and

R' and R'' independently at each occurrence are (C₁-C₆)alkyl;

or a pharmaceutically acceptable salt thereof.

Therefore in a further aspect of the invention there is provided a compound of formula
20 IA or IB (as depicted above) wherein:



is a 5-7 membered, nitrogen linked, heterocycle; wherein if said

heterocycle contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R₅;

R₁ at each occurrence is hydroxy, -NR'R'' or oxo;

25 n is 0 or 1;

R₂ is hydrogen, halo or (C₁-C₆)alkoxy; wherein R₂ may be optionally substituted on carbon by one or more (C₁-C₆)alkoxy or hydroxy;

R₃ at each occurrence is independently halo, (C₁-C₆)alkyl or (C₁-C₆)alkoxy; wherein R₃ may be optionally substituted on carbon by halo;

30 m is 1-3; wherein the values of R₃ may be the same or different;

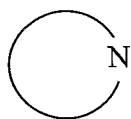
- 12 -

R₄ is hydrogen or fluoro;

R₅ is selected from (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, -C(O)-(C₁-C₆)alkyl and -CO₂(C₁-C₆)alkyl; wherein R₅ may be optionally substituted on carbon by one or more cyano, hydroxy, -OC(O)-(C₁-C₆)alkyl, -NR'R'', (C₃-C₆)cycloalkyl or (C₁-C₆)alkoxy; and

- 5 R' and R'' independently at each occurrence are (C₁-C₆)alkyl;
or a pharmaceutically acceptable salt thereof.

Therefore in a further aspect of the invention there is provided a compound of formula IA or IB (as depicted above) wherein:



- is piperazin-1-yl, *N*-methylpiperazin-1-yl, *N*-ethylpiperazin-1-yl,
10 *N*-isopropylpiperazin-1-yl, *N*-acetylpiperazin-1-yl, *N*-(2-hydroxyacetyl)piperazin-1-yl,
N-(2-dimethylaminoethyl)piperazin-1-yl, *N*-(2-methoxyethyl)piperazin-1-yl,
N-(2-cyanoethyl)piperazin-1-yl, *N*-(2-hydroxyethyl)piperazin-1-yl,
N-(cyclopropylmethyl)piperazin-1-yl, *N*-(cyclopropyl)piperazin-1-yl,
N-((*R*)-2-hydroxypropionyl)piperazin-1-yl, *N*-((*S*)-2-hydroxypropionyl)piperazin-1-yl,
15 *N*-(*t*-butoxycarbonyl)piperazin-1-yl, *N*-(acetoxycetyl)piperazin-1-yl, piperidin-1-yl,
morpholino, homopiperazin-1-yl, *N*-methylhomopiperazin-1-yl, *N*-ethylhomopiperazin-1-yl,
N-acetylhomopiperazin-1-yl, *N*-isopropylhomopiperazin-1-yl,
N-cyclopropylhomopiperazin-1-yl and pyrrolidin-1-yl;

R₁ is hydroxy;

- 20 n is 0 or 1;

R₂ is hydrogen, fluoro, methoxy, ethoxy or isopropoxy;

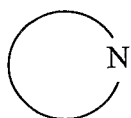
R₃ at each occurrence is independently fluoro, chloro, methyl, trifluoromethyl, ethyl, methoxy or trifluoromethoxy;

m is 1-3; wherein the values of R₃ may be the same or different;

- 25 R₄ is hydrogen or fluoro;

or a pharmaceutically acceptable salt thereof.

Therefore in a further aspect of the invention there is provided a compound of formula IA or IB (as depicted above) wherein:



- is piperazin-1-yl, *N*-methylpiperazin-1-yl, *N*-ethylpiperazin-1-yl,
30 *N*-isopropylpiperazin-1-yl, *N*-acetylpiperazin-1-yl, *N*-(2-hydroxyacetyl)piperazin-1-yl,

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N-(2-dimethylaminoethyl)piperazin-1-yl, *N*-(2-methoxyethyl)piperazin-1-yl,
N-(2-cyanoethyl)piperazin-1-yl, *N*-(2-hydroxyethyl)piperazin-1-yl,
N-(cyclopropylmethyl)piperazin-1-yl, *N*-(cyclopropyl)piperazin-1-yl,
N-((*R*)-2-hydroxypropionyl)piperazin-1-yl, *N*-((*S*)-2-hydroxypropionyl)piperazin-1-yl,
5 *N*-(*t*-butoxycarbonyl)piperazin-1-yl, *N*-(acetoxyacetyl)piperazin-1-yl, piperidin-1-yl,
morpholino, homopiperazin-1-yl, *N*-methylhomopiperazin-1-yl, *N*-ethylhomopiperazin-1-yl,
N-acetylhomopiperazin-1-yl, *N*-isopropylhomopiperazin-1-yl,
N-cyclopropylhomopiperazin-1-yl and pyrrolidin-1-yl;

R_1 at each occurrence is hydroxy, -NMe₂ or oxo;

10 n is 0 or 1;

R_2 is hydrogen, fluoro, methoxy, ethoxy, 2-(methoxy)ethoxy, 2-hydroxyethoxy or isopropoxy;

R_3 at each occurrence is independently fluoro, chloro, methyl, trifluoromethyl, ethyl, methoxy or trifluoromethoxy;

15 m is 1-3; wherein the values of R_3 may be the same or different;

R_4 is hydrogen or fluoro;

or a pharmaceutically acceptable salt thereof.

In another aspect of the invention, preferred compounds of the invention are any one of the Examples or a pharmaceutically acceptable salt thereof.

20 In another aspect of the invention, preferred compounds of the invention are any one of Examples 11, 12, 48, 70, 83, 88, 165, 166, 168 or 172 or a pharmaceutically acceptable salt thereof.

What is also provided is a compound which is one of the Examples.

25 What is also provided is a pharmaceutical composition which comprises a compound of formula IA or IB, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically-acceptable diluent or carrier.

What is also provided is a compound of formula IA or IB, or a pharmaceutically acceptable salt thereof, for use as a medicament.

30 What is also provided is the use of a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the production of a CSF-1R kinase inhibitory effect in a warm-blooded animal such as man.

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What is also provided is the use of a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as man.

What is also provided is the use of a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of melanoma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries.

10 What is also provided is the use of a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of breast, ovarian, bladder, cervical, endometrial, prostate, lung, kidney and pancreatic tumors; haematological malignancies including myelodysplastic syndrome, acute myelogenous leukemia, chronic myelogenous leukemia, non Hodgkin's lymphoma, Hodgkin's
15 disease, multiple myeloma and chronic lymphocytic leukemia; and glioma, squamous cell carcinoma of the esophagus, malignant uveal melanoma and follicular lymphoma. What is also provided is the use of a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of tumor-associated osteolysis, osteoporosis including ovariectomy-induced bone loss,
20 orthopedic implant failure, autoimmune disorders including systemic lupus erythematosus, arthritis including rheumatoid arthritis, osteoarthritis, renal inflammation and glomerulonephritis; inflammatory bowel disease; transplant rejection including renal and bone marrow allografts and skin xenograft, atherosclerosis, obesity, Alzheimer's Disease and Langerhans cell histiocytosis.

25 What is also provided is the use of a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of chronic obstructive pulmonary disease, diabetes and chronic skin disorders including psoriasis.

What is also provided is a method for producing a CSF-1R kinase inhibitory effect in
30 a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula IA or IB, or a pharmaceutically acceptable salt thereof.

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What is also provided is a method for producing an anti-cancer effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula IA or IB, or a pharmaceutically acceptable salt thereof.

5 What is also provided is a method of treating melanoma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries, in a warm-blooded animal, such as man, in need of such treatment which comprises
10 administering to said animal an effective amount of a compound of formula IA or IB or a pharmaceutically acceptable salt thereof.

What is also provided is a method of treating breast, ovarian, bladder, cervical, endometrial, prostate, lung, kidney and pancreatic tumors; haematological malignancies including myelodysplastic syndrome, acute myelogenous leukemia, chronic myelogenous
15 leukemia, non Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma and chronic lymphocytic leukemia; and glioma, squamous cell carcinoma of the esophagus, malignant uveal melanoma and follicular lymphoma, in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula IA or IB or a pharmaceutically acceptable salt thereof.

20 What is also provided is a method of treating tumor-associated osteolysis, osteoporosis including ovariectomy-induced bone loss, orthopedic implant failure, autoimmune disorders including systemic lupus erythematosus, arthritis including rheumatoid arthritis, osteoarthritis, renal inflammation and glomerulonephritis; inflammatory bowel disease; transplant rejection including renal and bone marrow allografts and skin xenograft, atherosclerosis, obesity,
25 Alzheimer's Disease and Langerhans cell histiocytosis, in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula IA or IB or a pharmaceutically acceptable salt thereof.

What is also provided is a method of treating chronic obstructive pulmonary disease, diabetes and chronic skin disorders including psoriasis, in a warm-blooded animal, such as
30 man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula IA or IB or a pharmaceutically acceptable salt thereof.

What is also provided is a pharmaceutical composition which comprises a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, in association with a

pharmaceutically-acceptable diluent or carrier for use in the production of a CSF-1R kinase inhibitory effect in a warm-blooded animal such as man.

What is also provided is a pharmaceutical composition which comprises a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, in association with a
5 pharmaceutically-acceptable diluent or carrier for use in the production of an anti-cancer effect in a warm-blooded animal such as man.

What is also provided is a pharmaceutical composition which comprises a compound of the formula IA or IB or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically-acceptable diluent or carrier for use in the treatment of melanoma, papillary
10 thyroid tumors, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries in a warm-blooded animal such as man.

What is also provided is a pharmaceutical composition which comprises a compound
15 of the formula IA or IB or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically-acceptable diluent or carrier for use in the treatment of breast, ovarian, bladder, cervical, endometrial, prostate, lung, kidney and pancreatic tumors; haematological malignancies including myelodysplastic syndrome, acute myelogenous leukemia, chronic myelogenous leukemia, non Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma and
20 chronic lymphocytic leukemia; and glioma, squamous cell carcinoma of the esophagus, malignant uveal melanoma and follicular lymphoma in a warm-blooded animal such as man.

What is also provided is a pharmaceutical composition which comprises a compound of the formula IA or IB or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically-acceptable diluent or carrier for use in the treatment of tumor-associated
25 osteolysis, osteoporosis including ovariectomy-induced bone loss, orthopedic implant failure, autoimmune disorders including systemic lupus erythematosus, arthritis including rheumatoid arthritis, osteoarthritis, renal inflammation and glomerulonephritis; inflammatory bowel disease; transplant rejection including renal and bone marrow allografts and skin xenograft, atherosclerosis, obesity, Alzheimer's Disease and Langerhans cell histiocytosis in a
30 warm-blooded animal such as man.

What is also provided is a pharmaceutical composition which comprises a compound of the formula IA or IB or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically-acceptable diluent or carrier for use in the treatment of chronic obstructive

pulmonary disease, diabetes and chronic skin disorders including psoriasis in a warm-blooded animal such as man.

What is also provided is a process for preparing a compound of formula IA or IB or a pharmaceutically acceptable salt thereof, as provided in the schemes 1 and 2, *infra*.

5 Definitions

“Alkyl” means a linear saturated monovalent hydrocarbon radical of, unless otherwise specified, one to six carbon atoms or a branched saturated monovalent hydrocarbon radical of, unless otherwise specified, three to six carbon atoms, e.g., methyl, ethyl, propyl, 2-propyl, pentyl, and the like. References to individual alkyl groups such as “propyl” are specific for
10 the straight chain version only and references to individual branched chain alkyl groups such as ‘isopropyl’ are specific for the branched chain version only. For example, “(C₁-C₆)alkyl” includes methyl, propyl, isopropyl and *t*-butyl.

The term “halo” refers to fluoro, chloro, bromo and iodo.

“Alkenyl” means a linear monovalent hydrocarbon radical of, unless otherwise
15 specified, two to six carbon atoms or a branched monovalent hydrocarbon radical of, unless otherwise specified, three to six carbon atoms, containing at least one double bond, e.g., ethenyl, propenyl, and the like. Examples of “(C₂-C₆)alkenyl” are vinyl, allyl and 1-propenyl.

“Alkynyl” means an alkyl group, as defined above, having one or more carbon-carbon triple bonds, e.g., ethynyl. Examples of “(C₂-C₆)alkynyl” are ethynyl, 1-propynyl and
20 2-propynyl.

“Cycloalkyl” means a saturated monovalent cyclic hydrocarbon radical of, unless otherwise specified, three to six ring carbons, e.g., cyclopropyl, cyclohexyl, and the like. Examples of “(C₃-C₆)cycloalkyl” include cyclopropyl and cyclohexyl.

“Aryl” means a monovalent monocyclic or bicyclic aromatic or totally unsaturated
25 hydrocarbon radical of 6 to 10 ring atoms.

“Heterocycle” or “heterocyclo” means a saturated or partially unsaturated cyclic radical of 3 to 8 ring atoms in which one or two ring atoms are heteroatoms selected from NR_a wherein R_a is as defined above, O, S, SO, or SO₂, which may be carbon or nitrogen linked unless otherwise specified.

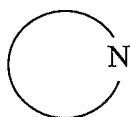
30 “Heteroaryl” means an monovalent monocyclic radical, which is totally unsaturated and/or aromatic ring of 5 or 6 ring atoms containing one, two, or three ring heteroatoms selected from N, O, or S, the remaining ring atoms being C, which may be carbon or nitrogen linked unless otherwise specified. The term heteroaryl includes, but is not limited to pyridyl,

pyrrolyl, thienyl, pyrazolyl, thiazolyl, imidazolyl, pyrimidinyl, thiadiazolyl and derivatives thereof.

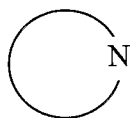
A “carbocyclyl” is a saturated, partially saturated or unsaturated, mono or bicyclic carbon ring that contains 3-12 atoms; wherein a -CH₂- group can optionally be replaced by a
 5 -C(O)-. Particularly “carbocyclyl” is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. Suitable values for “carbocyclyl” include cyclopropyl, cyclobutyl, 1-oxocyclopentyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, phenyl, naphthyl, tetralinyl, indanyl or 1-oxoindanyl. A particular example of “carbocyclyl” is phenyl.

“Two R₃ groups on adjacent carbons may optionally form a 5- or 6-membered
 10 saturated, partially unsaturated, unsaturated and/or aromatic ring optionally containing 0, 1, or 2 heteroatoms selected from S, O, or NR_a wherein R_a is absent, H or (C₁-C₆)alkyl”, said ring forms a bicyclic ring with the phenyl to which it is attached. For the avoidance of doubt the 5- or 6-members of the ring include two from the phenyl ring to which it is attached. Suitable examples of two R₃ groups on adjacent carbons forming a 5- or 6-membered ring together
 15 with the phenyl to which they are attached include naphthyl, indol-6-yl, isoindole-5-yl, benzofuran-4-yl, quinolin-8-yl and 1H-indazol-7-yl.

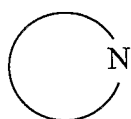
R' and R" “taken together with the nitrogen to which they are attached form a 3-6 membered ring saturated or partially unsaturated containing 0 or 1 additional heteroatom selected from NR_a”. Examples and suitable values of this ring are azetidin-1-yl,
 20 piperidin-1-yl, piperazin-1-yl, *N*-methylpiperazin-1-yl and pyrrolidin-1-yl.



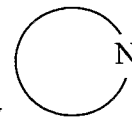
is a 3-10 membered, nitrogen linked, heterocycle or heteroaryl. Said ring may be mono- or bicyclic and/or bridged. Examples and suitable values of this ring include are azetidin-1-yl, morpholino, piperidin-1-yl, piperazin-1-yl, pyrrolidin-1-yl, thiomorpholino, homopiperazin-1-yl, pyrrol-1-yl, pyrazol-1-yl, imidazole-1-yl and triazol-1-yl. Additional



25 examples, where is a bicyclic ring include hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl and 3-methyl-5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8*H*)-yl. Additional examples, where



is a bridged ring include 2,5-diazabicyclo[2.2.1]hept-2-yl. Particularly is a 3-8 membered, nitrogen linked, heterocycle or heteroaryl.



- Examples of “(C₁-C₆)alkoxy” include methoxy, ethoxy and isopropoxy. An example of “-OC(O)-(C₁-C₆)alkyl” is acetoxy. “-CO₂H” is carboxy. Examples of “-C(O)-(C₁-C₆)alkyl” include propionyl and acetyl. Examples of “-C(O)-NR'R” wherein R' and R” are as defined above include carbamoyl, methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl and
- 5 *N*-phenyl-*N*-ethylcarbamoyl. Examples of “-CO₂(C₁-C₆)alkyl” include methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl. Examples of “-NR'R” wherein R' and R” are as defined above include amino, methylamino, ethylamino, dimethylamino, diisopropylamino and *N*-ethyl-*N*-phenylamino. Examples of “-NR'-C(O)-(C₁-C₆)alkyl” wherein R' is as defined above include formamido, acetamide, propionylamino and *N*-acetyl-*N*-phenylamino.
- 10 Examples of “-NR'-C(O)-O(C₁-C₆)alkyl” wherein R' is as defined above are methoxycarbonylamino and *N*-(*t*-butoxycarbonyl)-*N*-phenylamino. Examples of “-NR'-C(O)NR'R” wherein R' and R” are as defined above include ureido, *N,N'*-dimethylureido, *N*-methyl-*N'*-propylureido, *N',N'*-diethylureido, *N'*-methyl-*N'*-propylureido, *N*-(methyl)-*N'*-ethyl-*N'*-isopropylureido and
- 15 *N*-ethyl-*N',N'*-diethylureido. Examples of “-NR'-SO₂-(C₁-C₆)alkyl” wherein R' is as defined above include mesylamino, *N*-ethylsulphonyl-*N*-phenylamino and isopropylsulphonylamino. Examples of “-SO₂-NR'R” wherein R' and R” are as defined above include sulphamoyl, *N*-(methyl)sulphamoyl, *N*-(isopropyl)sulphamoyl, *N,N*-(dimethyl)sulphamoyl and *N*-(methyl)-*N*-(phenyl)sulphamoyl. Examples of “-SO_p-(C₁-C₆)alkyl” wherein p is as defined
- 20 above include mesyl, ethylsulphinyl and isopropylsulphonyl. Examples of “-SO_pNR'R” wherein p, R' and R” are as defined above include amino(oxido)sulfanyl, sulphamoyl, *N*-(methyl)sulphamoyl, *N*-(isopropyl)sulphamoyl, *N*-(isopropyl)amino(oxido)sulfanyl, *N,N*-(dimethyl)sulphamoyl and *N*-(methyl)-*N*-(phenyl)sulphamoyl. Examples of “-S(O)₂(C₁-C₆)alkyl” include mesyl, ethylsulphonyl and isopropylsulphonyl. Examples of
- 25 “-S-(C₁-C₆)alkyl” include methylthio, ethylthio and isopropylthio. Examples of “(C₁-C₆)alkylS(O)_a- wherein a is 0 to 2” include methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl. Examples of “halo(C₁-C₆)alkyl” include trifluoromethyl, 1-chloropropyl and 3-bromo-3-methylbutyl. Examples of “-O-(C₃-C₆)cycloalkyl” include cyclopropyloxy and cyclohexyloxy. Examples of
- 30 -OC(O)-NR'R” include carbamoyloxy, methylcarbamoyloxy, ethylcarbamoyloxy, dimethylcarbamoyloxy and *N*-phenyl-*N*-ethylcarbamoyloxy.

A suitable pharmaceutically acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for

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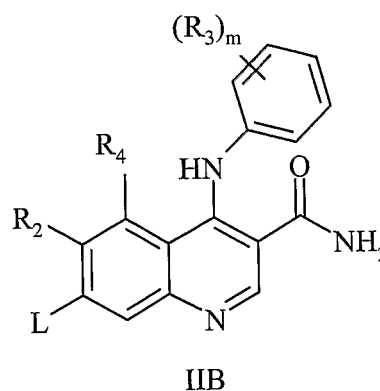
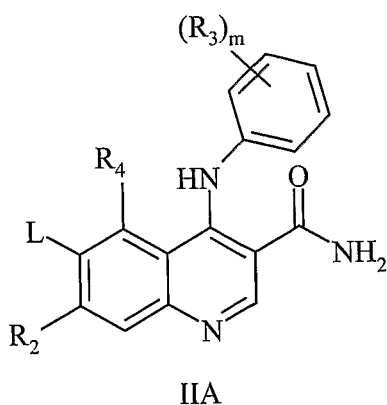
example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Some compounds of the formula IA or IB may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomers and geometric isomers that possess CSF-1R kinase inhibitory activity. The invention further relates to any and all tautomeric forms of the compounds of the formula IA or IB that possess CSF-1R kinase inhibitory activity.

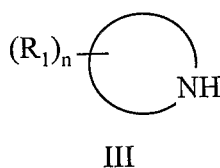
It is also to be understood that certain compounds of the formula IA or IB can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms that possess CSF-1R kinase inhibitory activity.

Another aspect of the present invention provides a process for preparing a compound of formula IA or IB or a pharmaceutically acceptable salt thereof which process (wherein variable groups are, unless otherwise specified, as defined in formula IA or IB) comprises of:

Process a) reacting a compound of formula IIA or IIB:

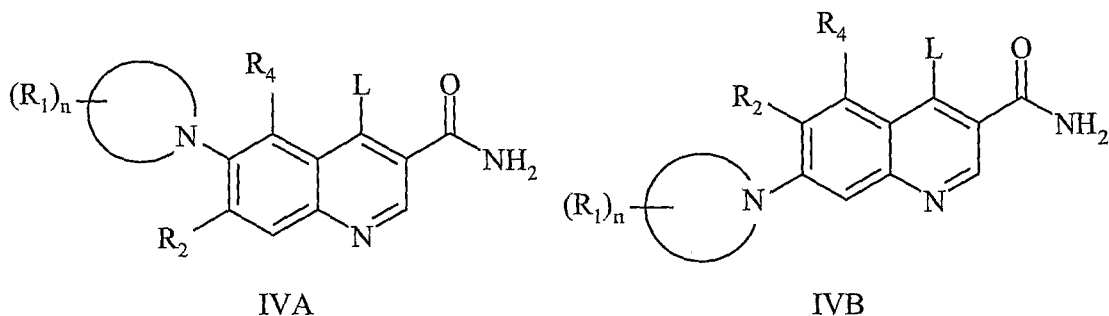


wherein L is a displaceable atom or group; with a compound of formula III:

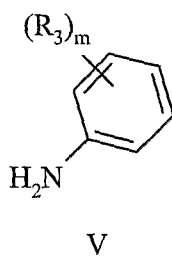


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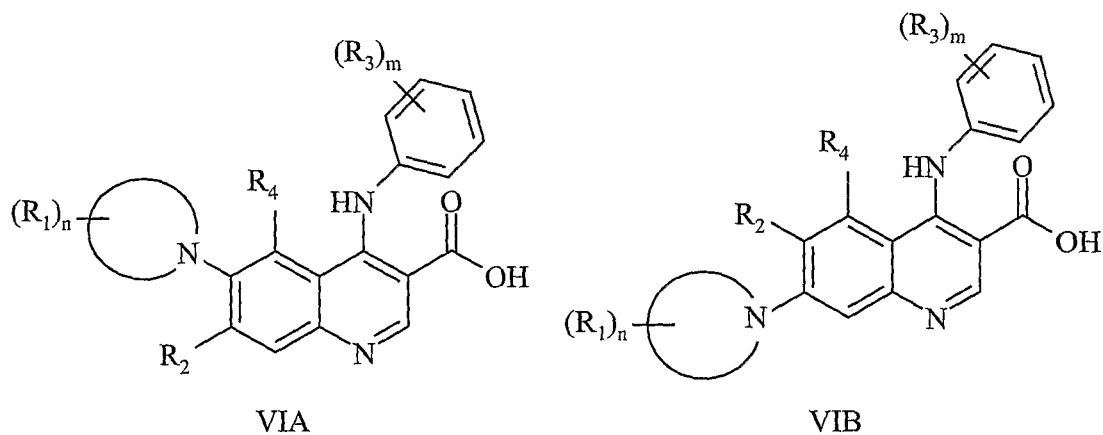
or

Process b) reacting a compound of formula IVA or IVB:

5 wherein L is a displaceable atom or group; with a compound of formula V:



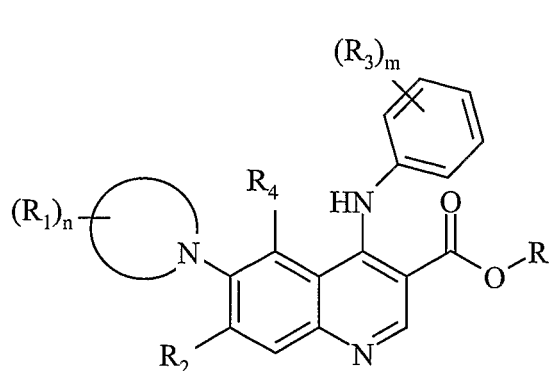
or

Process c) reacting a compound of formula VIA or VIB:

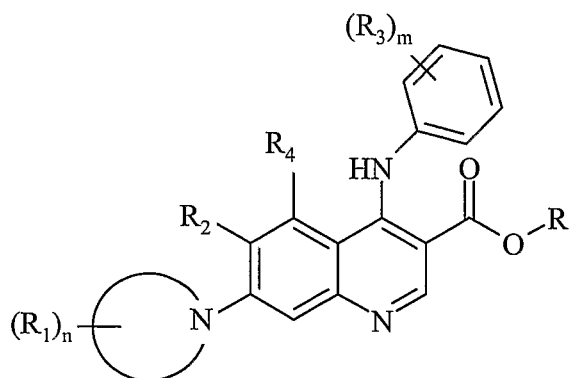
or an activated derivative thereof; with ammonia;

or

Process d) reacting a compound of formula VIIA or VIIB:



VIIA

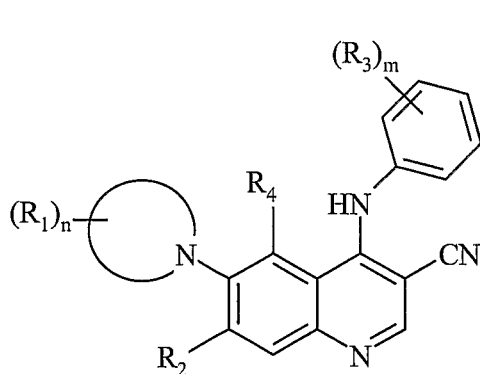


VIIB

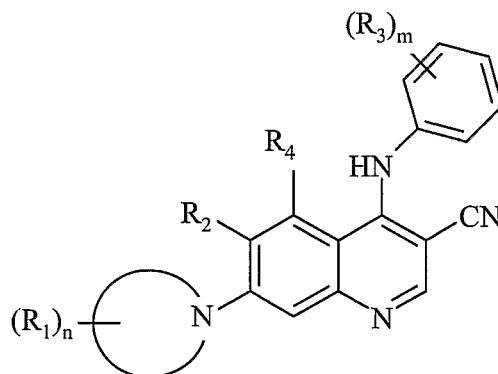
wherein R is (C₁-C₆)alkyl, in particular methyl and ethyl; with formamide and a base;

or

5 *Process e)* hydrolysis of a compound of formula VIIA or VIIB:



VIIIA



VIIB

and thereafter if necessary:

i) converting a compound of the formula IA or IB into another compound of the formula IA
10 or IB;

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt.

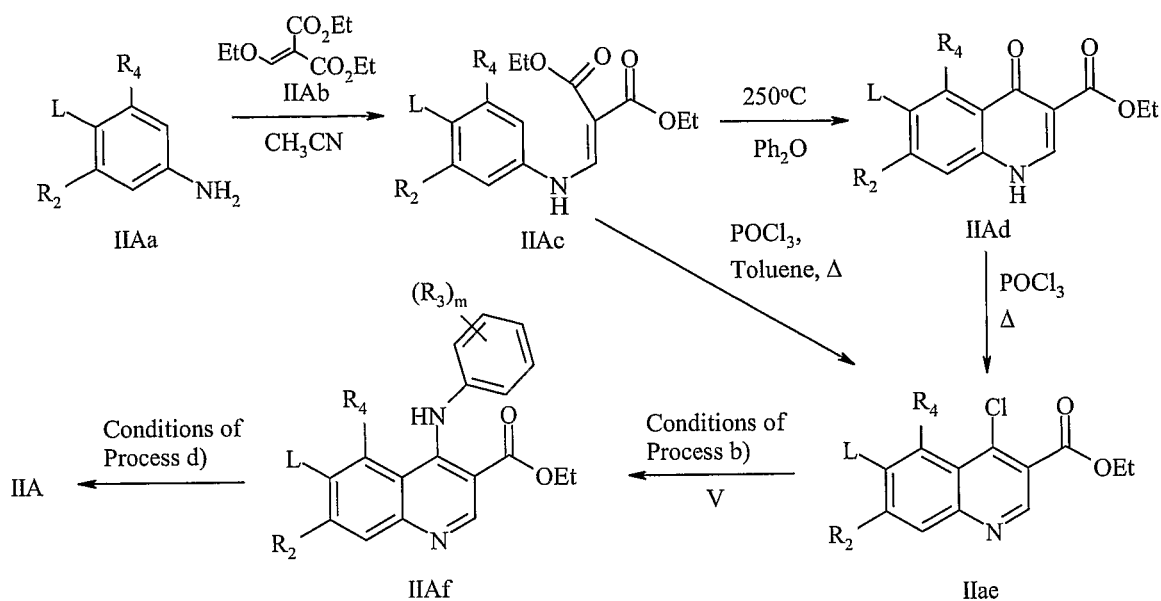
L is a displaceable group, suitable values for L include chloro, bromo, tosyl and trifluoromethylsulphonyloxy.

15 Specific reaction conditions for the above reactions are as follows.

Process a) Compounds of formula IIA or IIB can be reacted with compounds of formula III by coupling chemistry utilizing an appropriate catalyst and ligand such as Pd₂(dba)₃ and BINAP respectively and a suitable base such as sodium *tert*-butoxide or caesium carbonate. The reaction usually requires thermal conditions often in the range of 80 °C to 100 °C.

20 Compounds of formula IIA may be prepared according to the conditions of *Scheme I*:

- 23 -



Scheme 1

Compounds of formula IIB may be prepared by a modification of *Scheme 1*.

Compounds of formula IIAa, IIAb and III are commercially available compounds or

- 5 they are literature compounds or they are readily prepared by processes known to the person skilled in the art.

Process b) Compounds of formula IVA or IVB can be reacted with compounds of formula V in a solvent such as ethanol or dimethylformamide, usually under thermal conditions often in the range of 70 °C to 100 °C, and in some cases catalysed by the addition of acetic acid.

- 10 Alternatively, compounds of formula IVA or IVB can be reacted with compounds of formula V using coupling chemistry utilizing an appropriate catalyst and ligand such as Pd₂(dba)₃ and BINAP respectively and a suitable base such as sodium *tert*-butoxide or caesium carbonate. The reaction usually requires thermal conditions often in the range of 80 °C to 100 °C.

- 15 Compounds of formula IVA and IVB may be prepared by a modification of *Scheme 1*.

Compounds of formula V are commercially available compounds or they are literature compounds or they are readily prepared by processes known to the person skilled in the art.

- Process c)* Acids of formula VIA or VIB and ammonia may be coupled together in the presence of a suitable coupling reagent. Standard peptide coupling reagents known in the art
20 can be employed as suitable coupling reagents, for example carbonyldiimidazole and dicyclohexyl-carbodiimide, optionally in the presence of a catalyst such as dimethylaminopyridine or 4-pyrrolidinopyridine, optionally in the presence of a base for example triethylamine, pyridine, or 2,6-di-*alkyl*-pyridines such as 2,6-lutidine or 2,6-di-*tert*-

butylpyridine. Suitable solvents include dimethylacetamide, dichloromethane, benzene, tetrahydrofuran and dimethylformamide. The coupling reaction may conveniently be performed at a temperature in the range of -40 to 40 °C.

Suitable activated acid derivatives include acid halides, for example acid chlorides, and active esters, for example pentafluorophenyl esters. The reaction of these types of compounds with amines is well known in the art, for example they may be reacted in the presence of a base, such as those described above, and in a suitable solvent, such as those described above. The reaction may conveniently be performed at a temperature in the range of -40 to 40 °C.

10 Compounds of formula VIA or VIB may be prepared by a modification of *Scheme 1*, for example by adding a hydrolysis step and the procedure outlined in *Process a)*.

Process d) Esters of formula VIIA or VIIB may be reacted together with formamide and a base. Preferably this reaction occurs sequentially, addition of the formamide first, followed by the base. Suitable bases are alkoxide bases, for example methoxide and ethoxide bases, eg sodium methoxide. The reaction is typically performed at a temperature of 100 °C in a suitable solvent such as DMF. Compounds of formula VIIA or VIIB may be prepared by a modification of *Scheme 1*.

Process e) Compounds of formula VIIIA or VIIB can be hydrolysed under standard acidic or basic conditions.

20 Compounds of formula VIIIA or VIIB may be prepared by a modification of *Scheme 1*.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts

conditions; and the introduction of a halo group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

5 It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, *Protective Groups in Organic Synthesis*, John Wiley
10 and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group,
15 for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such
20 as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group
25 for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting
30 groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide.

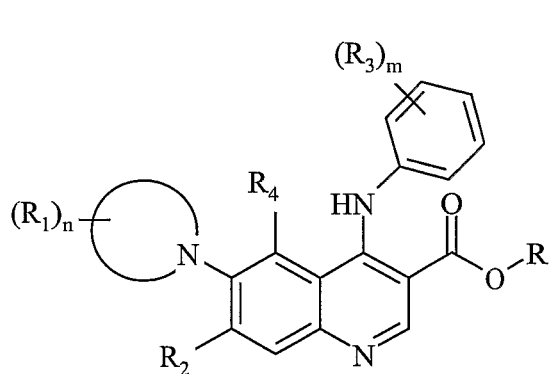
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Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

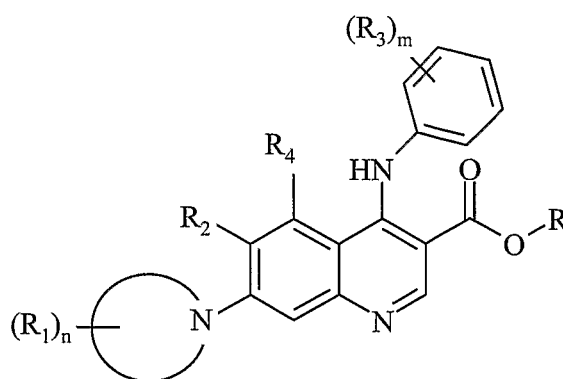
A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis
 5 with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using
 10 conventional techniques well known in the chemical art.

Certain intermediates described herein are novel and are thus provided as a further feature of the invention. For example compounds of formula VIIA and VIIB are provided as a further feature of the invention:



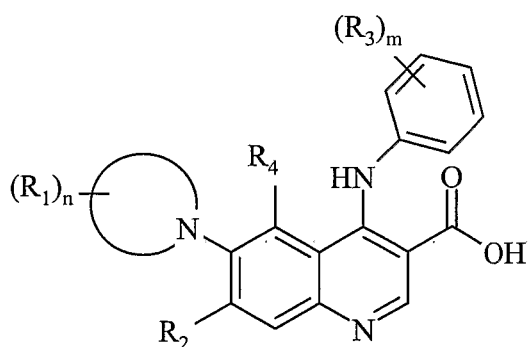
VIIA



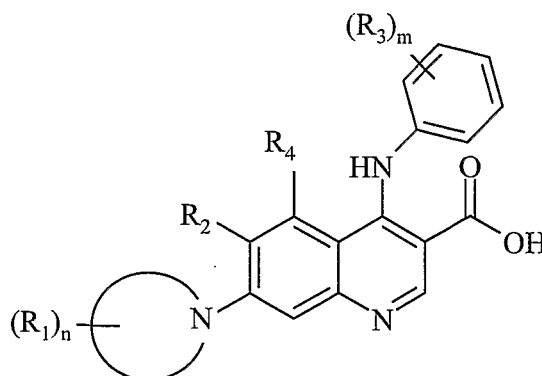
VIIB

wherein variable groups are as defined herein above.

Likewise compounds of formula VIA and VIB are provided as a further feature of the invention:



VIA



VIB

20

wherein variable groups are as defined herein above.

Likewise, novel compounds of formula IIA, IIB, IVA, IVB, VIIIA and VIIIB are considered further features of the invention.

As stated hereinbefore the compounds defined in the present invention possess
5 anti-cancer activity which is believed to arise from the CSF-1R kinase inhibitory activity of the compounds. These properties may be assessed, for example, using the procedure set out below.

Biological Activity

CSF-1R *in vitro* AlphaScreen assay

10 Activity of purified CSF-1R was determined *in vitro* using an Amplified Luminescent Proximity Homogeneous Assay (ALPHA)(Perkin Elmer), which measures phosphorylation of the CSF-1R substrate, biotinylated poly-glutamine-tyrosine peptide (pEY-HTRF CisBio 61GT0BLD), as described below. The His-tagged kinase domain of CSF-1R (i.e., amino acids 568-912, GeneBank ID NM_005211; (see page 25 lines 13-19 of WO 2006/067445 for the
15 sequence listing)) was purified from baculovirus infected SF+Express insect cells (1.4 x 10⁶ cells/ml), French pressed and chromatographed through subsequent Qiagen Ni-NTA, Superflow Mono Q HR 10/10, and Superdex 200 SEC columns. Typical yield was 245µg/l of cell pellet at >95% purity.

The phosphorylation of the CSF-1R substrate in the presence and absence of the
20 compound of interest was determined. Briefly, 0.57 nM of purified CSF-1R, 5nM pEY substrate, and compound were preincubated in 1x buffer for 30 minutes at 25 °C. Reactions were initiated with addition of 90µM adenosine triphosphate (ATP) in 1x buffer and incubated at 25 °C for 60 minutes and reactions stopped by addition of 5µl of detection mix consisting of 136mM NaCl, 102mM ethylenediamine tetraacetic acid, 1.65mg/ml BSA,
25 40ug/ml Streptavidin donor beads (Perkin Elmer 6760002), 40ug/ml pTyr100 acceptor beads (Perkin Elmer 6760620). Plates were incubated at 25°C for 18 hours in the dark. Phosphorylated substrate was detected by an EnVision plate reader (Perkin Elmer) 680nm excitation, 520-620nm emission. Data was graphed and IC₅₀s calculated using Excel Fit (Microsoft).

30 When tested in the above *in vitro* assay, the compounds of the present invention exhibited activity less than 30 µM. For example the following results were obtained:

Example No	IC ₅₀ (nM)
3	26

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Example No	IC ₅₀ (nM)
9	23
18	154

Pharmaceutical Formulations

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, as defined herein, in association with a pharmaceutically-acceptable
5 diluent 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) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.

10 In general the above compositions may be prepared in a conventional manner using conventional excipients.

The compound of formula IA or IB will normally be administered to a warm-blooded animal at a unit dose within the range 1-1000 mg/kg, and this normally provides a therapeutically-effective dose. Preferably a daily dose in the range of 10-100 mg/kg is
15 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.

Uses

20 According to a further aspect of the present invention there is provided a compound of the formula IA or IB, 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 the compounds defined in the present invention, or a pharmaceutically acceptable salt thereof, are effective anti-cancer agents which property is
25 believed to arise from their CSF-1R kinase inhibitory properties. Accordingly the compounds of the present invention are expected to be useful in the treatment of diseases or medical conditions mediated alone or in part by CSF-1R kinase, i.e. the compounds may be used to produce a CSF-1R kinase inhibitory effect in a warm-blooded animal in need of such treatment.

Thus the compounds of the present invention provide a method for treating cancer characterised by inhibition of CSF-1R kinase, i.e. the compounds may be used to produce an anti-cancer effect mediated alone or in part by the inhibition of CSF-1R kinase.

Such a compound of the invention is expected to possess a wide range of anti-cancer properties as aberrant expression of CSF1R and/or CSF1 has been observed in multiple human cancers and derived cell lines, including but not limited to, breast, ovarian, endometrial, prostate, lung, kidney and pancreatic tumors as well as haematological malignancies including, but not limited to, myelodysplastic syndrome, acute myelogenous leukemia, chronic myelogenous leukemia, non Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma and chronic lymphocytic leukemia. Activating mutations have also been reported in haematopoietic and lymphoid tissue and lung cancer. Further, tumor associated macrophages have been associated with poor prognosis in multiple tumor types including, but not limited to, breast, endometrial, kidney, lung, bladder and cervical cancers, glioma, squamous cell carcinoma of the esophagus, malignant uveal melanoma and follicular lymphoma. It is expected that a compound of the invention will possess anticancer activity against these cancers through direct effect on the tumor and/or indirectly through effect on tumor associated macrophages. Alternatively particular cancers include melanoma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries.

In a further aspect of the invention, compounds of formula IA or IB may be also be of value in the treatment of certain additional indications. These indications include, but are not limited to tumor-associated osteolysis, osteoporosis including ovariectomy-induced bone loss, orthopedic implant failure, autoimmune disorders including systemic lupus erythematosus, arthritis including rheumatoid arthritis, osteoarthritis, renal inflammation and glomerulonephritis; inflammatory bowel disease; transplant rejection including renal and bone marrow allografts and skin xenograft, atherosclerosis, obesity, Alzheimer's Disease and Langerhans cell histiocytosis. A further aspect of the present invention therefore includes the treatment of one of more of these diseases, particularly arthritis including rheumatoid arthritis and osteoarthritis. These indications also include, but are not limited to chronic obstructive pulmonary disease, diabetes and chronic skin disorders including psoriasis.

Thus according to this aspect of the invention there is provided a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, as defined hereinbefore for use as a medicament.

According to a further aspect of the invention there is provided the use of a compound
5 of the formula IA or IB, or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of a CSF-1R kinase inhibitory effect in a warm-blooded animal such as man.

According to this aspect of the invention there is provided the use of a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, as defined hereinbefore in
10 the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as man.

According to a further feature of the invention, there is provided the use of a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, as defined herein before in the manufacture of a medicament for use in the treatment of melanoma,
15 papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries.

According to a further feature of the invention, there is provided the use of a
20 compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, as defined herein before in the manufacture of a medicament for use in the treatment of breast, ovarian, bladder, cervical, endometrial, prostate, lung, kidney and pancreatic tumors; haematological malignancies including myelodysplastic syndrome, acute myelogenous leukemia, chronic myelogenous leukemia, non Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma and
25 chronic lymphocytic leukemia; and glioma, squamous cell carcinoma of the esophagus, malignant uveal melanoma and follicular lymphoma.

According to a further feature of the invention, there is provided the use of a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, as defined herein before in the manufacture of a medicament for use in the treatment of tumor-associated
30 osteolysis, osteoporosis including ovariectomy-induced bone loss, orthopedic implant failure, autoimmune disorders including systemic lupus erythematosus, arthritis including rheumatoid arthritis, osteoarthritis, renal inflammation and glomerulonephritis; inflammatory bowel disease; transplant rejection including renal and bone marrow allografts and skin xenograft,

atherosclerosis, obesity, Alzheimer's Disease, chronic obstructive pulmonary disease, diabetes and chronic skin disorders including psoriasis and Langerhans cell histiocytosis.

According to a further feature of this aspect of the invention there is provided a method for producing a CSF-1R kinase inhibitory effect in a warm-blooded animal, such as
5 man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula IA or IB, or a pharmaceutically acceptable salt thereof, as defined above.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-cancer effect in a warm-blooded animal, such as man, in need of
10 such treatment which comprises administering to said animal an effective amount of a compound of formula IA or IB, or a pharmaceutically acceptable salt thereof, as defined above.

According to an additional feature of this aspect of the invention there is provided a method of treating melanoma, papillary thyroid tumours, cholangiocarcinomas, colon cancer,
15 ovarian cancer, lung cancer, leukemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries, in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula IA or IB or a pharmaceutically acceptable salt thereof as
20 defined herein before.

According to an additional feature of this aspect of the invention there is provided a method of treating breast, ovarian, bladder, cervical, endometrial, prostate, lung, kidney and pancreatic tumors; haematological malignancies including myelodysplastic syndrome, acute myelogenous leukemia, chronic myelogenous leukemia, non Hodgkin's lymphoma, Hodgkin's
25 disease, multiple myeloma and chronic lymphocytic leukemia; and glioma, squamous cell carcinoma of the esophagus, malignant uveal melanoma and follicular lymphoma in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula IA or IB or a pharmaceutically acceptable salt thereof as defined herein before.

30 According to an additional feature of this aspect of the invention there is provided a method of treating tumor-associated osteolysis, osteoporosis including ovariectomy-induced bone loss, orthopedic implant failure, autoimmune disorders including systemic lupus erythematosus, arthritis including rheumatoid arthritis, osteoarthritis, renal inflammation and

glomerulonephritis; inflammatory bowel disease; transplant rejection including renal and bone marrow allografts and skin xenograft, atherosclerosis, obesity, Alzheimer's Disease, chronic obstructive pulmonary disease, diabetes and chronic skin disorders including psoriasis and Langerhans cell histiocytosis in a warm-blooded animal, such as man, in need of such
5 treatment which comprises administering to said animal an effective amount of a compound of formula IA or IB or a pharmaceutically acceptable salt thereof as defined herein before.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, as defined herein before in association with a pharmaceutically-acceptable diluent or
10 carrier for use in the production of a CSF-1R kinase inhibitory effect in a warm-blooded animal such as man.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, as defined herein before in association with a pharmaceutically-acceptable diluent or
15 carrier for use in the production of an anti-cancer effect in a warm-blooded animal such as man.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, as defined herein before in association with a pharmaceutically-acceptable diluent or
20 carrier for use in the treatment of melanoma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries in a warm-blooded animal such as man.

25 In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, as defined herein before in association with a pharmaceutically-acceptable diluent or carrier for use in the treatment of breast, ovarian, bladder, cervical, endometrial, prostate, lung, kidney and pancreatic tumors; haematological malignancies including myelodysplastic
30 syndrome, acute myelogenous leukemia, chronic myelogenous leukemia, non Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma and chronic lymphocytic leukemia; and glioma, squamous cell carcinoma of the esophagus, malignant uveal melanoma and follicular lymphoma in a warm-blooded animal such as man.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, as defined herein before in association with a pharmaceutically-acceptable diluent or carrier for use in the treatment of tumor-associated osteolysis, osteoporosis including
5 ovariectomy-induced bone loss, orthopedic implant failure, autoimmune disorders including systemic lupus erythematosus, arthritis including rheumatoid arthritis, osteoarthritis, renal inflammation and glomerulonephritis; inflammatory bowel disease; transplant rejection including renal and bone marrow allografts and skin xenograft, atherosclerosis, obesity, Alzheimer's Disease, chronic obstructive pulmonary disease, diabetes and chronic skin
10 disorders including psoriasis and Langerhans cell histiocytosis in a warm-blooded animal such as man.

According to a further aspect of the invention there is provided the use of a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the production of a CSF-1R kinase inhibitory effect in a warm-blooded animal such as
15 man.

According to this aspect of the invention there is provided the use of a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the production of an anti-cancer effect in a warm-blooded animal such as man.

According to a further feature of the invention, there is provided the use of a
20 compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, as defined herein before in the treatment of melanoma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries.

25 According to a further feature of the invention, there is provided the use of a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, as defined herein before in the treatment of breast, ovarian, bladder, cervical, endometrial, prostate, lung, kidney and pancreatic tumors; haematological malignancies including myelodysplastic syndrome, acute myelogenous leukemia, chronic myelogenous leukemia, non Hodgkin's
30 lymphoma, Hodgkin's disease, multiple myeloma and chronic lymphocytic leukemia; and glioma, squamous cell carcinoma of the esophagus, malignant uveal melanoma and follicular lymphoma.

According to a further feature of the invention, there is provided the use of a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, as defined herein before in the treatment of tumor-associated osteolysis, osteoporosis including ovariectomy-induced bone loss, orthopedic implant failure, autoimmune disorders including
5 systemic lupus erythematosus, arthritis including rheumatoid arthritis, osteoarthritis, renal inflammation and glomerulonephritis; inflammatory bowel disease; transplant rejection including renal and bone marrow allografts and skin xenograft, atherosclerosis, obesity, Alzheimer's Disease, chronic obstructive pulmonary disease, diabetes and chronic skin disorders including psoriasis and Langerhans cell histiocytosis.

10 The CSF-1R kinase inhibitory treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents :-

(i) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical
15 oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside and hydroxyurea; antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin,
20 mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene,
25 raloxifene, droloxifene and idoxifene), oestrogen receptor down regulators (for example fulvestrant), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuporelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5 α -reductase such as
30 finasteride;

(iii) Agents which inhibit cancer cell invasion (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);

- 35 -

- (iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies (for example the anti-erbB2 antibody trastuzumab [Herceptin™] and the anti-erbB1 antibody cetuximab [C225]), farnesyl transferase inhibitors, MEK inhibitors, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family;
- (v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, (for example the anti-vascular endothelial cell growth factor antibody bevacizumab [Avastin™], compounds such as those disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354) and compounds that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v \beta 3$ function and angiostatin);
- (vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO00/40529, WO 00/41669, WO01/92224, WO02/04434 and WO02/08213;
- (vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;
- (viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy;
- (ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies;

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(x) Cell cycle inhibitors including for example CDK inhibitors (eg flavopiridol) and other inhibitors of cell cycle checkpoints (eg checkpoint kinase); inhibitors of aurora kinase and other kinases involved in mitosis and cytokinesis regulation (eg mitotic kinesins); and histone deacetylase inhibitors; and

- 5 (xi) endothelin antagonists, including endothelin A antagonists, endothelin B antagonists and endothelin A and B antagonists; for example ZD4054 and ZD1611 (WO 96 40681), atrasentan and YM598.

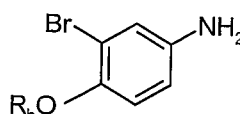
Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products
10 employ the compounds of this invention within the dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

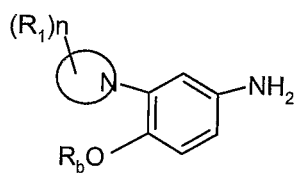
In addition to their use in therapeutic medicine, the compounds of formula IA or IB and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the
15 effects of inhibitors of CSF-1R kinase in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

20 Processes for Making

Compounds of formula 1A can be prepared as provided in Schemes 1 and 2. The routes depicted in the schemes can be readily adapted for preparation of compounds of

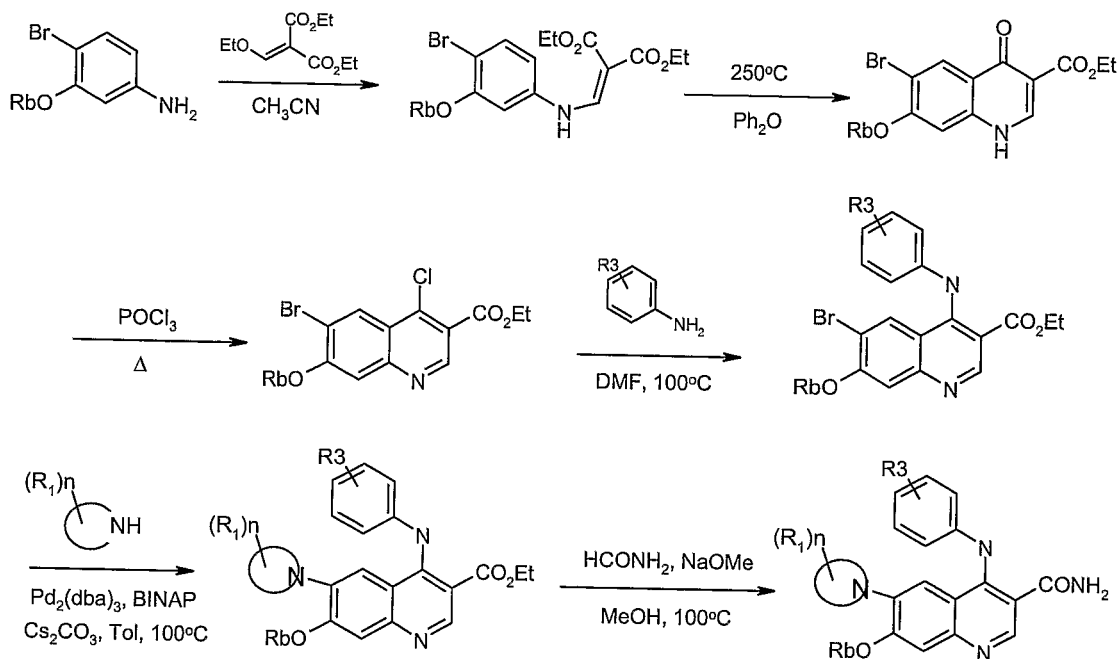
formula IB, by choice of starting material; that, is by using  as a starting

material in Scheme 1 or 

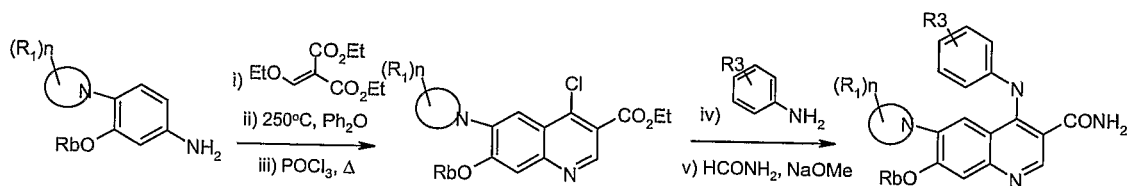
as a starting material in Scheme 2,

25 compounds of formula IB may be obtained.

Scheme 1



Scheme 2



5 Examples

The invention will now be illustrated by the following non limiting examples in which, unless stated otherwise:

- (i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature unless otherwise stated, that is, at a temperature in the range of 18-25°C;
- 10 (ii) organic solutions were dried over anhydrous sodium sulphate or magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mmHg) with a bath temperature of up to 60 °C;
- (iii) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;
- 15 (iv) final products had satisfactory proton nuclear magnetic resonance (NMR) spectra and/or mass spectral data;
- (v) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 400 MHz using perdeuterio dimethyl sulphoxide (DMSO-d₆) as solvent unless otherwise indicated;

5 (vii) chemical symbols have their usual meanings; SI units and symbols are used;

(viii) solvent ratios are given in volume:volume (v/v) terms; and

(ix) mass spectra were run with an electron energy of 70 electron volts in the chemical ionization (CI) mode using a direct exposure probe; where indicated ionization was effected by electron impact (EI), fast atom bombardment (FAB) or electrospray (ESP); values for m/z
10 are given; generally, only ions which indicate the parent mass are reported; and unless otherwise stated, the mass ion quoted is (MH)⁺;

(x) where a synthesis is described as being analogous to that described in a previous example the amounts used are the millimolar ratio equivalents to those used in the previous example;

(xi) the following abbreviations have been used:

15	DMF	<i>N,N</i> -dimethylformamide;
	EtOAc	ethyl acetate;
	MeOH	methanol;
	DIEA	<i>N,N</i> -diisopropylethylamine;
	HATU	<i>O</i> -(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium 20 hexafluorophosphate;
	MP-carbonate	macroporous triethylammonium methylpolystyrene carbonate;
	THF	tetrahydrofuran;
	DMSO	dimethylsulphoxide;

(xii) "ISCO" refers to normal phase flash column chromatography using 12 g and 40 g pre-
25 packed silica gel cartridges used according to the manufacturers instruction obtained from ISCO, Inc, 4700 superior street Lincoln, NE, USA.; and

(xiii) "Gilson HPLC" refers to a YMC-AQC18 reverse phase HPLC Column with dimension 20 mm/100 and 50 mm/250 in water/MeCN with 0.1% TFA as mobile phase.

Example 1**4-[(2,3-Dichlorophenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide**

To a solution of ethyl 4-[(2,3-dichlorophenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate (Intermediate 1; 117 mg, 0.24 mmol) and formamide (47 μ L, 1.2 mmol) in anhydrous DMF under N₂ at 100°C was added dropwise over 10 minutes a solution of NaOMe in MeOH (0.5 M, 1.44 mL, 0.72 mmol). After 2 hours at 100°C, the reaction mixture was cooled and poured into water. The aqueous layer was extracted with EtOAc, dried (Na₂SO₄), filtered, and concentrated to give 38 mg of a solid. ¹H NMR (CD₃OD): 8.92 (s, 1 H), 7.60 (dd, 1 H), 7.39 (m, 3 H), 7.01 (s, 1 H), 4.07 (s, 3 H), 3.50 (m, 2 H), 3.38 (m, 2 H), 3.23 (m, 2 H), 2.92 (s, 3 H), 2.73 (m, 2 H); *m/z*: 460.

Examples 2-173

The following Examples were prepared by a similar method to Example 1 using the appropriate starting materials wherein purification of intermediates and final compounds was in some cases performed using an ISCO column chromatography or a Gilson HPLC system.

Ex.	Compound	NMR	M/z	SM
2	4-[(2,4-Dichlorophenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	CD ₃ OD 8.82 (s, 1 H), 7.52 (d, 1 H), 7.28 (s, 1 H), 7.12 (dd, 1 H), 6.84 (s, 1 H), 6.71 (d, 1 H), 3.97 (s, 3 H), 2.97 (m, 4 H), 2.86 (m, 4 H), 2.52 (s, 3 H)	460	Intermediate 2
3	4-[(3,4-Dichlorophenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	CD ₃ OD 8.79 (s, 1 H), 7.60 (d, 1 H), 7.53 (s, 1 H), 7.44 (d, 2 H), 7.27 (d, 1 H), 4.11 (s, 3 H), 3.61 (m, 4 H), 3.27 (m, 2 H), 2.98 (m, 5 H)	460	Intermediate 3
4	4-[(2,4-Difluorophenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	CD ₃ OD 8.81 (s, 1 H), 7.52 (m, 1 H), 7.44 (s, 1 H), 7.35 (s, 1 H), 7.19 (m, 1 H), 7.12 (t, 1 H), 4.09 (s, 3 H), 3.55 (m, 4 H), 3.29 (m, 2 H), 2.96 (s, 3 H), 2.90 (m, 2 H)	428	Intermediate 4

Ex.	Compound	NMR	M/z	SM
5	4-[(2,3-Dichlorophenyl) amino]-7-methoxy-6-morpholin-4-ylquinoline-3-carboxamide	CD ₃ OD 8.89 (s, 1 H), 7.63 (d, 1 H), 7.42 (m, 2 H), 7.27 (s, 1 H), 6.91 (s, 1 H), 4.06 (s, 3 H), 3.70 (m, 4 H), 2.73 (m, 4 H)	447	Intermediate 5
6	4-[(2,4-Difluorophenyl) amino]-7-methoxy-6-morpholin-4-ylquinoline-3-carboxamide	CD ₃ OD 8.80 (s, 1 H), 7.51 (d, 1 H), 7.31 (s, 1 H), 7.19 (m, 1 H), 7.18 (s, 1 H), 7.14 (m, 1 H), 4.06 (s, 3 H), 3.74 (m, 4 H), 2.85 (m, 4 H)	415	Intermediate 6
7	4-[(3,4-Dichlorophenyl) amino]-7-methoxy-6-morpholin-4-ylquinoline-3-carboxamide	CD ₃ OD 8.78 (s, 1 H), 7.62 (d, 1 H), 7.52 (d, 1 H), 7.29 (m, 2 H), 7.20 (s, 1 H), 4.07 (s, 3 H), 3.76 (m, 4 H), 2.90 (m, 4 H)	447	Intermediate 7
8	4-[(3,4-Dichlorophenyl) amino]-7-methoxy-6-piperidin-1-ylquinoline-3-carboxamide	CD ₃ OD 8.79 (s, 1 H), 7.62 (d, 1 H), 7.51 (d, 1 H), 7.30 (s, 1 H), 7.28 (dd, 1 H), 7.13 (s, 1 H), 4.05 (s, 3 H), 2.81 (m, 4 H), 1.63 (m, 4 H), 1.55 (m, 2 H)	445	Intermediate 8
9	4-[(2,3-Dichlorophenyl) amino]-6-methoxy-7-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	CD ₃ OD 8.91 (s, 1 H), 7.78 (s, 1 H), 7.58 (dd, 1 H), 7.41 (m, 3 H), 6.95 (s, 1 H), 4.08 (m, 2 H), 3.67 (m, 2 H), 3.53 (s, 3 H), 3.33 (m, 4 H), 3.02 (s, 3 H)	460	Intermediate 9
10	4-[(3,4-Dichlorophenyl) amino]-6-methoxy-7-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	CD ₃ OD 8.74 (s, 1 H), 7.57 (d, 1 H), 7.51 (d, 1 H), 7.37 (s, 1 H), 7.34 (s, 1 H), 7.25 (dd, 1 H), 4.03 (m, 2 H), 3.75 (s, 3 H), 3.64 (m, 2 H), 3.30 (m, 4 H), 2.99 (s, 3 H)	460	Intermediate 10

Ex.	Compound	NMR	M/z	SM
11	4-[(2,4-Difluorophenyl) amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	CD ₃ OD 8.80 (s, 1 H), 7.51 (m, 1 H), 7.34 (s, 2 H), 7.20 (m, 1 H), 7.13 (d, 1 H), 4.32 (q, 2 H), 3.54 (m, 4 H), 3.29 (m, 2 H), 2.94 (s, 3 H), 2.85 (m, 2 H), 1.56 (t, 3 H)	441	Intermediate 11
12	4-[(2,3-Dichlorophenyl) amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	CD ₃ OD 8.87 (s, 1 H), 7.53 (dd, 1 H), 7.35 (m, 3 H), 6.93 (s, 1 H), 4.27 (q, 2 H), 3.43 (m, 4 H), 3.20 (m, 2 H), 2.89 (s, 3 H), 2.71 (m, 2 H), 1.49 (t, 3 H)	474	Intermediate 12
13	4-[(2,4-Difluorophenyl) amino]-7-ethoxy-6-morpholin-4-ylquinoline-3-carboxamide	CD ₃ OD 8.78 (s, 1 H), 7.52 (d, 1 H), 7.24 (m, 3 H), 7.14 (m, 1 H), 4.30 (t, 2 H), 3.75 (m, 4 H), 2.86 (m, 4 H), 1.52 (t, 3 H)	429	Intermediate 13
14	4-[(3,4-Dichlorophenyl) amino]-7-ethoxy-6-morpholin-4-ylquinoline-3-carboxamide	CD ₃ OD 8.68 (s, 1 H), 7.53 (d, 1 H), 7.43 (d, 1 H), 7.19 (m, 2 H), 7.10 (s, 1 H), 4.21 (q, 2 H), 3.65 (m, 4 H), 2.83 (m, 4 H), 1.44 (t, 3 H)	461	Intermediate 14
15	tert-Butyl 4-{3-(aminocarbonyl)-4-[(2,3-dichlorophenyl) amino]-7-methoxyquinolin-6-yl}piperazine-1-carboxylate	10.79 (s, 1 H), 8.94 (s, 1 H), 8.35 (s, 1 H), 7.75 (s, 1 H), 7.34 (s, 1 H), 7.25 (dd, 1 H), 7.14 (t, 1 H), 6.70 (s, 1 H), 6.59 (d, 1 H), 3.95 (s, 3 H), 3.33 (m, 4 H), 2.68 (m, 4 H), 1.39 (s, 9 H)	545	Intermediate 15
16	4-[(2,4-Difluorophenyl) amino]-7-fluoro-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.63 (s, 1 H), 8.86 (s, 1 H), 8.29 (s, 1 H), 7.71 (s, 1 H), 7.63 (d, 1 H), 7.38 (m, 1 H), 7.11 (m, 3 H), 2.82 (m, 4 H), 2.48 (m, 4 H), 2.26 (s, 3 H)	416	Intermediate 16

Ex.	Compound	NMR	M/z	SM
17	4-[(2,3-Dichlorophenyl)amino]-7-fluoro-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.84 (s, 1 H), 8.98 (s, 1 H), 8.44 (s, 1 H), 7.86 (s, 1 H), 7.70 (d, 1 H), 7.32 (d, 1 H), 7.19 (t, 1 H), 6.86 (d, 1 H), 6.69 (d, 1 H), 2.82 (m, 4 H), 2.48 (m, 4 H), 2.25 (s, 3 H)	448	Intermediate 17
18	4-[(2,4-Difluorophenyl)amino]-7-fluoro-6-morpholin-4-ylquinoline-3-carboxamide	CD ₃ OD 8.84 (s, 1 H), 7.66 (d, 1 H), 7.52 (m, 1 H), 7.45 (m, 1 H), 7.22 (m, 1 H), 7.14 (m, 1 H), 3.78 (m, 4 H), 2.95 (m, 4 H)	403	Intermediate 18
19	4-[(2,3-Dichlorophenyl)amino]-5-fluoro-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.90 (s, 1 H), 8.95 (s, 1 H), 8.46 (s, 1 H), 7.92 (s, 1 H), 7.79 (m, 1 H), 7.64 (t, 1 H), 7.19 (m, 1 H), 7.04 (t, 1 H), 6.47 (d, 1 H), 2.94 (m, 4 H), 2.38 (m, 4 H), 2.18 (s, 3 H)	448	Intermediate 19
20	7-Ethoxy-4-[(4-ethylphenyl)amino]-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.78 (s, 1 H), 8.82 (s, 1 H), 8.21 (s, 1 H), 7.57 (s, 1 H), 7.17 (s, 1 H), 7.12 (d, 2 H), 6.89 (d, 2 H), 6.80 (s, 1 H), 4.14 (q, 2 H), 2.63 (s, 4 H), 2.55 (q, 2 H), 2.30 (s, 4 H), 2.14 (s, 3 H), 1.38 (t, 3 H), 1.13 (t, 3 H)	434	Intermediate 20
21	4-[(3-Chloro-4-fluorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.35 (s, 1 H), 8.80 (s, 1 H), 8.17 (s, 1 H), 7.59 (s, 1 H), 7.22 - 7.34 (m, 2 H), 7.09 (dd, 1 H), 6.85 - 6.96 (m, 2 H), 4.18 (q, 2 H), 2.81 (s, 4 H), 2.37 (s, 4 H), 2.17 (s, 3 H), 1.40 (t, 3 H)	458	Intermediate 21

Ex.	Compound	NMR	M/z	SM
22	4-[(3,4-Dichlorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	8.78 (s, 1 H), 8.12 (s, 1 H), 7.59 (s, 1 H), 7.44 (d, 1 H), 7.28 (s, 1 H), 7.09 (d, 1 H), 6.96 (s, 1 H), 6.85 (dd, 1 H), 4.19 (q, 2 H), 2.88 (s, 4 H), 2.43 (s, 4 H), 2.19 (s, 3 H), 1.41 (t, 3 H)	474	Intermediate 22
23	4-[(2,3-Dichlorophenyl)amino]-7-ethoxy-6-(4-ethylpiperazin-1-yl)quinoline-3-carboxamide	10.80 (s, 1 H), 8.91 (s, 1 H), 8.37 (s, 1 H), 7.76 (s, 1 H), 7.29 (s, 1 H), 7.26 (d, 1 H), 7.14 (t, 1 H), 6.64 (s, 1 H), 6.57 (d, 1 H), 4.19 (q, 2 H), 2.75 (s, 4 H), 2.38 (s, 4 H), 2.35 (q, 2 H), 1.40 (t, 3 H), 0.97 (t, 3 H)	488	Intermediate 23
24	4-[(3-Chloro-2-fluorophenyl)amino]-7-ethoxy-6-morpholin-4-ylquinoline-3-carboxamide	CD ₂ Cl ₂ 10.42 (s, 1 H), 8.77 (s, 1 H), 7.30 (s, 1 H), 7.06 (m, 1 H), 6.88 (m, 2 H), 6.73 (m, 1 H), 6.05 (br s, 2 H), 4.21 (q, 2 H), 3.72 (m, 4 H), 2.80 (m, 4 H), 1.50 (t, 3 H)	445	Intermediate 24
25	7-Ethoxy-4-[(2-fluoro-5-methylphenyl)amino]-6-morpholin-4-ylquinoline-3-carboxamide	CD ₂ Cl ₂ 10.42 (s, 1 H), 8.74 (s, 1 H), 7.26 (s, 1 H), 7.01 (dd, 1 H), 6.95 (s, 1 H), 6.83 (m, 1 H), 6.77 (dd, 1 H), 6.02 (br s, 2 H), 4.20 (q, 2 H), 3.70 (m, 4 H), 2.74 (m, 4 H), 2.18 (s, 3 H), 1.49 (t, 3 H)	426	Intermediate 25
26	4-[(3-Chloro-4-fluorophenyl)amino]-7-ethoxy-6-morpholin-4-ylquinoline-3-carboxamide	CD ₂ Cl ₂ 10.51 (s, 1 H), 8.75 (s, 1 H), 7.27 (s, 1 H), 7.06 (m, 2 H), 6.92 (m, 1 H), 6.85 (s, 1 H), 6.08 (br s, 2 H), 4.20 (q, 2 H), 3.673 (m, 4 H), 2.79 (m, 4 H), 1.49 (t, 3 H)	447	Intermediate 26

Ex.	Compound	NMR	M/z	SM
27	7-Ethoxy-4-[(4-ethylphenyl)amino]-6-morpholin-4-ylquinoline-3-carboxamide	CD ₂ Cl ₂ 10.60 (s, 1 H), 8.69 (s, 1 H), 7.21 (s, 1 H), 7.11 (d, 2 H), 6.97 (d, 2 H), 6.90 (s, 1 H), 5.92 (br s, 2 H), 4.18 (q, 2 H), 3.66 (m, 4 H), 2.67 (m, 4 H), 2.59 (q, 2 H), 1.47 (t, 3 H), 1.18 (t, 3 H)	421	Intermediate 27
28	4-[(2,3-Dichlorophenyl)amino]-7-ethoxy-6-morpholin-4-ylquinoline-3-carboxamide	CD ₂ Cl ₂ 10.36 (s, 1 H), 8.80 (s, 1 H), 7.32 (s, 1 H), 7.11 (d, 1 H), 6.97 (dd, 1 H), 6.79 (s, 1 H), 6.60 (d, 1 H), 6.04 (br s, 2 H), 4.23 (q, 2 H), 3.72 (m, 4 H), 2.82 (m, 4 H), 1.50 (t, 3 H)	462	Intermediate 28
29	4-[(2,3-Dichlorophenyl)amino]-7-ethoxy-6-(4-isopropylpiperazin-1-yl)quinoline-3-carboxamide	11.10 (s, 1 H), 9.10 (s, 1 H), 8.55 (s, 1 H), 7.95 (s, 1 H), 7.70 (m, 2 H), 7.50 (m, 3 H), 7.36 (s, 1 H), 4.40 (q, 2 H), 3.60 (m, 4 H), 3.30 (m, 1 H), 3.20 (m, 4 H), 1.60 (t, 3 H), 1.50 (d, 6 H)	501	Intermediate 29
30	4-[(2,3-Dichlorophenyl)amino]-7-ethoxy-6-(4-methyl-1,4-diazepan-1-yl)quinoline-3-carboxamide	10.69 (s, 1 H), 8.85 (s, 1 H), 8.35 (s, 1 H), 7.74 (s, 1 H), 7.24 (m, 2 H), 7.12 (m, 1 H), 6.54 (m, 2 H), 4.17 (q, 2 H), 3.14 (m, 2 H), 2.99 (m, 2 H), 2.50 (m, 2 H), 2.42 (m, 2 H), 2.19 (s, 3 H), 1.69 (m, 2 H), 1.41 (t, 3 H)	487	Intermediate 30
31	4-[(2,3-Dichlorophenyl)amino]-7-ethoxy-6-(3-hydroxypyrrolidin-1-yl)quinoline-3-carboxamide	11.99 (s, 1 H), 8.83 (s, 1 H), 8.40 (s, 1 H), 7.90 (s, 1 H), 7.50 (d, 1 H), 7.33 (m, 1 H), 7.28 (s, 1 H), 7.23 (m, 1 H), 6.35 (s, 1 H), 4.12 (m, 3 H), 3.10 (m, 2 H), 2.90 (m, 2 H), 1.79 (m, 1 H), 1.69 (m, 1 H), 1.39 (t, 3 H)	460	Intermediate 31

Ex.	Compound	NMR	M/z	SM
32	4-[(2,3-Dichlorophenyl)amino]-6-{4-[2-(dimethylamino)ethyl]piperazin-1-yl}-7-ethoxyquinoline-3-carboxamide	10.80 (s, 1 H), 9.00 (s, 1 H), 8.42 (s, 1 H), 7.75 (s, 1 H), 7.60 (m, 2 H), 7.35 (m, 2 H), 7.20 (s, 1 H), 4.25 (q, 2 H), 3.80-3.00 (m, 12 H), 2.85 (s, 6 H), 1.48 (t, 3 H)	530	Intermediate 32
33	4-[(2,3-Dichlorophenyl)amino]-7-ethoxy-6-[4-(2-methoxyethyl)piperazin-1-yl]quinoline-3-carboxamide	11.10 (s, 1 H), 9.00 (s, 1 H), 8.45 (s, 1 H), 7.80 (s, 1 H), 7.60 (m, 2 H), 7.35 (m, 2 H), 7.22 (s, 1 H), 4.20 (q, 2 H), 3.71 (s, 3 H), 3.49-3.10 (m, 10 H), 2.95 (t, 2 H), 1.45 (t, 3 H)	517	Intermediate 33
34	4-[(3,4-Dichlorophenyl)amino]-7-ethoxy-6-(4-ethylpiperazin-1-yl)quinoline-3-carboxamide	CD ₂ Cl ₂ 10.42 (s, 1 H), 8.75 (s, 1 H), 7.31 (d, 1 H), 7.27 (s, 1 H), 7.03 (s, 1 H), 6.86 (s, 1 H), 6.83 (d, 1 H), 6.05 (br s, 2 H), 4.21 (q, 2 H), 2.86 (m, 4 H), 2.48 (m, 4 H), 2.39 (q, 2 H), 1.51 (t, 3 H), 1.05 (t, 3 H)	488	Intermediate 34
35	4-[(2,4-Difluorophenyl)amino]-7-ethoxy-6-(4-ethylpiperazin-1-yl)quinoline-3-carboxamide	10.72 (s, 1 H), 8.84 (s, 1 H), 8.27 (s, 1 H), 7.64 (s, 1 H), 7.36 (m, 1 H), 7.23 (s, 1 H), 7.00 (m, 2 H), 6.79 (s, 1 H), 4.16 (q, 2 H), 2.72 (m, 4 H), 2.38 (m, 4 H), 2.32 (q, 2 H), 1.40 (t, 3 H), 0.97 (t, 3 H)	456	Intermediate 35
36	4-[(3-Chloro-2-fluorophenyl)amino]-7-ethoxy-6-(4-ethylpiperazin-1-yl)quinoline-3-carboxamide	10.69 (s, 1 H), 8.86 (s, 1 H), 8.30 (s, 1 H), 7.71 (s, 1 H), 7.18 - 7.29 (m, 2 H), 7.06 (s, 1 H), 6.76 - 6.84 (m, 2 H), 4.18 (q, 2 H), 2.77 (s, 4 H), 2.35 (m, 6 H), 1.40 (t, 3 H), 0.97 (t, 3 H)	472	Intermediate 36

Ex.	Compound	NMR	M/z	SM
37	7-Ethoxy-6-(4-ethylpiperazin-1-yl)-4-[(2-fluoro-5-methylphenyl)amino]quinoline-3-carboxamide	10.78 (s, 1 H), 8.85 (s, 1 H), 8.29 (s, 1 H), 7.66 (s, 1 H), 7.17 (m, 2 H), 6.87 (m, 2 H), 6.69 (s, 1 H), 4.17 (q, 2 H), 2.71 (m, 4 H), 2.34 (m, 6 H), 2.13 (s, 3 H), 1.40 (t, 3 H), 0.97 (t, 3 H)	452	Intermediate 37
38	4-[(3-Chloro-4-fluorophenyl)amino]-7-ethoxy-6-(4-ethylpiperazin-1-yl)quinoline-3-carboxamide	CD ₂ Cl ₂ 10.47 (s, 1 H), 8.74 (s, 1 H), 7.26 (s, 1 H), 7.06 (d, 1 H), 7.04 (dd, 1 H), 6.88 (m, 1 H), 6.85 (s, 1 H), 6.08 (br s, 2 H), 4.20 (q, 2 H), 2.82 (m, 4 H), 2.47 (m, 4 H), 2.38 (q, 2 H), 1.50 (t, 3 H), 1.05 (t, 3 H)	472	Intermediate 38
39	7-Ethoxy-4-[(4-ethylphenyl)amino]-6-(4-ethylpiperazin-1-yl)quinoline-3-carboxamide	CD ₂ Cl ₂ 10.56 (s, 1 H), 8.69 (s, 1 H), 7.19 (s, 1 H), 7.10 (d, 2 H), 6.97 (d, 2 H), 6.91 (s, 1 H), 6.01 (br s, 2 H), 4.17 (q, 2 H), 2.70 (m, 4 H), 2.60 (q, 2 H), 2.39 (m, 4 H), 2.36 (q, 2 H), 1.47 (t, 3 H), 1.19 (t, 3 H), 1.04 (t, 3 H)	448	Intermediate 39
40	6-[4-(2-Cyanoethyl)piperazin-1-yl]-4-[(2,3-dichlorophenyl)amino]-7-ethoxyquinoline-3-carboxamide	10.80 (s, 1 H), 8.90 (s, 1 H), 8.35 (s, 1 H), 7.72 (s, 1 H), 7.30 (s, 1 H), 7.25 (d, 1 H), 7.15 (t, 1 H), 6.65 (s, 1 H), 6.52 (d, 1 H), 4.20 (q, 2 H), 2.80-2.45 (m, 12 H), 1.40 (t, 3 H)	512	Intermediate 40
41	4-[(2,3-Dichlorophenyl)amino]-7-ethoxy-6-(4-hydroxypiperidin-1-yl)quinoline-3-carboxamide	12.40 (s, 1 H), 9.11 (s, 1 H), 8.68 (s, 1 H), 8.00 (s, 1 H), 7.61 (d, 1 H), 7.50 (s, 1 H), 7.40 (m, 2 H), 6.86 (s, 1 H), 4.20 (q, 2 H), 3.55 (m, 1 H), 3.00 (m, 2 H), 2.45 (m, 2 H), 1.70 (m, 2 H), 1.32 (m, 5 H)	474	Intermediate 41

Ex.	Compound	NMR	M/z	SM
42	7-Ethoxy-4-[(4-ethylphenyl)amino]-6-(4-methyl-1,4-diazepan-1-yl)quinoline-3-carboxamide	10.71 (s, 1 H), 8.77 (s, 1 H), 8.20 (s, 1 H), 7.56 (s, 1 H), 7.14 (s, 1 H), 7.11 (d, 2 H), 6.86 (d, 2 H), 6.72 (s, 1 H), 4.13 (q, 2 H), 3.03 (m, 2 H), 2.86 (m, 2 H), 2.555 (m, 2 H), 2.41 (m, 2 H), 2.18 (s, 3 H), 1.65 (m, 2 H), 1.39 (t, 3 H), 1.13 (t, 3 H)	448	Intermediate 42
43	4-[(2,4-Difluorophenyl)amino]-7-ethoxy-6-(3-hydroxypyrrolidin-1-yl)quinoline-3-carboxamide	10.60 (s, 1 H), 8.80 (s, 1 H), 8.30 (s, 1 H), 7.69 (s, 1 H), 7.40 (m, 1 H), 7.25 (s, 1 H), 7.05 (m, 1 H), 6.97 (m, 1 H), 6.45 (s, 1 H), 4.87 (d, 1 H), 4.29 (m, 1 H), 4.20 (q, 2 H), 3.45 (m, 1 H), 3.22 (m, 1 H), 3.00 (m, 2 H), 1.90 (m, 1 H), 1.75 (m, 1 H), 1.46 (t, 3 H)	428	Intermediate 43
44	4-[(2,4-Difluorophenyl)amino]-7-ethoxy-6-(4-hydroxypiperidin-1-yl)quinoline-3-carboxamide	10.78 (s, 1 H), 8.90 (s, 1 H), 8.31 (s, 1 H), 7.70 (s, 1 H), 7.43 (m, 1 H), 7.28 (s, 1 H), 7.05 (m, 2 H), 6.88 (s, 1 H), 4.67 (d, 1 H), 4.21 (q, 2 H), 3.55 (m, 1 H), 3.10 (m, 2 H), 2.46 (m, 2 H), 1.75 (m, 2 H), 1.45 (m, 5 H)	442	Intermediate 44
45	4-[(3,4-Dichlorophenyl)amino]-7-ethoxy-6-(4-isopropylpiperazin-1-yl)quinoline-3-carboxamide	CD ₃ OD 8.79 (s, 1 H), 7.37 (d, 1 H), 7.26 (s, 1 H), 7.07 (s, 1 H), 7.04 (d, 1 H), 6.88 (dd, 1 H), 4.24 (q, 2 H), 2.96 (m, 4 H), 2.65 (m, 5 H), 1.51 (t, 3 H), 1.10 (d, 6 H)	502	Intermediate 45

Ex.	Compound	NMR	M/z	SM
46	4-[(2,4-Difluorophenyl)amino]-7-ethoxy-6-(4-isopropylpiperazin-1-yl)quinoline-3-carboxamide	CD ₃ OD 8.76 (s, 1 H), 7.46 (m, 1 H), 7.36 (s, 1 H), 7.34 (s, 1 H), 7.20 (m, 1 H), 7.13 (m, 1 H), 4.30 (q, 2 H), 3.58 (m, 5 H), 3.26 (m, 2 H), 2.95 (m, 2 H), 1.55 (t, 3 H), 1.42 (d, 6 H)	470	Intermediate 46
47	4-[(3-Chloro-2-fluorophenyl)amino]-7-ethoxy-6-(4-isopropylpiperazin-1-yl)quinoline-3-carboxamide	CD ₃ OD 8.81 (s, 1 H), 7.26 (s, 1 H), 7.16 (m, 1 H), 7.04 (m, 1 H), 6.98 (s, 1 H), 6.83 (m, 1 H), 4.24 (q, 2 H), 2.91 (m, 4 H), 2.69 (m, 5 H), 1.51 (t, 3 H), 1.11 (d, 6 H)	486	Intermediate 47
48	7-Ethoxy-4-[(2-fluoro-5-methylphenyl)amino]-6-(4-isopropylpiperazin-1-yl)quinoline-3-carboxamide	CD ₃ OD 8.78 (s, 1 H), 7.21 (s, 1 H), 7.03 (dd, 1 H), 7.00 (s, 1 H), 6.93 (m, 1 H), 6.78 (dd, 1 H), 4.23 (q, 2 H), 2.83 (m, 4 H), 2.68 (m, 1 H), 2.65 (m, 4 H), 2.19 (s, 3 H), 1.50 (t, 3 H), 1.11 (d, 6 H)	466	Intermediate 48
49	4-[(3-Chloro-4-fluorophenyl)amino]-7-ethoxy-6-(4-isopropylpiperazin-1-yl)quinoline-3-carboxamide	CD ₃ OD 8.77 (s, 1 H), 7.25 (s, 1 H), 7.16 (dd, 1 H), 7.07 (d, 1 H), 7.03 (s, 1 H), 6.95 (dd, 1 H), 4.24 (q, 2 H), 2.96 (m, 4 H), 2.77 (m, 1 H), 2.74 (m, 4 H), 1.51 (t, 3 H), 1.13 (d, 6 H)	486	Intermediate 49
50	4-[(2,4-Difluorophenyl)amino]-7-ethoxy-6-(4-methyl-1,4-diazepan-1-yl)quinoline-3-carboxamide	10.70 (s, 1 H), 8.85 (s, 1 H), 8.30 (s, 1 H), 7.61 (s, 1 H), 7.35 (m, 1 H), 7.25 (s, 1 H), 6.89 (m, 2 H), 6.63 (s, 1 H), 4.20 (q, 2 H), 3.20 (m, 2 H), 3.00 (m, 2 H), 2.55 (m, 7 H), 1.80 (m, 2 H), 1.40 (t, 3 H)	455	Intermediate 50

Ex.	Compound	NMR	M/z	SM
51	4-[(2,3-Dichlorophenyl) amino]-6-(4-isopropylpiperazin-1-yl)-7-methoxyquinoline-3-carboxamide	10.78 (s, 1 H), 8.92 (s, 1 H), 8.35 (s, 1 H), 7.75 (s, 1 H), 7.33 (s, 1 H), 7.26 (m, 1 H), 7.15 (m, 1 H), 6.65 (s, 1 H), 6.58 (d, 1 H), 3.95 (s, 3 H), 2.75 (m, 4 H), 2.60 (m, 1 H), 2.46 (m, 4 H), 0.95 (d, 6 H)	488	Intermediate 51
52	4-[(2,4-Difluorophenyl) amino]-6-(4-isopropylpiperazin-1-yl)-7-methoxyquinoline-3-carboxamide	10.72 (s, 1 H), 9.86 (s, 1 H), 8.30 (s, 1 H), 7.67 (s, 1 H), 7.35 (m, 1 H), 7.26 (s, 1 H), 7.01 (m, 2 H), 6.80 (s, 1 H), 3.92 (s, 3 H), 2.70-2.45 (m, 9 H), 0.95 (d, 6 H)	455	Intermediate 52
53	4-[(2,3-Dichlorophenyl) amino]-7-methoxy-6-(4-methyl-1,4-diazepan-1-yl)quinoline-3-carboxamide	8.90 (s, 1 H), 8.45 (s, 1 H), 7.75 (s, 1 H), 7.30 (m, 2 H), 7.17 (m, 1 H), 6.63 (s, 1 H), 6.58 (d, 1 H), 3.98 (s, 3 H), 3.20 (m, 2 H), 3.10 (m, 2 H), 2.50 (m, 4 H), 2.25 (s, 3 H), 1.75 (m, 2 H)	474	Intermediate 53
54	4-[(2,4-Difluorophenyl) amino]-7-methoxy-6-(4-methyl-1,4-diazepan-1-yl)quinoline-3-carboxamide	10.65 (s, 1 H), 8.80 (s, 1 H), 8.30 (s, 1 H), 7.60 (s, 1 H), 7.32 (m, 1 H), 7.20 (m, 1 H), 6.95 (m, 2 H), 6.75 (m, 1 H), 3.90 (s, 3 H), 3.10 (m, 4 H), 3.00 (m, 4 H), 2.20 (s, 3 H), 1.69 (m, 2 H)	441	Intermediate 54
55	4-[(2,3-Dichlorophenyl) amino]-6-(4-ethylpiperazin-1-yl)-7-methoxyquinoline-3-carboxamide	10.70 (s, 1 H), 8.85 (s, 1 H), 8.26 (s, 1 H), 7.67 (s, 1 H), 7.35 (m, 1 H), 7.28 (s, 1 H), 7.05 (m, 2 H), 6.80 (s, 1 H), 3.90 (s, 3 H), 2.75 (m, 4 H), 2.55 (m, 6 H), 0.95 (t, 3 H)	474	Intermediate 55

Ex.	Compound	NMR	M/z	SM
56	4-[(2,4-Difluorophenyl)amino]-6-(4-ethylpiperazin-1-yl)-7-methoxyquinoline-3-carboxamide	10.80 (s, 1 H), 8.92 (s, 1 H), 8.40 (s, 1 H), 7.80 (s, 1 H), 7.35 (s, 1 H), 7.25 (m, 1 H), 7.15 (m, 1 H), 6.69 (s, 1 H), 6.55 (d, 1 H), 3.95 (s, 3 H), 2.75 (m, 4 H), 2.38 (m, 4 H), 2.31 (q, 2 H), 1.00 (t, 3 H)	441	Intermediate 56
57	4-[(3,4-Dichlorophenyl)amino]-6-(4-ethylpiperazin-1-yl)-7-methoxyquinoline-3-carboxamide	CDCl ₃ 10.45 (s, 1 H), 8.74 (s, 1 H), 7.30 (m, 2 H), 7.03 (d, 1 H), 6.91 (s, 1 H), 6.80 (d, 1 H), 4.00 (s, 3 H), 2.89 (s, 4 H), 2.54 (s, 4 H), 2.44 (q, 2 H), 1.09 (t, 3 H)	474	Intermediate 57
58	4-[(3,4-Dichlorophenyl)amino]-6-(4-isopropylpiperazin-1-yl)-7-methoxyquinoline-3-carboxamide	10.11 (s, 1 H), 8.80 (s, 1 H), 8.13 (s, 1 H), 7.60 (s, 1 H), 7.44 (d, 1 H), 7.31 (s, 1 H), 7.10 (d, 1 H), 6.97 (s, 1 H), 6.84 (d, 1 H), 3.94 (s, 3 H), 2.84 (s, 4 H), 2.63 (s, 1 H), 2.48 (s, 4 H), 0.96 (d, 6 H)	488	Intermediate 58
59	4-[(3,4-Dichlorophenyl)amino]-7-methoxy-6-(4-methyl-1,4-diazepan-1-yl)quinoline-3-carboxamide	CDCl ₃ 10.40 (s, 1 H), 8.69 (s, 1 H), 7.28 (m, 2 H), 7.02 (d, 1 H), 6.80 (m, 2 H), 3.98 (s, 3 H), 3.25 (m, 2 H), 3.08 (m, 2 H), 2.64 (m, 4 H), 2.40 (br s, 3 H), 1.87 (m, 2 H)	474	Intermediate 59
60	4-[(3,4-Dichlorophenyl)amino]-7-ethoxy-6-(4-methyl-1,4-diazepan-1-yl)quinoline-3-carboxamide	CD ₃ OD 8.72 (s, 1 H), 7.38 (d, 1 H), 7.22 (s, 1 H), 7.04 (s, 1 H), 6.86 (m, 2 H), 4.23 (q, 2 H), 3.29 (m, 2 H), 3.11 (m, 2 H), 2.76 (m, 2 H), 2.65 (m, 2 H), 2.36 (s, 3 H), 1.92 (m, 2 H), 1.53 (t, 3 H)	488	Intermediate 60

Ex.	Compound	NMR	M/z	SM
61	7-Ethoxy-4-[(2-fluoro-5-methylphenyl)amino]-6-(4-methyl-1,4-diazepan-1-yl)quinoline-3-carboxamide	CD ₃ OD 8.73 (s, 1 H), 7.19 (s, 1 H), 7.04 (dd, 1 H), 6.89 (m, 2 H), 6.75 (d, 1 H), 4.21 (q, 2 H), 3.17 (m, 2 H), 2.96 (m, 2 H), 2.73 (m, 2 H), 2.64 (m, 2 H), 2.35 (s, 3 H), 2.19 (s, 3 H), 1.89 (m, 2 H), 1.52 (t, 3 H)	452	Intermediate 61
62	4-[(3-Chloro-4-fluorophenyl)amino]-7-ethoxy-6-(4-methyl-1,4-diazepan-1-yl)quinoline-3-carboxamide	CD ₃ OD 8.71 (s, 1 H), 7.21 (s, 1 H), 7.15 (m, 1 H), 7.04 (m, 1 H), 6.94 (m, 1 H), 6.87 (s, 1 H), 4.23 (q, 2 H), 3.24 (m, 2 H), 3.07 (m, 2 H), 2.78 (m, 2 H), 2.68 (m, 2 H), 2.37 (s, 3 H), 1.94 (m, 2 H), 1.52 (t, 3 H)	472	Intermediate 62
63	4-[(2-Fluorophenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.85 (s, 1 H), 8.71 (s, 1 H), 7.53 (s, 1 H), 7.19 (s, 1 H), 6.68 - 7.06 (m, 6 H), 3.84 (s, 3 H), 2.65 (s, 4 H), 2.24 (s, 4 H), 2.08 (s, 3 H)	410	Intermediate 63
64	tert-Butyl 4-{3-(aminocarbonyl)-4-[(3-chloro-4-fluorophenyl)amino]-7-ethoxyquinolin-6-yl}piperazine-1-carboxylate	CD ₂ Cl ₂ 10.42 (s, 1 H), 8.78 (s, 1 H), 7.31 (s, 1 H), 7.08 (m, 1 H), 6.90 (m, 1 H), 6.88 (s, 1 H), 6.72 (m, 1 H), 4.22 (q, 2 H), 3.44 (m, 4 H), 2.76 (m, 4 H), 1.50 (t, 3 H), 1.44 (s, 9 H)	544	Intermediate 64
65	tert-Butyl 4-{3-(aminocarbonyl)-7-ethoxy-4-[(2-fluoro-5-methylphenyl)amino]quinolin-6-yl}piperazine-1-carboxylate	CD ₂ Cl ₂ 10.50 (s, 1 H), 8.76 (s, 1 H), 7.29 (s, 1 H), 7.02 (m, 1 H), 6.94 (s, 1 H), 6.88 (m, 1 H), 6.77 (d, 1 H), 4.21 (q, 2 H), 3.42 (m, 4 H), 2.70 (m, 4 H), 2.18 (s, 3 H), 1.49 (t, 3 H), 1.44 (s, 9 H)	523	Intermediate 65

Ex.	Compound	NMR	M/z	SM
66	tert-Butyl 4-{3-(aminocarbonyl)-4-[(3-chloro-2-fluorophenyl)amino]-7-ethoxyquinolin-6-yl}piperazine-1-carboxylate	CD ₂ Cl ₂ 10.51 (s, 1 H), 8.75 (s, 1 H), 7.29 (s, 1 H), 7.07 (m, 2 H), 6.85 (m, 2 H), 4.22 (q, 2 H), 3.46 (m, 4 H), 2.76 (m, 4 H), 1.50 (t, 3 H), 1.44 (s, 9 H)	544	Intermediate 66
67	7-Methoxy-4-[(3-methoxy-2-methylphenyl)amino]-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.96 (s, 1 H), 8.64 (s, 1 H), 7.44 (s, 1 H), 7.10 (s, 1 H), 6.80-6.85 (m, 1 H), 6.72 (s, 1 H), 6.70 (s, 1 H), 6.57 (d, 1 H), 6.28 (d, 1 H), 3.80 (s, 3 H), 3.69 (s, 3 H), 2.54 (s, 4 H), 2.22 (s, 4 H), 2.12 (s, 3 H), 2.08 (s, 3 H)	436	Intermediate 67
68	4-[(4-Chloro-2-methylphenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.73 (s, 1 H), 8.87 (s, 1 H), 8.30 (s, 1 H), 7.65 (s, 1 H), 7.40-7.41 (m, 1 H), 7.25 (s, 1 H), 7.10-7.13 (m, 1 H), 6.67 (m, 2 H), 3.89 (s, 3 H), 3.34 (s, 3 H), 2.68 (s, 4 H), 2.34 (s, 4 H), 2.17 (s, 3 H)	440	Intermediate 68
69	4-[(3-Chloro-2-methylphenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.85 (s, 1 H), 8.90 (s, 1 H), 8.30 (s, 1 H), 7.60 (s, 1 H), 7.20 (m, 2 H), 7.09 (t, 1 H), 6.65 (m, 2 H), 4.15 (q, 2 H), 2.65 (m, 4 H), 2.50 (s, 3 H), 2.30 (m, 4 H), 1.40 (t, 3 H)	453	Intermediate 69
70	4-[(3-Chloro-2-fluorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.70 (s, 1 H), 8.85 (s, 1 H), 8.30 (s, 1 H), 7.55 (s, 1 H), 7.20 (m, 2 H), 7.05 (m, 1 H), 6.80 (m, 2 H), 4.20 (q, 2 H), 2.75 (m, 4 H), 2.49 (s, 3 H), 2.30 (m, 4 H), 1.40 (t, 3 H)	457	Intermediate 70

Ex.	Compound	NMR	M/z	SM
71	7-Ethoxy-4-[(3-ethylphenyl)amino]-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.70 (s, 1 H), 8.85 (s, 1 H), 8.20 (s, 1 H), 7.60 (s, 1 H), 7.20 (m, 2 H), 6.90-6.70 (m, 4 H), 4.20 (q, 2 H), 2.70 (m, 4 H), 2.50 (m, 5 H), 2.30 (m, 4 H), 1.40 (t, 3 H), 1.10 (t, 3 H)	433	Intermediate 71
72	4-[(3-Chlorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	THF-d8 10.38 (s, 1 H), 8.86 (s, 1 H), 7.60 (s, 1 H), 7.09-7.15 (m, 3 H), 6.74-6.81 (m, 4 H), 4.07 (q, 2 H), 2.70 (s, 4 H), 2.26 (s, 4 H), 2.09 (s, 3 H), 1.86 (t, 3 H)	440	Intermediate 72
73	4-[(2-Chloro-4-fluorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.85 (s, 1 H), 8.95 (s, 1 H), 8.38 (s, 1 H), 7.75 (s, 1 H), 7.65 (d, 1 H), 7.30 (s, 1 H), 7.15 (m, 1 H), 6.85 (m, 1 H), 6.69 (s, 1 H), 4.22 (q, 2 H), 2.80 (m, 4 H), 2.40 (m, 4 H), 2.21 (s, 3 H), 1.45 (t, 3 H)	457	Intermediate 73
74	4-[(4-Chloro-2-fluorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.64 (s, 1 H), 8.85 (s, 1 H), 8.30 (s, 1 H), 7.69 (s, 1 H), 7.50 (d, 1 H), 7.27 (s, 1 H), 7.15 (d, 1 H), 6.89 (m, 1 H), 6.80 (s, 1 H), 4.20 (q, 2 H), 2.80 (m, 4 H), 2.35 (m, 4 H), 2.18 (s, 3 H), 1.40 (t, 3 H)	457	Intermediate 74
75	7-Ethoxy-4-[(3-methylphenyl)amino]-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.70 (s, 1 H), 8.90 (s, 1 H), 8.27 (s, 1 H), 7.65 (s, 1 H), 7.28 (s, 1 H), 7.20 (m, 1 H), 6.93 (m, 2 H), 6.80 (m, 2 H), 4.22 (q, 2 H), 2.75 (m, 4 H), 2.37 (m, 4 H), 2.26 (s, 3 H), 2.20 (s, 3 H), 1.45 (t, 3 H)	419	Intermediate 75

Ex.	Compound	NMR	M/z	SM
76	4-[(2-Chloro-3-methylphenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.80 (s, 1 H), 8.89 (s, 1 H), 8.32 (s, 1 H), 7.65 (s, 1 H), 7.22 (s, 1 H), 7.00 (m, 2 H), 6.70 (s, 1 H), 6.53 (m, 1 H), 4.18 (q, 2 H), 2.69 (m, 4 H), 2.38 (s, 3 H), 2.30 (m, 4 H), 2.15 (s, 3 H), 1.39 (t, 3 H)	453	Intermediate 76
77	7-Ethoxy-4-[(3-fluoro-2-methylphenyl)amino]-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.75 (s, 1 H), 8.86 (s, 1 H), 8.30 (s, 1 H), 7.65 (s, 1 H), 7.20 (s, 1 H), 7.05 (m, 1 H), 6.90 (m, 1 H), 6.66 (s, 1 H), 6.49 (d, 1 H), 4.20 (q, 2 H), 2.70 (m, 4 H), 2.35 (m, 4 H), 2.22 (s, 3 H), 2.15 (s, 3 H), 1.39 (t, 3 H)	437	Intermediate 77
78	4-[(3,4-Difluorophenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	THF-d8 10.99 (s, 1 H), 8.85 (s, 1 H), 7.70 (s, 1 H), 7.34 (s, 1 H), 7.16 (m, 1 H), 6.99 (s, 1 H), 6.89 (m, 2 H), 6.73 (m, 1 H), 3.99 (s, 3 H), 2.84 (s, 4 H), 2.41 (s, 4 H), 2.23 (s, 3 H)	428	Intermediate 78
79	7-Methoxy-6-(4-methylpiperazin-1-yl)-4-{[2-methyl-3-(trifluoromethyl)phenyl]amino}quinoline-3-carboxamide	THF-d8 10.96 (s, 1 H), 8.72 (s, 1 H), 7.67 (s, 1 H), 7.25 (d, 1 H), 7.18 (s, 1 H), 7.02 (t, 1 H), 6.87 (s, 1 H), 6.78 (d, 1 H), 6.64 (s, 1 H), 3.83 (s, 3 H), 2.63 (s, 4 H), 2.45 (s, 3 H), 2.21 (s, 4 H), 2.06 (s, 3 H)	474	Intermediate 79
80	4-[(4-Chlorophenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	THF-d8 10.86 (s, 1 H), 8.70 (s, 1 H), 7.62 (s, 1 H), 7.18 (s, 1 H), 7.10 (d, 2 H), 6.78 (m, 4 H), 3.84 (s, 3 H), 2.68 (s, 4 H), 2.25 (s, 4 H), 2.09 (s, 3 H)	426	Intermediate 80

Ex.	Compound	NMR	M/z	SM
81	4-[(2-Fluoro-4-methylphenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	THF-d8 10.85 (s, 1 H), 8.67 (s, 1 H), 7.48 (s, 1 H), 7.16 (s, 1 H), 6.64-6.89 (m, 5 H), 3.82 (s, 3 H), 2.63 (s, 4 H), 2.24 (s, 4 H), 2.18 (s, 3 H), 2.08 (s, 3 H)	424	Intermediate 81
82	7-Methoxy-6-(4-methylpiperazin-1-yl)-4-{[3-(trifluoromethyl)phenyl]amino}quinoline-3-carboxamide	THF-d8 10.96 (s, 1 H), 8.79 (s, 1 H), 7.60 (s, 1 H), 7.23 (m, 3 H), 6.89 (m, 4 H), 4.09 (s, 3 H), 2.81 (s, 4 H), 2.37 (s, 4 H), 2.20 (s, 3 H)	460	Intermediate 82
83	7-Ethoxy-4-[(2-fluoro-5-methylphenyl)amino]-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	CD ₂ Cl ₂ 10.47 (s, 1 H), 8.76 (s, 1 H), 7.26 (s, 1 H), 7.01 (m, 1 H), 6.95 (s, 1 H), 6.85 (m, 1 H), 6.76 (d, 1 H), 6.02 (br s, 2 H), 4.20 (q, 2 H), 2.81 (m, 4 H), 2.48 (m, 4 H), 2.29 (s, 3 H), 2.19 (s, 3 H), 1.49 (t, 3 H)	438	Intermediate 83
84	4-[(3-Chloro-2-methylphenyl)amino]-7-ethoxy-6-(4-ethylpiperazin-1-yl)quinoline-3-carboxamide	10.80 (s, 1 H), 8.86 (s, 1 H), 8.30 (s, 1 H), 7.65 (s, 1 H), 7.20 (m, 2 H), 7.06 (m, 1 H), 6.65 (s, 2 H), 4.15 (q, 2 H), 2.66 (m, 4 H), 2.50 (s, 3 H), 2.35 (m, 6 H), 1.40 (t, 3 H), 0.98 (t, 3 H)	467	Intermediate 84
85	4-[(3-Chloro-2-methylphenyl)amino]-7-ethoxy-6-(4-methyl-1,4-diazepan-1-yl)quinoline-3-carboxamide	CD ₂ Cl ₂ 10.46 (s, 1 H), 8.68 (s, 1 H), 7.19 (s, 1 H), 7.12 (d, 1 H), 6.96 (m, 1 H), 6.68 (d, 1 H), 6.63 (s, 1 H), 6.05 (br s, 2 H), 4.17 (q, 2 H), 3.08 (m, 2 H), 2.93 (m, 2 H), 2.52 (m, 4 H), 2.46 (s, 3 H), 2.29 (s, 3 H), 1.68 (m, 2 H), 1.49 (t, 3 H)	467	Intermediate 85

Ex.	Compound	NMR	M/z	SM
86	7-Ethoxy-6-(4-ethylpiperazin-1-yl)-4-[(3-fluoro-2-methylphenyl)amino]quinoline-3-carboxamide	10.80 (s, 1 H), 8.90 (s, 1 H), 8.34 (s, 1 H), 7.70 (s, 1 H), 7.30 (s, 1 H), 7.12 (m, 1 H), 6.95 (m, 1 H), 6.75 (s, 1 H), 6.54 (m, 1 H), 4.21 (q, 2 H), 2.66 (m, 4 H), 2.55 (s, 3 H), 2.40 (m, 6 H), 1.45 (t, 3 H), 1.05 (t, 3 H)	451	Intermediate 86
87	7-Ethoxy-4-[(3-fluoro-2-methylphenyl)amino]-6-(4-methyl-1,4-diazepan-1-yl)quinoline-3-carboxamide	CD ₂ Cl ₂ 10.30 (s, 1 H), 8.60 (s, 1 H), 7.10 (s, 1 H), 6.85 (m, 1 H), 6.65 (m, 1 H), 6.56 (s, 1 H), 6.42 (d, 1 H), 4.05 (q, 2 H), 3.00 (m, 2 H), 2.80 (m, 2 H), 2.49 (m, 2 H), 2.40 (m, 2 H), 2.20 (s, 6 H), 1.69 (m, 2 H), 1.36 (t, 3 H)	451	Intermediate 87
88	7-Ethoxy-4-[(2-fluoro-4-methylphenyl)amino]-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.79 (s, 1 H), 8.83 (s, 1 H), 8.26 (s, 1 H), 7.63 (s, 1 H), 7.20 (s, 1 H), 7.09 (d, 1 H), 6.91 (m, 2 H), 6.80 (s, 1 H), 4.17 (q, 2 H), 2.68 (s, 4 H), 2.32 (s, 4 H), 2.27 (s, 3 H), 2.15 (s, 3 H), 1.39 (t, 3 H)	439	Intermediate 88
89	7-Ethoxy-4-[(3-methoxy-2-methylphenyl)amino]-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.89 (s, 1 H), 8.83 (s, 1 H), 8.28 (s, 1 H), 7.58 (s, 1 H), 7.16 (s, 1 H), 7.05 (m, 1 H), 6.77 (d, 1 H), 6.70 (s, 1 H), 6.38 (d, 1 H), 4.14 (q, 2 H), 3.80 (s, 3 H), 2.59 (s, 4 H), 2.27 (s, 4 H), 2.16 (s, 3 H), 2.14 (s, 3 H), 1.39 (t, 3 H)	450	Intermediate 89
90	4-[(2,5-Difluorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	CD ₃ OD 8.82 (s, 1 H), 7.29 (s, 1 H), 7.19 (m, 1 H), 7.03 (s, 1 H), 6.79 (m, 1 H), 6.58 (m, 1 H), 4.25 (q, 2 H), 2.93 (m, 4 H), 2.55 (m, 4 H), 2.30 (s, 3 H), 1.52 (t, 3 H)	442	Intermediate 90

Ex.	Compound	NMR	M/z	SM
91	4-[(2,5-Difluorophenyl)amino]-7-ethoxy-6-(4-ethylpiperazin-1-yl)quinoline-3-carboxamide	CD ₃ OD 8.82 (s, 1 H), 7.29 (s, 1 H), 7.20 (m, 1 H), 7.04 (s, 1 H), 6.79 (m, 1 H), 6.58 (m, 1 H), 4.25 (q, 2 H), 2.95 (m, 4 H), 2.59 (m, 4 H), 2.48 (q, 2 H), 1.52 (t, 3 H), 1.11 (t, 3 H)	456	Intermediate 91
92	4-[(2,5-Difluorophenyl)amino]-7-ethoxy-6-(4-methyl-1,4-diazepan-1-yl)quinoline-3-carboxamide	CD ₃ OD 8.76 (s, 1 H), 7.26 (s, 1 H), 7.17 (m, 1 H), 6.88 (s, 1 H), 6.76 (m, 1 H), 6.51 (m, 1 H), 4.25 (q, 2 H), 3.29 (m, 2 H), 3.08 (m, 2 H), 2.80 (m, 2 H), 2.68 (m, 2 H), 2.37 (s, 3 H), 1.93 (m, 2 H), 1.54 (t, 3 H)	456	Intermediate 92
93	7-Ethoxy-6-(4-ethylpiperazin-1-yl)-4-[(2-fluoro-4-methylphenyl)amino]quinoline-3-carboxamide	10.79 (s, 1 H), 8.84 (s, 1 H), 8.27 (s, 1 H), 7.63 (s, 1 H), 7.20 (s, 1 H), 7.13 (d, 1 H), 6.90 (m, 2 H), 6.80 (s, 1 H), 4.16 (q, 2 H), 2.68 (s, 4 H), 2.36 (s, 4 H), 2.31 (s, 2 H), 2.27 (s, 3 H), 1.38 (t, 3 H), 0.97 (t, 3 H)	453	Intermediate 93
94	4-[(3,4-Dimethylphenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.74 (s, 1 H), 8.80 (s, 1 H), 8.18 (s, 1 H), 7.54 (s, 1 H), 7.16 (s, 1 H), 7.03 (d, 1 H), 6.85 (s, 1 H), 6.79 (s, 1 H), 6.72 (d, 1 H), 4.15 (q, 2 H), 2.65 (s, 4 H), 2.29 (s, 4 H), 2.16 (s, 3 H), 2.14 (s, 3 H), 2.13 (s, 3 H), 1.38 (t, 3 H)	435	Intermediate 94

Ex.	Compound	NMR	M/z	SM
95	4-[(2,4-Difluorophenyl)amino]-6-ethoxy-7-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.55 (s, 1 H), 8.83 (s, 1 H), 8.25 (s, 1 H), 7.63 (s, 1 H), 7.35 (m, 1 H), 7.19 (s, 1 H), 6.98 (d, 2 H), 6.80 (s, 1 H), 3.65 (q, 2 H), 3.15 (s, 4 H), 2.48 (s, 4 H), 2.22 (s, 3 H), 1.21 (t, 3 H)	442	Intermediate 95
96	4-[(2,3-Dichlorophenyl)amino]-6-ethoxy-7-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.65 (s, 1 H), 8.91 (s, 1 H), 8.35 (s, 1 H), 7.75 (s, 1 H), 7.25 (s, 1 H), 7.22 (d, 1 H), 7.14 (m, 1 H), 6.66 (s, 1 H), 6.54 (d, 1 H), 3.66 (q, 2 H), 3.17 (s, 4 H), 2.49 (s, 4 H), 2.23 (s, 3 H), 1.21 (t, 3 H)	474	Intermediate 96
97	4-[(2,3-Difluorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.65 (s, 1 H), 8.89 (s, 1 H), 8.30 (s, 1 H), 7.70 (s, 1 H), 7.25 (s, 1 H), 7.05 (m, 2 H), 6.85 (s, 1 H), 6.65 (m, 1 H), 4.16 (q, 2 H), 2.75 (m, 4 H), 2.35 (m, 4 H), 2.15 (s, 3 H), 1.40 (t, 3 H)	441	Intermediate 97
98	4-[(2,3-Dimethylphenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.98 (s, 1 H), 8.85 (s, 1 H), 8.25 (s, 1 H), 7.55 (s, 1 H), 7.16 (s, 1 H), 7.00 (m, 2 H), 6.65 (m, 2 H), 4.15 (q, 2 H), 2.60 (m, 4 H), 2.30 (m, 7 H), 2.20 (s, 3 H), 2.15 (s, 3 H), 1.40 (t, 3 H)	433	Intermediate 98
99	4-[(4-Chloro-3-fluorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.15 (s, 1 H), 8.80 (s, 1 H), 8.12 (s, 1 H), 7.60 (s, 1 H), 7.39 (m, 1 H), 7.28 (s, 1 H), 6.98-6.90 (m, 2 H), 6.70 (d, 1 H), 4.20 (q, 2 H), 2.90 (m, 4 H), 2.40 (m, 4 H), 1.40 (t, 3 H)	458	Intermediate 99

Ex.	Compound	NMR	M/z	SM
100	4-[(2,3-Dichlorophenyl)amino]-6-ethoxy-7-(4-ethylpiperazin-1-yl)quinoline-3-carboxamide	10.65 (s, 1 H), 8.92 (br s, 1 H), 8.35 (s, 1 H), 7.74 (s, 1 H), 7.23 (d, 2 H), 7.14 (m, 1 H), 6.66 (s, 1 H), 6.54 (d, 1 H), 3.66 (q, 2 H), 3.18 (s, 4 H), 2.51 (s, 4 H), 2.37 (q, 2 H), 1.21 (t, 3 H), 1.03 (t, 3 H)	488	Intermediate 100
101	4-[(2,4-Difluorophenyl)amino]-6-ethoxy-7-(4-ethylpiperazin-1-yl)quinoline-3-carboxamide	10.57 (s, 1 H), 8.85 (s, 1 H), 8.27 (s, 1 H), 7.64 (s, 1 H), 7.37 (m, 1 H), 7.21 (s, 1 H), 6.99 (m, 2 H), 6.81 (s, 1 H), 3.66 (q, 2 H), 3.17 (s, 4 H), 2.51 (s, 4 H), 2.39 (q, 2 H), 1.21 (t, 3 H), 1.04 (t, 3 H)	456	Intermediate 101
102	4-[(3-Chloro-2,4-difluorophenyl)amino]-7-ethoxy-6-(4-ethylpiperazin-1-yl)quinoline-3-carboxamide	10.60 (s, 1 H), 8.85 (s, 1 H), 8.27 (s, 1 H), 7.65 (s, 1 H), 7.25 (m, 2 H), 6.95 (m, 1 H), 6.85 (s, 1 H), 4.20 (q, 2 H), 2.80 (m, 4 H), 2.40 (m, 4 H), 2.31 (m, 2 H), 1.40 (t, 3 H), 1.00 t, 3 H)	489	Intermediate 102
103	4-[(3-Chloro-2,4-difluorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.60 (s, 1 H), 8.83 (s, 1 H), 8.28 (s, 1 H), 7.65 (s, 1 H), 7.25 (m, 2 H), 7.00 (m, 1 H), 6.88 (s, 1 H), 4.20 (q, 2 H), 3.80 (m, 4 H), 2.39 (m, 4 H), 2.20 (s, 3 H), 1.40 (t, 3 H)	475	Intermediate 103
104	4-[(3-Chloro-4-fluorophenyl)amino]-6-ethoxy-7-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.12 (s, 1 H), 8.82 (s, 1 H), 8.15 (s, 1 H), 7.59 (s, 1 H), 7.27 (m, 2 H), 7.14 (d, 1 H), 6.97 (s, 1 H), 6.88 (d, 1 H), 3.81 (q, 2 H), 3.19 (s, 4 H), 2.48 (s, 4 H), 2.25 (s, 3 H), 1.27 (t, 3 H)	458	Intermediate 104

Ex.	Compound	NMR	M/z	SM
105	4-[(3-Chloro-4-fluorophenyl)amino]-6-ethoxy-7-(4-ethylpiperazin-1-yl)quinoline-3-carboxamide	10.17 (s, 1 H), 8.86 (s, 1 H), 8.19 (s, 1 H), 7.63 (s, 1 H), 7.34 (m, 1 H), 7.29 (s, 1 H), 7.19 (d, 1 H), 7.01 (s, 1 H), 6.92 (d, 1 H), 3.85 (q, 2 H), 3.24 (s, 4 H), 2.61 (s, 4 H), 2.44 (q, 2 H), 1.32 (t, 3 H), 1.10 (t, 3 H)	472	Intermediate 105
106	4-{[4-Fluoro-2-(trifluoromethyl)phenyl]amino}-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	THF-d8 11.14 (s, 1 H), 8.75 (s, 1 H), 7.58 (s, 1 H), 7.42 (m, 1 H), 7.20 (s, 1 H), 7.02 (m, 1 H), 6.88 (s, 1 H), 6.64 (m, 1 H), 6.58 (s, 1 H), 3.83 (s, 3 H), 2.72 (s, 4 H), 2.23 (s, 4 H), 2.08 (s, 3 H)	478	Intermediate 106
107	4-[(2-Chloro-4-fluorophenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.95 (s, 1 H), 8.83 (s, 1 H), 7.63 (s, 1 H), 7.32 (m, 1 H), 7.30 (s, 1 H), 6.92 (s, 1 H), 6.87 (m, 1 H), 6.74 (s, 1 H), 6.71 (m, 1 H), 3.95 (s, 3 H), 2.79 (s, 4 H), 2.37 (s, 4 H), 2.19 (s, 3 H)	444	Intermediate 107
108	7-Methoxy-6-(4-methylpiperazin-1-yl)-4-{[3-(trifluoromethoxy)phenyl]amino}quinoline-3-carboxamide	10.37 (s, 1 H), 8.86 (s, 1 H), 8.23 (s, 1 H), 7.65 (s, 1 H), 7.31-7.38 (m, 2 H), 6.85-6.96 (m, 4 H), 3.94 (s, 3 H), 2.76 (s, 4 H), 2.35 (s, 4 H), 2.16 (s, 3 H)	476	Intermediate 108
109	4-[(2,6-Dimethylphenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	11.39 (s, 1 H), 8.82 (s, 1 H), 8.21 (s, 1 H), 7.51 (s, 1 H), 7.15-7.20 (m, 4 H), 6.64 (s, 1 H), 3.87 (s, 3 H), 2.44 (s, 4 H), 2.28 (s, 4 H), 2.15 (s, 3 H), 2.06 (s, 6 H)	420	Intermediate 109

Ex.	Compound	NMR	M/z	SM
110	4-[(2,4-Difluorophenyl) amino]-7-ethoxy-6-(4-ethyl-1,4-diazepan-1-yl)quinoline-3-carboxamide	10.55 (s, 1 H), 8.81 (s, 1 H), 8.30 (s, 1 H), 7.80 (s, 1 H), 7.45 (m, 3 H), 7.20 (m, 2 H), 4.25 (m, 2 H), 3.15 (m, 6 H), 2.80 (m, 2 H), 2.30 (m, 2 H), 2.10 (m, 2 H), 1.50 (t, 3 H), 1.25 (t, 3 H)	469	Intermediate 110
111	4-[(2,3-Dichlorophenyl) amino]-6-(4-ethyl-1,4-diazepan-1-yl)-7-methoxyquinoline-3-carboxamide	9.00 (s, 1 H), 8.51 (s, 1 H), 7.95 (s, 1 H), 7.60 (m, 1 H), 7.48 (s, 1 H), 7.40-7.32 (m, 2 H), 6.89 (s, 1 H), 4.00 (s, 3 H), 3.20 (m, 4 H), 2.95 (m, 2 H), 2.70 (m, 2 H), 2.20 (m, 2 H), 2.05 (m, 2 H), 1.29 (t, 3 H)	487	Intermediate 111
112	4-[(2,3-Dichlorophenyl) amino]-7-ethoxy-6-(4-ethyl-1,4-diazepan-1-yl)quinoline-3-carboxamide	10.00 (s, 1 H), 8.90 (s, 1 H), 8.40 (s, 1 H), 7.90 (s, 1 H), 7.65 (d, 1 H), 7.30 (m, 3 H), 6.80 (s, 1 H), 4.15 (q, 2 H), 3.15 (m, 4 H), 2.85 (m, 2 H), 2.60 (m, 2 H), 2.15 (m, 2 H), 2.00 (m, 2 H), 1.40 (t, 3 H), 1.15 (t, 3 H)	501	Intermediate 112
113	4-[(2,4-Difluorophenyl) amino]-7-isopropoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.74 (s, 1 H), 8.83 (s, 1 H), 8.28 (s, 1 H), 7.65 (s, 1 H), 7.36 (t, 1 H), 7.23 (s, 1 H), 7.02 (m, 2 H), 6.79 (s, 1 H), 4.81 (m, 1 H), 2.71 (s, 4 H), 2.35 (s, 4 H), 2.16 (s, 3 H), 1.34 (d, 6 H)	457	Intermediate 254
114	4-[(3,4-Dichlorophenyl) amino]-7-isopropoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.13 (s, 1 H), 8.78 (s, 1 H), 8.12 (s, 1 H), 7.59 (s, 1 H), 7.46 (d, 1 H), 7.28 (s, 1 H), 7.11 (s, 1 H), 6.96 (s, 1 H), 6.87 (m, 1 H), 4.83 (m, 1 H), 2.86 (s, 4 H), 2.39 (s, 4 H), 2.18 (s, 3 H), 1.36 (d, 6 H)	490	Intermediate 255

Ex.	Compound	NMR	M/z	SM
115	4-[(3-Chloro-2-fluorophenyl)amino]-7-isopropoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.66 (s, 1 H), 8.86 (s, 1 H), 8.29 (s, 1 H), 7.69 (s, 1 H), 7.29 (s, 1 H), 7.21 (t, 1 H), 7.07 (t, 1 H), 6.88 (s, 1 H), 6.76 (m, 1 H), 4.85 (m, 1 H), 2.83-2.50 (m, 8 H), 2.36 (s, 3 H), 1.37 (d, 6 H)	474	Intermediate 256
116	4-[(2,3-Dichlorophenyl)amino]-7-isopropoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.83 (s, 1 H), 8.92 (s, 1 H), 8.38 (s, 1 H), 7.77 (s, 1 H), 7.30 (s, 1 H), 7.26 (s, 1 H), 7.16 (m, 1 H), 6.67 (s, 1 H), 6.62 (d, 1 H), 4.85 (m, 1 H), 2.74 (s, 4 H), 2.36 (s, 4 H), 2.17 (s, 3 H), 1.37 (d, 6 H)	490	Intermediate 257
117	4-[(3-Chloro-4-fluorophenyl)amino]-7-isopropoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.37 (s, 1 H), 8.81 (s, 1 H), 8.18 (s, 1 H), 7.61 (s, 1 H), 7.31 (m, 1 H), 7.27 (s, 1 H), 7.12 (m, 1 H), 6.91 (s, 2 H), 4.86 (m, 1 H), 2.82 (s, 4 H), 2.41 (s, 4 H), 2.20 (s, 3 H), 1.36 (d, 6 H)	474	Intermediate 258
118	4-[(2,4-Difluorophenyl)amino]-6-morpholin-4-ylquinoline-3-carboxamide	10.39 (s, 1 H), 8.80 (s, 1 H), 8.26 (s, 1 H), 7.82 (d, 1 H), 7.69 (s, 1 H), 7.59 (d, 1 H), 7.35 (t, 1 H), 7.01 (m, 2 H), 6.86 (s, 1 H), 3.68 (m, 4 H), 2.94 (m, 4 H)	384	Intermediate 259
119	4-[(3-Chloro-4-fluorophenyl)amino]-6-morpholin-4-ylquinoline-3-carboxamide	9.83 (s, 1 H), 8.72 (s, 1 H), 8.09 (s, 1 H), 7.84 (d, 1 H), 7.64 (d, 1 H), 7.59 (m, 1 H), 7.28 (t, 1 H), 7.10 (m, 1 H), 7.01 (s, 1 H), 6.86 (m, 1 H), 3.71 (m, 4 H), 3.05 (m, 4 H)	401	Intermediate 260

Ex.	Compound	NMR	M/z	SM
120	4-[(2,3-Dichlorophenyl) amino]-6-morpholin-4-ylquinoline-3-carboxamide	10.56 (s, 1 H), 8.91 (s, 1 H), 8.42 (s, 1 H), 7.89 (d, 2 H), 7.65 (m, 1 H), 7.25 (m, 1 H), 7.14 (t, 1 H), 6.66 (s, 1 H), 6.55 (d, 1 H), 3.66 (m, 4 H), 2.94 (m, 4 H)	417	Intermediate 261
121	4-[(2,4-Difluorophenyl) amino]-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.40 (s, 1 H), 8.77 (s, 1 H), 8.27 (s, 1 H), 7.77 (s, 1 H), 7.67 (s, 1 H), 7.55 (d, 1 H), 7.33 (t, 1 H), 6.99 (m, 2 H), 6.79 (s, 1 H), 2.94 (m, 4 H), 2.34 (m, 4 H), 2.16 (s, 3 H)	398	Intermediate 262
122	4-[(2,4-Dichlorophenyl) amino]-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.52 (s, 1 H), 8.86 (s, 1 H), 8.37 (s, 1 H), 7.82 (m, 2 H), 7.70 (d, 1 H), 7.60 (m, 1 H), 7.21 (m, 1 H), 6.58 (m, 2 H), 2.96 (m, 4 H), 2.34 (m, 4 H), 2.16 (s, 3 H)	430	Intermediate 263
123	4-[(3,4-Dichlorophenyl) amino]-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	9.67 (s, 1 H), 8.69 (s, 1 H), 8.05 (s, 1 H), 7.83 (d, 1 H), 7.61 (m, 2 H), 7.43 (d, 1 H), 7.05 (m, 2 H), 6.84 (m, 1 H), 3.16 (m, 4 H), 2.48 (m, 4 H), 2.25 (s, 3 H)	430	Intermediate 264
124	4-[(2,3-Dichlorophenyl) amino]-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	CD ₃ OD 8.83 (s, 1 H), 7.89 (d, 1 H), 7.83 (d, 1 H), 7.55 (d, 1 H), 7.39 (m, 2 H), 7.08 (d, 1 H), 3.62 (m, 2 H), 3.54 (m, 2 H), 3.21 (m, 2 H), 3.06 (m, 2 H), 2.90 (s, 3 H)	429	Intermediate 265
125	tert-Butyl 4-{3-(aminocarbonyl)-4-[(2,3-dichlorophenyl)amino]-7-ethoxyquinolin-6-yl}piperazine-1-carboxylate	CD ₂ Cl ₂ 10.20 (s, 1 H), 8.65 (s, 1 H), 7.15 (s, 1 H), 6.95 (d, 1 H), 6.80 (m, 1 H), 6.60 (s, 1 H), 6.40 (d, 1 H), 4.05 (q, 2 H), 3.25 (m, 4 H), 2.60 (m, 4 H), 1.32 (t, 3 H), 1.28 (s, 9 H)	560	Intermediate 113

Ex.	Compound	NMR	M/z	SM
126	tert-Butyl 4-{3-(aminocarbonyl)-4-[(2,4-difluorophenyl)amino]-7-methoxyquinolin-6-yl}piperazine-1-carboxylate	10.60 (s, 1 H), 8.78 (s, 1 H), 8.20 (s, 1 H), 7.60 (s, 1 H), 7.30 (m, 1 H), 7.22 (s, 1 H), 6.98 (m, 2 H), 6.80 (s, 1 H), 3.86 (s, 3 H), 3.25 (m, 4 H), 2.59 (m, 4 H), 1.31 (s, 9 H)	513	Intermediate 114
127	tert-Butyl 4-{3-(aminocarbonyl)-4-[(2,4-difluorophenyl)amino]-7-methoxyquinolin-6-yl}-1,4-diazepane-1-carboxylate		527	Intermediate 115
128	tert-Butyl 4-{3-(aminocarbonyl)-4-[(2,3-dichlorophenyl)amino]-7-ethoxyquinolin-6-yl}-1,4-diazepane-1-carboxylate	CDCl ₃ 10.63 (s, 1 H), 8.75 (s, 1 H), 8.20 (s, 1 H), 7.88 (s, 1 H), 7.56 (s, 1 H), 7.30 (m, 1 H), 7.18 (m, 1 H), 6.90 (m, 1 H), 6.70 (m, 1 H), 3.85 (s, 3 H), 3.20 (m, 4 H), 3.13 (m, 1 H), 3.01 (m, 1 H), 2.95 (m, 2 H), 1.58 (m, 2 H), 1.25-1.18 (d, 9 H)	573	Intermediate 116
129	tert-Butyl 4-{3-(aminocarbonyl)-4-[(2,4-difluorophenyl)amino]-7-ethoxyquinolin-6-yl}piperazine-1-carboxylate	CDCl ₃ 10.60 (s, 1 H), 8.85 (s, 1 H), 7.31 (s, 1 H), 6.90 (m, 3 H), 6.75 (m, 1 H), 4.20 (q, 2 H), 3.50 (m, 4 H), 2.75 (m, 4 H), 1.40 (t, 3 H), 1.38 (s, 9 H)	527	Intermediate 117
130	tert-Butyl 4-{3-(aminocarbonyl)-4-[(2,4-difluorophenyl)amino]-7-ethoxyquinolin-6-yl}-1,4-diazepane-1-carboxylate		541	Intermediate 118

Ex.	Compound	NMR	M/z	SM
131	tert-Butyl 4-{3-(aminocarbonyl)-4-[(2,3-dichlorophenyl)amino]-7-methoxyquinolin-6-yl}-1,4-diazepane-1-carboxylate		560	Intermediate 119
132	4-[(2-Fluoro-5-methylphenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.82 (s, 1 H), 8.88 (s, 1 H), 8.31 (s, 1 H), 7.68 (s, 1 H), 7.27 (s, 1 H), 7.17 (m, 1 H), 6.86 (m, 2 H), 6.72 (m, 1 H), 3.94 (s, 3 H), 2.69 (s, 4 H), 2.34 (s, 4 H), 2.17 (s, 3 H), 2.15 (s, 3 H)	424	Intermediate 120
133	4-[(2,5-Difluorophenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.68 (s, 1 H), 8.90 (s, 1 H), 8.33 (s, 1 H), 7.73 (s, 1 H), 7.33 (m, 2 H), 6.88 (m, 2 H), 6.64 (m, 1 H), 3.96 (s, 3 H), 2.78 (s, 4 H), 2.38 (s, 4 H), 2.18 (s, 3 H)	428	Intermediate 121
134	4-[(3-Chloro-2-methylphenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.86 (s, 1 H), 8.88 (s, 1 H), 8.31 (s, 1 H), 7.66 (s, 1 H), 7.24 (s, 1 H), 7.19 (m, 1 H), 7.08 (m, 1 H), 6.68 (m, 2 H), 3.92 (s, 3 H), 2.64 (s, 4 H), 2.38 (s, 3 H), 2.33 (s, 4 H), 2.17 (s, 3 H)	440	Intermediate 122
135	4-[(2-Chloro-3-methylphenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.81 (s, 1 H), 8.90 (s, 1 H), 8.32 (s, 1 H), 7.69 (s, 1 H), 7.27 (s, 1 H), 7.05 (d, 1 H), 7.03 (s, 1 H), 6.69 (s, 1 H), 6.54 (m, 1 H), 3.92 (s, 3 H), 2.66 (s, 4 H), 2.40 (s, 3 H), 2.33 (s, 4 H), 2.15 (s, 3 H)	440	Intermediate 123

Ex.	Compound	NMR	M/z	SM
136	4-[(2,4-Difluorophenyl)amino]-6-[3-(dimethylamino)pyrrolidin-1-yl]-7-methoxyquinoline-3-carboxamide	THF-d ₈ 10.76 (s, 1 H), 8.62 (s, 1 H), 7.50 (s, 1 H), 7.14 (s, 1 H), 6.93 (m, 1 H), 6.71 (m, 3 H), 6.37 (s, 1 H), 3.82 (s, 3 H), 3.20 (m, 1 H), 3.00 (t, 1 H), 2.89 (t, 1 H), 2.43 (m, 2 H), 2.04 (s, 6 H), 1.85 (m, 1 H), 1.56 (m, 1 H)	442	Intermediate 124
137	4-[(3-Chloro-2-fluorophenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.69 (s, 1 H), 8.87 (s, 1 H), 8.30 (s, 1 H), 7.71 (s, 1 H), 7.30 (s, 1 H), 7.24 (m, 1 H), 7.07 (m, 1 H), 6.85 (s, 1 H), 6.79 (m, 1 H), 3.94 (s, 3 H), 2.74 (s, 4 H), 2.36 (s, 4 H), 2.17 (s, 3 H)	444	Intermediate 125
138	4-[(3-Chloro-5-fluorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	CDCl ₃ 10.37 (s, 1 H), 8.75 (s, 1 H), 7.30 (s, 1 H), 6.92 (s, 1 H), 6.71 (m, 2 H), 6.51 (d, 1 H), 4.23 (q, 2 H), 2.93 (s, 4 H), 2.53 (s, 4 H), 2.31 (s, 3 H), 1.54 (t, 3 H)	459	Intermediate 126
139	7-Ethoxy-6-(4-methylpiperazin-1-yl)-4-[(2,3,4-trifluorophenyl)amino]quinoline-3-carboxamide	CDCl ₃ 10.41 (s, 1 H), 8.74 (s, 1 H), 7.28 (s, 1 H), 6.87 (s, 1 H), 6.79 (m, 1 H), 6.61 (m, 1 H), 4.21 (q, 2 H), 2.87 (s, 4 H), 2.52 (s, 4 H), 2.31 (s, 3 H), 1.52 (t, 3 H)	460	Intermediate 127
140	4-[(5-Chloro-2-methylphenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	CDCl ₃ 10.46 (s, 1 H), 8.71 (s, 1 H), 7.26 (s, 1 H), 7.16 (d, 1 H), 6.97 (dd, 1 H), 6.79 (m, 2 H), 4.21 (q, 2 H), 2.80 (s, 4 H), 2.49 (s, 4 H), 2.35 (s, 3 H), 2.30 (s, 3 H), 1.52 (t, 3 H)	455	Intermediate 128

Ex.	Compound	NMR	M/z	SM
141	7-Ethoxy-4-[(4-methoxy-2-methylphenyl)amino]-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	CDCl ₃ 10.68 (s, 1 H), 8.65 (s, 1 H), 7.18 (s, 1 H), 6.89 (m, 2 H), 6.78 (d, 1 H), 6.62 (dd, 1 H), 5.92 (br s, 2 H), 4.15 (q, 2 H), 3.75 (s, 3 H), 2.71 (s, 4 H), 2.44 (s, 4 H), 2.29 (s, 3 H), 2.25 (s, 3 H), 1.48 (t, 3 H)	451	Intermediate 129
142	4-{[2-Chloro-5-(trifluoromethyl)phenyl]amino}-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	CDCl ₃ 10.43 (s, 1 H), 8.81 (s, 1 H), 7.55 (d, 1 H), 7.35 (s, 1 H), 7.15 (dd, 1 H), 6.88 (s, 1 H), 6.77 (s, 1 H), 6.00 (br s, 2 H), 4.23 (q, 2 H), 2.86 (s, 4 H), 2.50 (s, 4 H), 2.32 (s, 3 H), 1.53 (t, 3 H)	509	Intermediate 130
143	4-[(2,4-Difluorophenyl)amino]-7-ethoxy-6-(4-methyl-3-oxopiperazin-1-yl)quinoline-3-carboxamide	10.26 (s, 1 H), 8.50 (s, 1 H), 7.91 (s, 1 H), 7.30 (s, 1 H), 7.01 (t, 1 H), 6.95 (s, 1 H), 6.64 (m, 2 H), 6.53 (s, 1 H), 3.87 (q, 2 H), 2.91 - 3.04 (m, 5 H), 2.82 (s, 2 H), 2.16 (s, 2 H), 1.08 (t, 3 H)	474	Intermediate 131
144	4-[(2,3-Dichlorophenyl)amino]-7-(4-ethylpiperazin-1-yl)-6-methoxyquinoline-3-carboxamide	10.71 (s, 1 H), 8.92 (s, 1 H), 8.36 (s, 1 H), 7.75 (s, 1 H), 7.25 (s, 1 H), 7.23 (d, 1 H), 7.15 (m, 1 H), 6.67 (s, 1 H), 6.57 (d, 1 H), 3.16 (m, 4 H), 2.52 (m, 4 H), 2.37 (q, 2 H), 1.02 (t, 3 H)	474	Intermediate 132
145	4-[(2-Fluoro-5-methylphenyl)amino]-6-methoxy-7-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	CD ₂ Cl ₂ 10.37 (s, 1 H), 8.76 (s, 1 H), 7.30 (s, 1 H), 7.01 (m, 1 H), 6.87 (m, 2 H), 6.76 (d, 1 H), 6.09 (br, 2 H), 3.43 (s, 3 H), 3.22 (s, 4 H), 2.55 (s, 4 H), 2.30 (s, 3 H), 2.19 (s, 3 H)	424	Intermediate 133

Ex.	Compound	NMR	M/z	SM
146	7-(4-Ethylpiperazin-1-yl)-4-[(2-fluoro-5-methylphenyl)amino]-6-methoxyquinoline-3-carboxamide	CD ₂ Cl ₂ 10.36 (s, 1 H), 8.76 (s, 1 H), 7.31 (s, 1 H), 7.01 (m, 1 H), 6.87 (m, 2 H), 6.77 (d, 1 H), 6.06 (br, 2 H), 3.43 (s, 3 H), 3.23 (s, 4 H), 2.60 (s, 4 H), 2.44 (q, 2 H), 2.19 (s, 3 H), 1.09 (t, 3 H)	438	Intermediate 134
147	4-[(3-Chloro-2-fluorophenyl)amino]-6-methoxy-7-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	CD ₂ Cl ₂ 10.33 (s, 1 H), 8.78 (s, 1 H), 7.34 (s, 1 H), 7.06 (m, 1 H), 6.91 (m, 1 H), 6.81 (s, 1 H), 6.71 (m, 1 H), 6.04 (br, 2 H), 3.51 (s, 3 H), 3.24 (s, 4 H), 2.55 (s, 4 H), 2.31 (s, 3 H)	444	Intermediate 135
148	4-[(3-Chloro-2-fluorophenyl)amino]-7-(4-ethylpiperazin-1-yl)-6-methoxyquinoline-3-carboxamide	CD ₂ Cl ₂ 10.33 (s, 1 H), 8.78 (s, 1 H), 7.34 (s, 1 H), 7.06 (m, 1 H), 6.91 (m, 1 H), 6.82 (s, 1 H), 6.71 (m, 1 H), 6.02 (br, 2 H), 3.51 (s, 3 H), 3.25 (s, 4 H), 2.60 (s, 4 H), 2.45 (q, 2 H), 1.09 (t, 3 H)	458	Intermediate 136
149	4-[(2-Fluoro-5-methylphenyl)amino]-6-methoxy-7-(4-methyl-1,4-diazepan-1-yl)quinoline-3-carboxamide	CD ₂ Cl ₂ 10.35 (s, 1 H), 8.73 (s, 1 H), 7.15 (s, 1 H), 7.01 (m, 1 H), 6.82 (m, 2 H), 6.77 (d, 1 H), 6.16 (br, 2 H), 3.48 (m, 4 H), 3.40 (s, 3 H), 2.77 (m, 2 H), 2.64 (m, 2 H), 2.35 (s, 3 H), 2.19 (s, 3 H), 2.03 (m, 2 H)	437	Intermediate 137
150	4-[(2,4-Difluorophenyl)amino]-6-methoxy-7-(4-methyl-1,4-diazepan-1-yl)quinoline-3-carboxamide	CD ₂ Cl ₂ 10.36 (s, 1 H), 8.70 (s, 1 H), 7.16 (s, 1 H), 6.94 (m, 2 H), 6.79 (m, 1 H), 6.73 (s, 1 H), 5.91 (br, 2 H), 3.49 (m, 4 H), 3.44 (s, 3 H), 2.76 (m, 2 H), 2.63 (m, 2 H), 2.35 (s, 3 H), 2.02 (m, 2 H)	441	Intermediate 138

Ex.	Compound	NMR	M/z	SM
151	4-[(2-Chloro-3-fluorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	CD ₂ Cl ₂ 10.39 (s, 1 H), 8.75 (s, 1 H), 7.28 (s, 1 H), 7.24 (m, 1 H), 6.87 (s, 1 H), 6.71 (m, 2 H), 5.95 (br, 2 H), 4.22 (q, 2 H), 2.86 (s, 4 H), 2.44 (s, 4 H), 2.26 (s, 3 H), 1.50 (t, 3 H)	458	Intermediate 139
152	4-[(2-Chloro-3-fluorophenyl)amino]-7-ethoxy-6-(4-ethylpiperazin-1-yl)quinoline-3-carboxamide	CD ₂ Cl ₂ 10.38 (s, 1 H), 8.75 (s, 1 H), 7.27 (s, 1 H), 7.24 (m, 1 H), 6.87 (s, 1 H), 6.71 (m, 2 H), 6.10 (br, 2 H), 4.21 (q, 2 H), 2.87 (s, 4 H), 2.48 (s, 4 H), 2.39 (q, 2 H), 1.50 (t, 3 H), 1.05 (t, 3 H)	472	Intermediate 140
153	4-[(2-Chloro-3-fluorophenyl)amino]-7-ethoxy-6-(4-isopropylpiperazin-1-yl)quinoline-3-carboxamide	CD ₂ Cl ₂ 10.36 (s, 1 H), 8.75 (s, 1 H), 7.28 (s, 1 H), 7.24 (m, 1 H), 6.87 (s, 1 H), 6.71 (m, 2 H), 5.98 (br, 2 H), 4.22 (q, 2 H), 2.85 (s, 4 H), 2.64 (m, 1 H), 2.57 (s, 4 H), 1.51 (t, 3 H), 1.03 (d, 6 H)	486	Intermediate 141
154	<i>tert</i> -Butyl 4-{3-(aminocarbonyl)-7-ethoxy-4-[(2-fluoro-4-methylphenyl)amino]quinolin-6-yl}piperazine-1-carboxylate	CD ₂ Cl ₂ 10.61 (s, 1 H), 8.85 (s, 1 H), 7.29 (s, 1 H), 6.99 (d, 1 H), 6.90 (s, 1 H), 6.79 (m, 2 H), 4.20 (q, 2 H), 3.46 (m, 4 H), 2.71 (m, 4 H), 2.35 (s, 3 H), 1.51 (t, 3 H), 1.49 (s, 9 H)	524	Intermediate 142
155	4-[(2,3-Dichlorophenyl)amino]-7-ethoxy-6-(3-oxopiperazin-1-yl)quinoline-3-carboxamide	10.80 (s, 1 H), 8.93 (s, 1 H), 8.38 (s, 1 H), 7.87 (s, 1 H), 7.76 (s, 1 H), 7.34 (s, 1 H), 7.24 (d, 1 H), 7.14 (m, 1 H), 6.69 (s, 1 H), 6.57 (d, 1 H), 4.22 (q, 2 H), 3.27 (s, 2 H), 3.18 (s, 2 H), 3.11 (s, 2 H), 1.42 (t, 3 H)	474	Intermediate 143

Ex.	Compound	NMR	M/z	SM
156	7-Ethoxy-4-[(2-fluoro-5-methylphenyl)amino]-6-(3-oxopiperazin-1-yl)quinoline-3-carboxamide	10.72 (s, 1 H), 8.86 (s, 1 H), 8.29 (s, 1 H), 7.86 (s, 1 H), 7.64 (s, 1 H), 7.27 (s, 1 H), 7.14 (m, 1 H), 6.88 (s, 2 H), 6.73 (d, 1 H), 4.20 (q, 2 H), 3.18 (m, 4 H), 3.03 (m, 2 H), 1.41 (t, 3 H)	438	Intermediate 144
157	4-[(2,4-Difluorophenyl)amino]-7-ethoxy-6-(3-oxopiperazin-1-yl)quinoline-3-carboxamide	MeOD 8.78 (s, 1 H), 7.27 (s, 1 H), 7.07 (m, 2 H), 7.03 (s, 1 H), 6.92 (m, 1 H), 4.25 (q, 2 H), 3.45 (s, 2 H), 3.34 (m, 2 H), 3.15 (m, 2 H), 1.51 (t, 3 H)	442	Intermediate 145
158	4-[(2-Chloro-4-methylphenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.85 (s, 1 H), 8.90 (s, 1 H), 8.30 (s, 1 H), 7.69 (s, 1 H), 7.38 (s, 1 H), 7.20 (s, 1 H), 7.00 (d, 1 H), 6.65 (m, 2 H), 4.15 (q, 2 H), 2.69 (s, 4 H), 2.30 (s, 4 H), 2.20 (s, 3 H), 2.15 (s, 3 H), 1.40 (t, 3 H)	454	Intermediate 146
159	7-Ethoxy-4-[[2-fluoro-3-(trifluoromethyl)phenyl]amino]-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.65 (s, 1 H), 8.85 (s, 1 H), 8.30 (s, 1 H), 7.70 (s, 1 H), 7.40-7.15 (m, 4 H), 6.85 (s, 1 H), 4.20 (q, 2 H), 2.80 (s, 4 H), 2.35 (s, 4 H), 2.15 (s, 3 H), 1.40 (t, 3 H)	492	Intermediate 147
160	4-[(2,4-Dimethoxyphenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.75 (s, 1 H), 8.80 (s, 1 H), 8.20 (s, 1 H), 7.50 (s, 1 H), 7.16 (s, 1 H), 6.85-6.70 (m, 3 H), 6.50 (d, 1 H), 4.15 (q, 2 H), 3.75 (s, 6 H), 2.65 (s, 4 H), 2.30 (s, 4 H), 2.17 (s, 3 H), 1.40 (t, 3 H)	466	Intermediate 148

Ex.	Compound	NMR	M/z	SM
161	4-[(2-Chloro-4-fluoro-5-methylphenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.95 (s, 1 H), 8.96 (s, 1 H), 8.40 (s, 1 H), 7.75 (s, 1 H), 7.55 (d, 1 H), 7.30 (s, 1 H), 6.80 (d, 1 H), 6.70 (s, 1 H), 4.21 (q, 2 H), 2.80 (s, 4 H), 2.35 (s, 4 H), 2.20 (s, 3 H), 2.10 (s, 3 H), 1.45 (t, 3 H)	472	Intermediate 149
162	4-[(5-Chloro-2-fluorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.70 (s, 1 H), 8.90 (s, 1 H), 8.35 (s, 1 H), 7.75 (s, 1 H), 7.30 (m, 2 H), 7.10 (m, 1 H), 6.85 (s, 1 H), 6.80 (d, 1 H), 4.20 (q, 2 H), 3.80 (s, 4 H), 2.35 (s, 4 H), 2.20 (s, 3 H), 1.40 (t, 3 H)	458	Intermediate 150
163	7-Ethoxy-4-{[2-methoxy-5-(trifluoromethyl)phenyl]amino}-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.55 (s, 1 H), 8.90 (s, 1 H), 8.35 (s, 1 H), 7.65 (s, 1 H), 7.30 (m, 3 H), 6.70 (m, 2 H), 4.21 (q, 2 H), 3.95 (s, 3 H), 2.75 (s, 4 H), 2.30 (s, 4 H), 2.15 (s, 3 H), 1.40 (t, 3 H)	504	Intermediate 151
164	4-[(2,3-Dichlorophenyl)amino]-7-(2-methoxyethoxy)-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	11.33 (s, 1 H), 9.47 (s, 1 H), 8.34 (s, 1 H), 7.78 (s, 1 H), 7.67 (m, 2 H), 7.50 (s, 1 H), 7.23 (s, 1 H), 7.10 (m, 1 H), 4.79 (m, 2 H), 4.32 (m, 2 H), 3.89 (s, 3 H), 3.30 (m, 4 H), 2.86 (m, 4 H), 2.66 (s, 3 H)	506	Intermediate 159
165	4-[(2,4-Difluorophenyl)amino]-7-(2-methoxyethoxy)-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.73 (s, 1 H), 8.86 (s, 1 H), 8.28 (s, 1 H), 7.66 (s, 1 H), 7.37 (m, 1 H), 7.26 (s, 1 H), 7.03 (m, 2 H), 6.81 (s, 1 H), 4.25 (m, 2 H), 3.73 (m, 2 H), 3.35 (s, 3 H), 2.75 (s, 4 H), 2.35 (s, 4 H), 2.17 (s, 3 H)	472	Intermediate 160

Ex.	Compound	NMR	M/z	SM
166	4-[(2-Fluoro-4-methylphenyl)amino]-7-(2-methoxyethoxy)-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.80 (s, 1 H), 8.85 (s, 1 H), 8.28 (s, 1 H), 7.64 (s, 1 H), 7.23 (s, 1 H), 7.15 (d, 1 H), 6.92 (m, 2 H), 6.82 (s, 1 H), 4.23 (m, 2 H), 3.74 (m, 2 H), 3.31 (s, 3 H), 2.70 (s, 4 H), 2.32 (s, 4 H), 2.29 (s, 3 H), 2.16 (s, 3 H)	468	Intermediate 161
167	4-[(2-Chloro-3-fluorophenyl)amino]-7-(2-methoxyethoxy)-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	11.14 (s, 1 H), 9.43 (s, 1 H), 8.27 (s, 1 H), 7.84 (m, 1 H), 7.76 (s, 1 H), 7.42 (s, 1 H), 7.36 (s, 1 H), 7.34 (d, 1 H), 7.24 (d, 1 H), 4.78 (m, 2 H), 4.29 (m, 2 H), 3.88 (s, 3 H), 3.34 (s, 4 H), 2.88 (s, 4 H), 2.67 (s, 3 H)	488	Intermediate 164
168	4-[(2-Fluoro-5-methylphenyl)amino]-7-(2-methoxyethoxy)-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	11.36 (s, 1 H), 9.41 (s, 1 H), 8.27 (s, 1 H), 7.72 (s, 1 H), 7.56 (m, 1 H), 7.39 (m, 3 H), 7.20 (m, 1 H), 4.75 (m, 2 H), 4.28 (m, 2 H), 3.88 (s, 3 H), 3.27 (s, 4 H), 2.84 (s, 4 H), 2.65 (s, 3 H), 2.44 (s, 3 H)	468	Intermediate 156
169	4-[(2,5-Difluorophenyl)amino]-7-(2-methoxyethoxy)-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.66 (s, 1 H), 8.88 (s, 1 H), 8.32 (s, 1 H), 7.73 (s, 1 H), 7.23 (s, 1 H), 7.32 (m, 2 H), 6.86 (m, 2 H), 6.62 (m, 1 H), 4.27 (m, 2 H), 3.75 (m, 2 H), 3.35 (s, 3 H), 2.81 (s, 4 H), 2.37 (s, 4 H), 2.17 (s, 3 H)	472	Intermediate 157

Ex.	Compound	NMR	M/z	SM
170	4-[(3-Chloro-2-fluorophenyl)amino]-7-(2-methoxyethoxy)-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.70 (s, 1 H), 8.84 (s, 1 H), 8.40 (s, 1 H), 7.60 (s, 1 H), 7.24 (s, 1 H), 7.13 (m, 1 H), 7.03 (m, 1 H), 6.85 (s, 1 H), 6.75 (m, 1 H), 4.23 (s, 2 H), 3.74 (s, 2 H), 3.33 (s, 3 H), 2.74 (s, 4 H), 2.34 (s, 4 H), 2.15 (s, 3 H)	488	Intermediate 158
171	4-[(2-Fluoro-4-methylphenyl)amino]-7-(2-methoxyethoxy)-6-morpholin-4-ylquinoline-3-carboxamide	10.82 (s, 1 H), 8.86 (s, 1 H), 8.29 (s, 1 H), 7.65 (s, 1 H), 7.26 (s, 1 H), 7.14 (d, 1 H), 6.92 (m, 3 H), 4.24 (m, 2 H), 3.73 (m, 2 H), 3.62 (m, 4 H), 3.36 (s, 3 H), 2.69 (s, 4 H), 2.27 (s, 3 H)	455	Intermediate 152
172	4-[(2-Fluoro-4-methylphenyl)amino]-6-(4-isopropylpiperazin-1-yl)-7-(2-methoxyethoxy)quinoline-3-carboxamide	10.78 (s, 1 H), 8.83 (s, 1 H), 8.27 (s, 1 H), 7.63 (s, 1 H), 7.22 (s, 1 H), 7.14 (d, 1 H), 6.89 (m, 2 H), 6.79 (s, 1 H), 4.23 (m, 2 H), 3.72 (m, 2 H), 3.33 (s, 3 H), 2.68 (s, 4 H), 2.60 (m, 1 H), 2.43 (s, 4 H), 2.27 (s, 3 H), 0.96 (d, 6 H)	496	Intermediate 153
173	4-[(2-Fluoro-5-methylphenyl)amino]-6-(4-isopropylpiperazin-1-yl)-7-(2-methoxyethoxy)quinoline-3-carboxamide	10.75 (s, 1 H), 8.95 (s, 1 H), 8.27 (s, 1 H), 7.64 (s, 1 H), 7.25 (s, 1 H), 7.15 (m, 1 H), 6.89 (m, 1 H), 6.83 (s, 1 H), 6.71 (d, 1 H), 4.25 (m, 2 H), 3.75 (m, 2 H), 3.34 (s, 3 H), 2.71 (s, 4 H), 2.60 (m, 1 H), 2.45 (s, 4 H), 2.13 (s, 3 H), 0.96 (d, 6 H)	496	Intermediate 154

Example 174**4-[(2,3-Dichlorophenyl)amino]-7-methoxy-6-piperazin-1-ylquinoline-3-carboxamide dihydrochloride**

To a solution of trifluoroacetic acid/dichloromethane (10 mL, 1:1) was added *tert*-butyl 4-{3-(aminocarbonyl)-4-[(2,3-dichlorophenyl)amino]-7-methoxyquinolin-6-yl}piperazine-1-carboxylate (Example 15, 250 mg, 0.46 mmol). After 2 hours, the solvent was removed under reduced pressure, the residue was taken up in MeOH (3 mL) and acidified with ethereal HCl. The resulting crystals were collected, washed with Et₂O and dried to give a solid (160 mg). ¹H NMR: 11.95 (s, 1 H), 9.28 (s, 2 H), 9.00 (s, 1 H), 8.45 (s, 1 H), 7.86 (s, 1 H), 7.59 (m, 2 H), 7.37 (m, 2 H), 7.21 (s, 1 H), 4.01 (s, 3 H), 3.17 (m, 4 H), 3.07 (m, 4 H); *m/z*: 445

Examples 175-185

The following compounds were prepared by a similar method to Example 174 using the appropriate starting materials. Some examples were isolated as the hydrochloride salts.

Ex.	Compound	NMR	M/z	SM
175	4-[(2,3-Dichlorophenyl)amino]-7-methoxy-6-piperazin-1-ylquinoline-3-carboxamide	10.78 (s, 1 H), 8.92 (s, 1 H), 8.36 (s, 1 H), 7.76 (s, 1 H), 7.31 (s, 1 H), 7.24 (d, 1 H), 7.13 (m, 1 H), 6.66 (s, 1 H), 6.57 (d, 1 H), 4.20 (q, 2 H), 2.86 (m, 4 H), 2.75 (m, 4 H), 1.41 (t, 3 H)	460	Example 125
176	4-[(2,4-Difluorophenyl)amino]-7-methoxy-6-piperazin-1-ylquinoline-3-carboxamide	10.80 (s, 1 H), 8.91 (s, 1 H), 8.35 (s, 1 H), 7.70 (s, 1 H), 7.40 (m, 1 H), 7.32 (s, 1 H), 7.06 (m, 2 H), 6.85 (s, 1 H), 4.15 (m, 1 H), 3.99 (s, 3 H), 3.45 (m, 2 H), 3.20 (m, 2 H), 2.80 (m, 2 H), 2.70 (m, 2 H)	413	Example 126
177	6-(1,4-Diazepan-1-yl)-4-[(2,4-difluorophenyl)amino]-7-methoxyquinoline-3-carboxamide	10.60 (s, 1 H), 8.76 (s, 1 H), 8.20 (s, 1 H), 7.56 (s, 1 H), 7.29 (m, 1 H), 7.15 (s, 1 H), 6.90 (m, 2 H), 6.65 (m, 1 H), 3.86 (s, 3 H), 3.70 (m, 1 H), 3.00 (m, 4 H), 2.65 (m, 4 H), 1.55 (m, 2 H)	427	Example 127

Ex.	Compound	NMR	M/z	SM
178	4-[(3-Chloro-4-fluorophenyl)amino]-7-ethoxy-6-piperazin-1-ylquinoline-3-carboxamide	CD ₂ Cl ₂ 10.41 (s, 1 H), 8.77 (s, 1 H), 7.28 (s, 1 H), 7.07 (m, 1 H), 6.87 (m, 2 H), 6.72 (m, 1 H), 6.14 (br s, 2 H), 4.21 (q, 2 H), 2.89 (m, 4 H), 2.76 (m, 4 H), 1.50 (t, 3 H)	444	Example 64
179	7-Ethoxy-4-[(2-fluoro-5-methylphenyl)amino]-6-piperazin-1-ylquinoline-3-carboxamide	CD ₂ Cl ₂ 10.45 (s, 1 H), 8.75 (s, 1 H), 7.26 (s, 1 H), 7.01 (m, 1 H), 6.95 (s, 1 H), 6.85 (m, 1 H), 6.76 (m, 1 H), 4.20 (q, 2 H), 2.90 (m, 4 H), 2.73 (m, 4 H), 2.18 (s, 3 H), 1.49 (t, 3 H)	424	Example 65
180	4-[(3-Chloro-2-fluorophenyl)amino]-7-ethoxy-6-piperazin-1-ylquinoline-3-carboxamide	CD ₂ Cl ₂ 10.51 (s, 1 H), 8.75 (s, 1 H), 7.27 (s, 1 H), 7.06 (m, 2 H), 6.90 (m, 1 H), 6.85 (m, 1 H), 5.96 (br s, 2 H), 4.20 (q, 2 H), 2.92 (m, 4 H), 2.76 (m, 4 H), 1.50 (t, 3 H)	444	Example 66
181	6-(1,4-Diazepan-1-yl)-4-[(2,3-dichlorophenyl)amino]-7-ethoxyquinoline-3-carboxamide	10.70 (s, 1 H), 8.85 (s, 1 H), 8.35 (s, 1 H), 7.75 (s, 1 H), 7.26 (m, 2 H), 7.15 (m, 1 H), 6.55 (m, 2 H), 4.20 (q, 2 H), 4.10 (m, 1 H), 3.05 (m, 4 H), 2.70 (m, 4 H), 1.65 (m, 2 H), 1.44 (t, 3 H)	473	Example 128
182	4-[(2,4-Difluorophenyl)amino]-7-ethoxy-6-piperazin-1-ylquinoline-3-carboxamide	10.71 (s, 1 H), 8.84 (s, 1 H), 8.27 (s, 1 H), 7.64 (s, 1 H), 7.36 (m, 1 H), 7.22 (s, 1 H), 7.00 (m, 2 H), 6.77 (s, 1 H), 4.16 (q, 2 H), 2.73 (m, 4 H), 2.63 (m, 4 H), 1.39 (t, 3 H)	427	Example 129
183	6-(1,4-Diazepan-1-yl)-4-[(2,4-difluorophenyl)amino]-7-ethoxyquinoline-3-carboxamide	10.65 (s, 1 H), 8.80 (s, 1 H), 8.25 (s, 1 H), 7.63 (s, 1 H), 7.35 (m, 1 H), 7.20 (s, 1 H), 6.95 (m, 2 H), 6.70 (s, 1 H), 4.16 (q, 2 H), 3.05 (m, 4 H), 2.75 (m, 4 H), 1.61 (m, 2 H), 1.40 (t, 3 H)	441	Example 130

Ex.	Compound	NMR	M/z	SM
184	6-(1,4-Diazepan-1-yl)-4-[(2,3-dichlorophenyl)amino]-7-methoxyquinoline-3-carboxamide	10.79 (s, 1 H), 8.95 (s, 1 H), 8.42 (s, 1 H), 7.80 (s, 1 H), 7.32 (m, 2 H), 7.20 (m, 1 H), 6.65 (m, 2 H), 4.00 (s, 3 H), 3.85 (m, 1 H), 3.16 (m, 4 H), 2.78 (m, 4 H), 1.65 (m, 2 H)	460	Example 131
185	7-Ethoxy-4-[(2-fluoro-4-methylphenyl)amino]-6-piperazin-1-ylquinoline-3-carboxamide	CD ₂ Cl ₂ 10.37 (s, 1 H), 8.63 (s, 1 H), 7.15 (s, 1 H), 6.85 (m, 1 H), 6.80 (m, 3 H), 4.10 (q, 2 H), 2.78 (m, 4 H), 2.60 (m, 4 H), 2.22 (s, 3 H), 1.40 (t, 3 H)	424	Example 154

Example 186

2-(4-{3-(Aminocarbonyl)-4-[(2,3-dichlorophenyl)amino]-7-methoxyquinolin-6-yl}piperazin-1-yl)-2-oxoethyl acetate

5 To a solution of 4-[(2,3-dichlorophenyl)amino]-7-methoxy-6-piperazin-1-ylquinoline-3-carboxamide dihydrochloride (Example 174, 120 mg, 0.23 mmol) and diisopropylethylamine (160 μ L, 0.92 mmol) in THF (10 mL) at -10° C under N₂, was added dropwise over 10 minutes a solution of 2-chloro-2-oxoethyl acetate (30 μ L, 0.28 mmol) in THF (10 mL). After stirring for 1 hour at -10° C, the solvent was removed under reduced
10 pressure and the residue partitioned between EtOAc and saturated aqueous Na₂CO₃ solution. The organic layer was dried (Na₂SO₄), filtered and concentrated, and the residue was crystallized from Et₂O / EtOAc to give 100 mg solid. NMR: 8.98 (s, 1 H), 8.46 (s, 1 H), 7.78 (s, 1 H), 7.37 (s, 1 H), 7.25 (d, 1 H), 7.14 (t, 1 H), 6.72 (s, 1 H), 6.58 (d, 1 H), 4.77 (s, 2 H), 3.98 (s, 3 H), 3.44 (m, 4 H), 2.78 (m, 4 H), 2.07 (s, 3 H); *m/z*: 545.

15

Examples 187-190

The following compounds were prepared by a similar method to Example 186 using the appropriate starting materials.

Ex.	Compound	NMR	M/z	SM
187	6-(4-Acetylpiperazin-1-yl)-4-[(2,3-dichlorophenyl)amino]-7-methoxyquinoline-3-carboxamide	CD ₃ OD 8.77 (s, 1 H), 7.23 (s, 1 H), 7.13 (dd, 1 H), 7.00 (t, 1 H), 6.75 (s, 1 H), 6.57 (dd, 1 H), 3.93 (s, 3 H), 3.50 (m, 4 H), 2.75 (m, 2 H), 2.67 (m, 2 H), 1.99 (s, 3 H)	487	Example 174
188	6-(4-Acetylpiperazin-1-yl)-4-[(2,3-dichlorophenyl)amino]-7-ethoxyquinoline-3-carboxamide	CD ₂ Cl ₂ 10.42 (s, 1 H), 8.82 (s, 1 H), 7.34 (s, 1 H), 7.13 (d, 1 H), 6.97 (m, 1 H), 6.79 (s, 1 H), 6.60 (d, 1 H), 4.24 (q, 2 H), 3.62 (m, 2 H), 3.50 (m, 2 H), 2.79 (m, 4 H), 2.04 (s, 3 H), 1.51 (t, 3 H)	502	Example 175
189	6-(4-Acetyl-1,4-diazepan-1-yl)-4-[(2,3-dichlorophenyl)amino]-7-ethoxyquinoline-3-carboxamide	10.75 (d, 1 H), 8.95 (s, 1 H), 8.42 (s, 1 H), 7.80 (s, 1 H), 7.34 (m, 2 H), 7.20 (m, 1 H), 6.70 (s, 1 H), 6.65 (d, 1 H), 4.28 (q, 2 H), 3.55-3.12 (m, 11 H), 1.80 (m, 1 H), 1.70 (m, 1 H), 1.50 (t, 3 H)	516	Example 181
190	6-(4-Acetylpiperazin-1-yl)-7-ethoxy-4-[(2-fluoro-4-methylphenyl)amino]quinoline-3-carboxamide	CD ₂ Cl ₂ 10.49 (s, 1 H), 8.72 (s, 1 H), 7.26 (s, 1 H), 6.95 (d, 1 H), 6.91 (s, 1 H), 6.87 (m, 2 H), 5.97 (br, 2 H), 4.20 (q, 2 H), 3.58 (m, 2 H), 3.46 (m, 2 H), 2.78 (m, 2 H), 2.66 (m, 2 H), 2.32 (s, 3 H), 2.04 (s, 3 H), 1.49 (t, 3 H)	466	Example 185

Example 1914-[(2,3-Dichlorophenyl)amino]-6-(4-glycoloylpiperazin-1-yl)-7-methoxyquinoline-3-carboxamide

5 A mixture of 2-(4-{3-(aminocarbonyl)-4-[(2,3-dichlorophenyl)amino]-7-methoxyquinolin-6-yl}piperazin-1-yl)-2-oxoethyl acetate (Example 186, 70 mg, 0.13 mmol), K₂CO₃ (0.5 g, 3.6 mmol), MeOH (5 mL), and water (1 mL) was stirred vigorously for 1 hour. Most of the solvent was removed under reduced pressure, and the residue partitioned between water (10 mL) and EtOAc (10 mL). The desired product precipitated in the separatory funnel,

10 and was collected by filtration. The aqueous layer was further extracted with EtOAc, and the combined organic extracts were dried (Na₂SO₄), filtered, and concentrated under reduced

pressure to give a solid identical by NMR and LC-MS to the earlier material. The solids were combined to give 25 mg. NMR: 10.85 (s, 1 H), 9.01 (s, 1 H), 8.43 (s, 1 H), 7.83 (s, 1 H), 7.43 (s, 1 H), 7.33 (dd, 1 H), 7.21 (t, 1 H), 6.78 (s, 1 H), 6.65 (d, 1 H), 4.63 (t, 1 H), 4.14 (d, 2 H), 4.04 (s, 3 H), 3.57 (m, 2 H), 3.45 (m, 2 H), 2.82 (m, 4 H); *m/z*: 503.

5

Example 192**4-[(2,3-Dichlorophenyl)amino]-7-ethoxy-6-[4-(2-hydroxyethyl)piperazin-1-yl]quinoline-3-carboxamide**

A mixture of 4-[(2,3-dichlorophenyl)amino]-7-ethoxy-6-piperazin-1-ylquinoline-3-carboxamide (Example 175, 67 mg, 0.146 mmol) and glycolaldehyde (26 mg, 0.43 mmol) in 10 toluene:MeOH (6 mL, 5:1) was heated to reflux for 1 hour. The reaction mixture was concentrated and dissolved in THF (15 mL). Sodium triacetoxyborohydride (155 mg, 0.73 mmol) and acetic acid (0.1 mL) were added and the reaction mixture was heated to reflux for 1 hour. Water was added, and the mixture extracted with EtOAc (4 x 50 mL). The combined 15 organic extracts were dried (MgSO₄), filtered, concentrated, and the residue purified with reverse phase HPLC to give 36 mg of a yellow solid. NMR: 10.50 (s, 1 H), 8.95 (s, 1 H), 8.40 (s, 1 H), 7.85 (s, 1 H), 7.60 (d, 1 H), 7.52 (s, 1 H), 7.39 (m, 2 H), 7.20 (s, 1 H), 4.25 (q, 2 H), 3.80 (m, 2 H), 3.50 (m, 4 H), 3.20 (m, 4 H), 2.95 (m, 2 H), 1.43 (t, 3 H); *m/z*: 503.

20 **Examples 193-200**

The following compounds were prepared by the procedure of Example 192 using the appropriate starting materials.

Ex.	Compound	NMR	M/z	SM
193	4-[(2,3-Dichlorophenyl)amino]-7-ethoxy-6-(4-isopropyl-1,4-diazepan-1-yl)quinoline-3-carboxamide	10.69 (s, 1 H), 8.85 (s, 1 H), 8.33 (s, 1 H), 7.70 (s, 1 H), 7.23 (m, 2 H), 7.14 (m, 1 H), 6.65 (m, 2 H), 4.20 (q, 2 H), 3.35 (m, 1 H), 3.10 (m, 4 H), 2.90-2.55 (m, 4 H), 1.65 (m, 2 H), 1.45 (t, 3 H), 0.92 (m, 6 H)	515	Example 181

Ex.	Compound	NMR	M/z	SM
194	4-[(2,4-Difluorophenyl) amino]-7-ethoxy-6-[4-(2-hydroxyethyl) piperazin-1-yl]quinoline-3-carboxamide	11.00 (s, 1 H), 8.80 (s, 1 H), 8.20 (s, 1 H), 7.70 (s, 1 H), 7.40-7.10 (m, 5 H), 4.22 (q, 2 H), 3.78 (m, 2 H), 3.55-2.95 (m, 10 H), 1.45 (t, 3 H)	471	Example 182
195	6-[4-(Cyclopropylmethyl) piperazin-1-yl]-4-[(2,4-difluorophenyl) amino]-7-ethoxyquinoline-3-carboxamide	10.10 (s, 1 H), 8.80 (s, 1 H), 8.20 (s, 1 H), 7.70 (s, 1 H), 7.45 (m, 4 H), 7.15 (m, 1 H), 4.29 (q, 2 H), 3.50 (m, 4 H), 3.15 (m, 4 H), 2.90 (m, 2 H), 1.45 (t, 3 H), 1.09 (m, 1 H), 0.65 (m, 2 H), 0.35 (m, 2 H)	481	Example 182
196	4-[(2,4-Difluorophenyl) amino]-7-ethoxy-6-(4-isopropyl-1,4-diazepan-1-yl)quinoline-3-carboxamide	10.70 (s, 1 H), 8.87 (s, 1 H), 8.32 (s, 1 H), 7.70 (s, 1 H), 7.40 (m, 1 H), 7.26 (s, 1 H), 7.05 (m, 2 H), 6.75 (s, 1 H), 4.22 (q, 2 H), 3.10 (m, 4 H), 2.90 (m, 1 H), 2.65 (m, 4 H), 1.75 (m, 2 H), 1.49 (t, 3 H), 1.00 (m, 6 H)	484	Example 183
197	4-[(2,4-Difluorophenyl) amino]-6-(4-isopropyl-1,4-diazepan-1-yl)-7-methoxyquinoline-3-carboxamide	10.55 (s, 1 H), 8.70 (s, 1 H), 8.20 (s, 1 H), 7.55 (s, 1 H), 7.25 (m, 1 H), 7.10 (s, 1 H), 6.85 (m, 2 H), 6.62 (s, 1 H), 3.80 (s, 3 H), 3.30 (m, 4 H), 2.95 (m, 4 H), 2.69 (m, 1 H), 1.47 (m, 2 H), 0.80 (d, 6 H)	469	Example 177
198	4-[(2,4-Difluorophenyl) amino]-6-(4-ethyl-1,4-diazepan-1-yl)-7-methoxyquinoline-3-carboxamide	10.35 (s, 1 H), 8.82 (s, 1 H), 8.33 (s, 1 H), 7.77 (s, 1 H), 7.42 (m, 3 H), 7.20 (m, 2 H), 4.00 (s, 3 H), 3.50-3.10 (m, 6 H), 2.90 (m, 2 H), 2.28 (m, 2 H), 2.10 (m, 2 H), 1.28 (t, 3 H)	455	Example 177
199	4-[(2,3-Dichlorophenyl) amino]-6-(4-isopropyl-1,4-diazepan-1-yl)-7-methoxyquinoline-3-carboxamide	10.77 (s, 1 H), 8.92 (s, 1 H), 8.40 (s, 1 H), 7.79 (s, 1 H), 7.30 (m, 2 H), 7.20 (m, 1 H), 6.70 (s, 1 H), 6.60 (d, 1 H), 4.00 (s, 3 H), 3.40 (m, 4 H), 3.18 (m, 4 H), 2.80 (m, 1 H), 1.65 (m, 2 H), 0.95 (m, 6 H)	502	Example 184

Ex.	Compound	NMR	M/z	SM
200	7-Ethoxy-4-[(2-fluoro-4-methylphenyl)amino]-6-[4-(2-hydroxyethyl)piperazin-1-yl]quinoline-3-carboxamide	CD ₂ Cl ₂ 10.44 (s, 1 H), 8.70 (s, 1 H), 7.23 (s, 1 H), 6.94 (d, 1 H), 6.91 (s, 1 H), 6.86 (m, 2 H), 5.97 (br, 2 H), 4.19 (q, 2 H), 3.56 (t, 2 H), 2.78 (s, 4 H), 2.53 (m, 6 H), 2.31 (s, 3 H), 1.48 (t, 3 H)	468	Example 185

Example 2014-[(2,3-Dichlorophenyl)amino]-7-ethoxy-6-(4-glycoloylpiperazin-1-yl)quinoline-3-carboxamide

- 5 A mixture of 4-[(2,3-dichlorophenyl)amino]-7-ethoxy-6-piperazin-1-ylquinoline-3-carboxamide hydrochloride (Example 175, 80 mg, 0.14 mmol), glycolic acid (38 mg, 0.5 mmol), HATU (106 mg, 0.28 mmol) and DIEA (72 mg, 0.56 mmol) in anhydrous DMF (3 ml) was stirred at room temperature for 5 hours. The crude mixture was purified with reverse phase HPLC to give 30 mg of a yellow solid. NMR: 12.10 (s, 1 H), 8.98 (s, 1 H), 8.46 (s, 1 H), 7.95 (s, 1 H), 7.65 (d, 1 H), 7.42 (m, 2 H), 7.35 (d, 1 H), 6.96 (s, 1 H), 4.25 (q, 2 H), 4.09 (s, 2 H), 3.60 (m, 4 H), 2.80 (m, 2 H), 2.70 (m, 2 H), 1.25 (t, 3 H); *m/z*: 518.

Examples 202-206

- 15 The following compounds were prepared by a similar method to Example 201 using the appropriate starting materials.

Ex.	Compound	NMR	M/z	SM
202	4-[(2,3-Dichlorophenyl)amino]-7-ethoxy-6-{4-[(2S)-2-hydroxypropanoyl]piperazin-1-yl}quinoline-3-carboxamide	12.15 (s, 1 H), 8.96 (s, 1 H), 8.45 (s, 1 H), 7.95 (s, 1 H), 7.65 (d, 1 H), 7.40 (m, 3 H), 6.99 (s, 1 H), 4.40 (m, 1 H), 4.26 (q, 2 H), 3.55 (m, 4 H), 2.80 (m, 4 H), 1.48 (t, 3 H), 1.15 (d, 3 H)	532	Example 175
203	4-[(2,3-Dichlorophenyl)amino]-7-ethoxy-6-{4-[(2R)-2-hydroxypropanoyl]piperazin-1-yl}quinoline-3-carboxamide	12.29 (s, 1 H), 9.05 (s, 1 H), 8.57 (s, 1 H), 7.96 (s, 1 H), 7.65 (d, 1 H), 7.50 (s, 1 H), 7.40 (m, 2 H), 6.98 (s, 1 H), 4.42 (m, 1 H), 4.25 (q, 2 H), 3.60 (m, 4 H), 2.80 (m, 4 H), 1.45 (t, 3 H), 1.20 (d, 3 H)	532	Example 175

Ex.	Compound	NMR	M/z	SM
204	7-Ethoxy-4-[(2-fluoro-4-methylphenyl)amino]-6-(4-glycoloylpiperazin-1-yl)quinoline-3-carboxamide	CD ₂ Cl ₂ 10.48 (s, 1 H), 8.73 (s, 1 H), 7.26 (s, 1 H), 6.95 (d, 1 H), 6.92 (s, 1 H), 6.86 (m, 2 H), 5.97 (br, 2 H), 4.20 (q, 2 H), 4.11 (s, 2 H), 3.66 (m, 2 H), 3.27 (m, 2 H), 2.78 (m, 2 H), 2.71 (m, 2 H), 2.32 (s, 3 H), 1.49 (t, 3 H)	481	Example 185
205	7-Ethoxy-4-[(2-fluoro-4-methylphenyl)amino]-6-{4-[(2S)-2-hydroxypropanoyl]piperazin-1-yl}quinoline-3-carboxamide	CD ₂ Cl ₂ 10.47 (s, 1 H), 8.72 (s, 1 H), 7.26 (s, 1 H), 6.95 (d, 1 H), 6.92 (s, 1 H), 6.87 (m, 2 H), 5.96 (br, 2 H), 4.41 (q, 1 H), 4.20 (q, 2 H), 3.66 (m, 2 H), 3.42 (m, 2 H), 2.79 (m, 2 H), 2.72 (m, 2 H), 2.32 (s, 3 H), 1.49 (t, 3 H), 1.27 (d, 3 H)	496	Example 185
206	7-Ethoxy-4-[(2-fluoro-4-methylphenyl)amino]-6-{4-[(2R)-2-hydroxypropanoyl]piperazin-1-yl}quinoline-3-carboxamide	CD ₂ Cl ₂ 10.47 (s, 1 H), 8.72 (s, 1 H), 7.26 (s, 1 H), 6.95 (d, 1 H), 6.92 (s, 1 H), 6.87 (m, 2 H), 5.96 (br, 2 H), 4.41 (q, 1 H), 4.21 (q, 2 H), 3.66 (m, 2 H), 3.42 (m, 2 H), 2.79 (m, 2 H), 2.73 (m, 2 H), 2.32 (s, 3 H), 1.49 (t, 3 H), 1.27 (d, 3 H)	496	Example 185

Example 2076-(4-Cyclopropyl-1,4-diazepan-1-yl)-4-[(2,4-difluorophenyl)amino]-7-ethoxyquinoline-3-carboxamide

- 5 To a solution of 6-(1,4-diazepan-1-yl)-4-[(2,4-difluorophenyl)amino]-7-ethoxyquinoline-3-carboxamide (Example 183, 100 mg, 0.227 mmol) in MeOH (10 mL) was added [(1-ethoxycyclopropyl)oxy]trimethyl silane (237 mg, 1.36 mmol), acetic acid (136 mg, 2.27 mmol), 4Å molecular sieves (2 g) and sodium cyanoborohydride (291 mg, 4.54 mmol). The resulting reaction mixture was stirred at reflux overnight. Water was added, the mixture
- 10 was extracted with EtOAc (3 x 30 mL), and the combined organic extracts were dried (Na₂SO₄), concentrated and the residue purified with an ISCO chromatography system to give 100 mg of a light yellow solid. NMR: 10.66 (s, 1 H), 8.89 (s, 1 H), 8.25 (s, 1 H), 7.65 (s, 1 H),

7.35 (m, 1 H), 7.20 (s, 1 H), 6.95 (m, 2 H), 6.68 (s, 1 H), 4.17 (q, 2 H), 3.03 (m, 4 H), 2.73 (m, 4 H), 1.86 (m, 1 H), 1.70 (m, 2 H), 1.42 (t, 3 H), 0.41 (m, 2 H), 0.27 (m, 2 H); m/z : 482.

Examples 208-215

- 5 The following compounds were prepared by a similar method to Example 207 using the appropriate starting materials.

Ex.	Compound	NMR	M/z	SM
208	6-(4-Cyclopropyl piperazin-1-yl)-4-[(2,4-difluorophenyl)amino]-7-ethoxyquinoline-3-carboxamide	10.79 (s, 1 H), 8.90 (s, 1 H), 8.31 (s, 1 H), 7.70 (s, 1 H), 7.40 (m, 1 H), 7.30 (s, 1 H), 7.09 (m, 2 H), 6.86 (s, 1 H), 4.25 (q, 2 H), 2.79 (m, 8 H), 2.65 (m, 1 H), 1.46 (t, 3 H), 0.71 (m, 2 H), 0.63 (m, 2 H)	467	Example 182
209	6-(4-Cyclopropyl piperazin-1-yl)-4-[(2,4-difluorophenyl)amino]-7-methoxyquinoline-3-carboxamide	10.65 (s, 1 H), 8.91 (s, 1 H), 8.30 (s, 1 H), 7.68 (s, 1 H), 7.38 (m, 1 H), 7.30 (s, 1 H), 7.06 (m, 2 H), 6.86 (s, 1 H), 3.95 (s, 3 H), 2.70 (m, 4 H), 2.56 (m, 4 H), 1.65 (m, 1 H), 0.41 (m, 2 H), 0.30 (m, 2 H)	453	Example 176
210	6-(4-Cyclopropyl piperazin-1-yl)-4-[(2,3-dichlorophenyl)amino]-7-methoxyquinoline-3-carboxamide	10.80 (s, 1 H), 8.95 (s, 1 H), 8.40 (s, 1 H), 7.79 (s, 1 H), 7.35 (s, 1 H), 7.28 (d, 1 H), 7.15 (m, 1 H), 6.69 (s, 1 H), 6.60 (d, 1 H), 3.98 (s, 3 H), 2.71 (m, 4 H), 2.56 (m, 4 H), 1.65 (m, 1 H), 0.40 (m, 2 H), 0.20 (m, 2 H)	486	Example 174
211	6-(4-Cyclopropyl-1,4-diazepan-1-yl)-4-[(2,4-difluorophenyl)amino]-7-methoxyquinoline-3-carboxamide	10.69 (s, 1 H), 8.80 (s, 1 H), 8.28 (s, 1 H), 7.65 (s, 1 H), 7.36 (m, 1 H), 7.24 (s, 1 H), 6.97 (m, 2 H), 6.70 (s, 1 H), 3.91 (s, 3 H), 3.05 (m, 4 H), 2.70 (m, 4 H), 1.82 (m, 1 H), 1.67 (m, 2 H), 0.40 (m, 2 H), 0.27 (m, 2 H)	467	Example 177

Ex.	Compound	NMR	M/z	SM
212	6-(4-Cyclopropyl-1,4-diazepan-1-yl)-4-[(2,3-dichlorophenyl)amino]-7-methoxyquinoline-3-carboxamide	10.70 (s, 1 H), 8.89 (s, 1 H), 8.35 (s, 1 H), 7.63 (s, 1 H), 7.25 (m, 2 H), 7.12 (m, 1 H), 6.55 (m, 2 H), 3.95 (s, 3 H), 3.12 (m, 2 H), 3.07 (m, 2 H), 2.65 (m, 4 H), 1.85 (m, 1 H), 1.65 (m, 2 H), 0.42 (m, 2 H), 0.26 (m, 2 H)	500	Example 184
213	4-[(3-Chloro-4-fluorophenyl)amino]-6-(4-cyclopropyl piperazin-1-yl)-7-ethoxyquinoline-3-carboxamide	CD ₃ OD 8.81 (s, 1 H), 7.26 (s, 1 H), 7.20 (m, 1 H), 7.03 (m, 1 H), 7.00 (s, 1 H), 6.90 (m, 1 H), 4.25 (q, 2 H), 2.88 (m, 4 H), 2.79 (m, 4 H), 1.84 (m, 1 H), 1.52 (t, 3 H), 0.55 (m, 2 H), 0.48 (m, 2 H)	484	Example 178
214	6-(4-Cyclopropyl piperazin-1-yl)-7-ethoxy-4-[(2-fluoro-5-methylphenyl)amino]quinoline-3-carboxamide	CD ₃ OD 8.78 (s, 1 H), 7.23 (s, 1 H), 7.06 (dd, 1 H), 7.01 (s, 1 H), 6.94 (m, 1 H), 6.79 (d, 1 H), 4.23 (q, 2 H), 2.80 (m, 4 H), 2.69 (m, 4 H), 2.20 (s, 3 H), 1.69 (m, 1 H), 1.51 (t, 3 H), 0.50 (m, 2 H), 0.42 (m, 2 H)	464	Example 179
215	4-[(3-Chloro-2-fluorophenyl)amino]-6-(4-cyclopropyl piperazin-1-yl)-7-ethoxyquinoline-3-carboxamide	CD ₃ OD 8.76 (s, 1 H), 7.25 (s, 1 H), 7.17 (dd, 1 H), 7.06 (d, 1 H), 7.02 (s, 1 H), 6.95 (m, 1 H), 4.24 (q, 2 H), 2.88 (m, 4 H), 2.72 (m, 4 H), 1.70 (m, 1 H), 1.52 (t, 3 H), 0.50 (m, 2 H), 0.43 (m, 2 H)	484	Example 180

Example 216

4-[(2,4-Difluorophenyl)amino]-7-(2-hydroxyethoxy)-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide

- 5 To a solution of ethyl 7-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethoxy)-4-[(2,4-difluorophenyl)amino]-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate (Intermediate 162, 0.200 g, 0.33 mmol) and formamide (0.132 mL, 3.33 mmol) in DMF (5 mL), heated at 100°C for 30 minutes, was added a solution of sodium methoxide in MeOH (0.5 M, 0.85 mL, 0.43

mmol). After 16 hours, the reaction was cooled, water (50 mL) was added, and the reaction mixture extracted with EtOAc (3 x 50 mL). The combined organic extracts were concentrated and tetrabutylammonium fluoride solution (1.0 M in THF, 1 mL) added. The mixture was allowed to stand for 1 hour. Water (10 mL) was added and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were concentrated and the residue purified with reverse phase HPLC. The product was recrystallized (hexanes/acetone) to give 85 mg (56%) of a yellow solid. ¹H NMR: 10.73 (s, 1 H), 8.85 (s, 1 H), 8.29 (s, 1 H), 7.66 (s, 1 H), 7.37 (t, 1 H), 7.26 (s, 1 H), 7.03 (m, 2 H), 6.80 (s, 1 H), 4.87 (t, 1 H), 4.16 (m, 2 H), 3.79 (m, 2 H), 2.76 (s, 4 H), 2.37 (s, 4 H), 2.18 (s, 3 H); *m/z*: 458.

10

Example 217

The following compound was prepared by a similar method to Example 216 using the appropriate starting material.

Ex.	Compound	NMR	M/z	SM
217	4-[(3-Chloro-2-fluorophenyl)amino]-7-(2-hydroxyethoxy)-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide	10.69 (s, 1 H), 8.88 (s, 1 H), 8.31 (s, 1 H), 7.70 (s, 1 H), 7.30 (s, 1 H), 7.23 (t, 1 H), 7.08 (s, 1 H), 6.84 (m, 2 H), 4.87 (t, 1 H), 4.18 (m, 2 H), 3.80 (m, 2 H), 2.81 (s, 4 H), 2.37 (s, 4 H), 2.18 (s, 3 H)	474	Intermediate 163

15 Preparation of Starting Materials**Intermediate 1**

Ethyl 4-[(2,3-dichlorophenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate

20 A mixture of ethyl 6-bromo-4-[(2,3-dichlorophenyl)amino]-7-methoxyquinoline-3-carboxylate (Intermediate 155; 400 mg, 0.82 mmol), tris(dibenzylideneacetone) dipalladium(0) (60 mg, 0.066 mmol), (R,S)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (124 mg, 0.20 mmol), Cs₂CO₃ (390 mg, 1.2 mmol), and *N*-methylpiperazine (227 μ L, 2.05 mmol) in anhydrous toluene under N₂ was heated at 100°C for 18 hours. The reaction mixture was
 25 filtered, concentrated, and the crude oil purified by reverse phase HPLC to give 117 mg of a solid; *m/z*: 489.

Intermediates 2-154

The following compounds were prepared by a method similar to Intermediate 1 using the appropriate starting materials.

Int	Compound	M/z/NMR	SM
2	Ethyl 4-[(2,4-dichlorophenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate		Intermediate 165
3	Ethyl 4-[(3,4-dichlorophenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate		Intermediate 166
4	Ethyl 4-[(2,4-difluorophenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	458	Intermediate 167
5	Ethyl 4-[(2,3-dichlorophenyl)amino]-7-methoxy-6-morpholin-4-ylquinoline-3-carboxylate		Intermediate 155
6	Ethyl 4-[(2,4-difluorophenyl)amino]-7-methoxy-6-morpholin-4-ylquinoline-3-carboxylate		Intermediate 167
7	Ethyl 4-[(3,4-dichlorophenyl)amino]-7-methoxy-6-morpholin-4-ylquinoline-3-carboxylate		Intermediate 166
8	Ethyl 4-[(3,4-dichlorophenyl)amino]-7-methoxy-6-piperidin-1-ylquinoline-3-carboxylate		Intermediate 166
9	Ethyl 4-[(2,3-dichlorophenyl)amino]-6-methoxy-7-(4-methylpiperazin-1-yl)quinoline-3-carboxylate		Intermediate 168
10	Ethyl 4-[(3,4-dichlorophenyl)amino]-6-methoxy-7-(4-methylpiperazin-1-yl)quinoline-3-carboxylate		Intermediate 169

Int	Compound	M/z/NMR	SM
11	Ethyl 4-[(2,4-difluorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	471	Intermediate 170
12	Ethyl 4-[(2,3-dichlorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	504	Intermediate 171
13	Ethyl 4-[(2,4-difluorophenyl)amino]-7-ethoxy-6-morpholin-4-ylquinoline-3-carboxylate		Intermediate 170
14	Ethyl 4-[(3,4-dichlorophenyl)amino]-7-ethoxy-6-morpholin-4-ylquinoline-3-carboxylate		Intermediate 172
15	Ethyl 6-[4-(tert-butoxycarbonyl)piperazin-1-yl]-4-[(2,3-dichlorophenyl)amino]-7-methoxyquinoline-3-carboxylate	575	Intermediate 155
16	Ethyl 4-[(2,4-difluorophenyl)amino]-7-fluoro-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	445	Intermediate 173
17	Ethyl 4-[(2,3-dichlorophenyl)amino]-7-fluoro-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate		Intermediate 174
18	Ethyl 4-[(2,4-difluorophenyl)amino]-7-fluoro-6-morpholin-4-ylquinoline-3-carboxylate		Intermediate 173
19	Ethyl 4-[(2,3-dichlorophenyl)amino]-5-fluoro-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate		Intermediate 175
20	Ethyl 7-ethoxy-4-[(4-ethylphenyl)amino]-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	463	Intermediate 176
21	Ethyl 4-[(3-chloro-4-fluorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	487	Intermediate 177

Int	Compound	M/z/NMR	SM
22	Ethyl 4-[(3,4-dichlorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	503	Intermediate 172
23	Ethyl 4-[(2,3-dichlorophenyl)amino]-7-ethoxy-6-(4-ethylpiperazin-1-yl)quinoline-3-carboxylate	517	Intermediate 171
24	Ethyl 4-[(3-chloro-2-fluorophenyl)amino]-7-ethoxy-6-morpholin-4-ylquinoline-3-carboxylate	474	Intermediate 178
25	Ethyl 7-ethoxy-4-[(2-fluoro-5-methylphenyl)amino]-6-morpholin-4-ylquinoline-3-carboxylate	454	Intermediate 179
26	Ethyl 4-[(3-chloro-4-fluorophenyl)amino]-7-ethoxy-6-morpholin-4-ylquinoline-3-carboxylate	454	Intermediate 177
27	Ethyl 7-ethoxy-4-[(4-ethylphenyl)amino]-6-morpholin-4-ylquinoline-3-carboxylate	450	Intermediate 176
28	Ethyl 4-[(2,3-dichlorophenyl)amino]-7-ethoxy-6-morpholin-4-ylquinoline-3-carboxylate	490	Intermediate 171
29	Ethyl 4-[(2,3-dichlorophenyl)amino]-7-ethoxy-6-(4-isopropylpiperazin-1-yl)quinoline-3-carboxylate	530	Intermediate 171
30	Ethyl 4-[(2,3-dichlorophenyl)amino]-7-ethoxy-6-(4-methyl-1,4-diazepan-1-yl)quinoline-3-carboxylate	516	Intermediate 171
31	Ethyl 4-[(2,3-dichlorophenyl)amino]-7-ethoxy-6-(3-hydroxypyrrolidin-1-yl)quinoline-3-carboxylate	489	Intermediate 171
32	Ethyl 4-[(2,3-dichlorophenyl)amino]-6-{4-[2-(dimethylamino)ethyl]piperazin-1-yl}-7-ethoxyquinoline-3-carboxylate	559	Intermediate 171

Int	Compound	M/z/NMR	SM
33	Ethyl 4-[(2,3-dichlorophenyl)amino]-7-ethoxy-6-[4-(2-methoxyethyl)piperazin-1-yl]quinoline-3-carboxylate	546	Intermediate 171
34	Ethyl 4-[(3,4-dichlorophenyl)amino]-7-ethoxy-6-(4-ethylpiperazin-1-yl)quinoline-3-carboxylate	517	Intermediate 172
35	Ethyl 4-[(2,4-difluorophenyl)amino]-7-ethoxy-6-(4-ethylpiperazin-1-yl)quinoline-3-carboxylate	485	Intermediate 170
36	Ethyl 4-[(3-chloro-2-fluorophenyl)amino]-7-ethoxy-6-(4-ethylpiperazin-1-yl)quinoline-3-carboxylate	501	Intermediate 178
37	Ethyl 7-ethoxy-6-(4-ethylpiperazin-1-yl)-4-[(2-fluoro-5-methylphenyl)amino]quinoline-3-carboxylate	481	Intermediate 179
38	Ethyl 4-[(3-chloro-4-fluorophenyl)amino]-7-ethoxy-6-(4-ethylpiperazin-1-yl)quinoline-3-carboxylate	501	Intermediate 177
39	Ethyl 7-ethoxy-4-[(4-ethylphenyl)amino]-6-(4-ethylpiperazin-1-yl)quinoline-3-carboxylate	477	Intermediate 176
40	Ethyl 6-[4-(2-cyanoethyl)piperazin-1-yl]-4-[(2,3-dichlorophenyl)amino]-7-ethoxyquinoline-3-carboxylate	541	Intermediate 171
41	Ethyl 4-[(2,3-dichlorophenyl)amino]-7-ethoxy-6-(4-hydroxypiperidin-1-yl)quinoline-3-carboxylate	503	Intermediate 171
42	Ethyl 7-ethoxy-4-[(4-ethylphenyl)amino]-6-(4-methyl-1,4-diazepan-1-yl)quinoline-3-carboxylate	477	Intermediate 176

Int	Compound	M/z/NMR	SM
43	Ethyl 4-[(2,4-difluorophenyl)amino]-7-ethoxy-6-(3-hydroxypyrrolidin-1-yl)quinoline-3-carboxylate	457	Intermediate 170
44	Ethyl 4-[(2,4-difluorophenyl)amino]-7-ethoxy-6-(4-hydroxypiperidin-1-yl)quinoline-3-carboxylate	471	Intermediate 170
45	Ethyl 4-[(3,4-dichlorophenyl)amino]-7-ethoxy-6-(4-isopropylpiperazin-1-yl)quinoline-3-carboxylate	531	Intermediate 172
46	Ethyl 4-[(2,4-difluorophenyl)amino]-7-ethoxy-6-(4-isopropylpiperazin-1-yl)quinoline-3-carboxylate	499	Intermediate 170
47	Ethyl 4-[(3-chloro-2-fluorophenyl)amino]-7-ethoxy-6-(4-isopropylpiperazin-1-yl)quinoline-3-carboxylate	515	Intermediate 178
48	Ethyl 7-ethoxy-4-[(2-fluoro-5-methylphenyl)amino]-6-(4-isopropylpiperazin-1-yl)quinoline-3-carboxylate	515	Intermediate 179
49	Ethyl 4-[(3-chloro-4-fluorophenyl)amino]-7-ethoxy-6-(4-isopropylpiperazin-1-yl)quinoline-3-carboxylate	491	Intermediate 177
50	Ethyl 4-[(2,4-difluorophenyl)amino]-7-ethoxy-6-(4-methyl-1,4-diazepan-1-yl)quinoline-3-carboxylate	484	Intermediate 170
51	Ethyl 4-[(2,3-dichlorophenyl)amino]-6-(4-isopropylpiperazin-1-yl)-7-methoxyquinoline-3-carboxylate	517	Intermediate 155
52	Ethyl 4-[(2,4-difluorophenyl)amino]-6-(4-isopropylpiperazin-1-yl)-7-methoxyquinoline-3-carboxylate	484	Intermediate 167

Int	Compound	M/z/NMR	SM
53	Ethyl 4-[(2,3-dichlorophenyl)amino]-7-methoxy-6-(4-methyl-1,4-diazepan-1-yl)quinoline-3-carboxylate	503	Intermediate 155
54	Ethyl 4-[(2,4-difluorophenyl)amino]-7-methoxy-6-(4-methyl-1,4-diazepan-1-yl)quinoline-3-carboxylate	470	Intermediate 167
55	Ethyl 4-[(2,3-dichlorophenyl)amino]-6-(4-ethylpiperazin-1-yl)-7-methoxyquinoline-3-carboxylate	503	Intermediate 155
56	Ethyl 4-[(2,4-difluorophenyl)amino]-6-(4-ethylpiperazin-1-yl)-7-methoxyquinoline-3-carboxylate	470	Intermediate 167
57	Ethyl 4-[(3,4-dichlorophenyl)amino]-6-(4-ethylpiperazin-1-yl)-7-methoxyquinoline-3-carboxylate	503	Intermediate 166
58	Ethyl 4-[(3,4-dichlorophenyl)amino]-6-(4-isopropylpiperazin-1-yl)-7-methoxyquinoline-3-carboxylate	517	Intermediate 166
59	Ethyl 4-[(3,4-dichlorophenyl)amino]-7-methoxy-6-(4-methyl-1,4-diazepan-1-yl)quinoline-3-carboxylate	503	Intermediate 166
60	Ethyl 4-[(3,4-dichlorophenyl)amino]-7-ethoxy-6-(4-methyl-1,4-diazepan-1-yl)quinoline-3-carboxylate	517	Intermediate 172
61	Ethyl 7-ethoxy-4-[(2-fluoro-5-methylphenyl)amino]-6-(4-methyl-1,4-diazepan-1-yl)quinoline-3-carboxylate	481	Intermediate 179
62	Ethyl 4-[(3-chloro-4-fluorophenyl)amino]-7-ethoxy-6-(4-methyl-1,4-diazepan-1-yl)quinoline-3-carboxylate	487	Intermediate 177

Int	Compound	M/z/NMR	SM
63	Ethyl 4-[(2-fluorophenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate		Intermediate 180
64	Ethyl 6-[4-(tert-butoxycarbonyl)piperazin-1-yl]-4-[(3-chloro-4-fluorophenyl)amino]-7-ethoxyquinoline-3-carboxylate	573	Intermediate 177
65	Ethyl 6-[4-(tert-butoxycarbonyl)piperazin-1-yl]-7-ethoxy-4-[(2-fluoro-5-methylphenyl)amino]quinoline-3-carboxylate	553	Intermediate 179
66	Ethyl 6-[4-(tert-butoxycarbonyl)piperazin-1-yl]-4-[(3-chloro-2-fluorophenyl)amino]-7-ethoxyquinoline-3-carboxylate	573	Intermediate 178
67	Ethyl 7-methoxy-4-[(3-methoxy-2-methylphenyl)amino]-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	465	Intermediate 181
68	Ethyl 4-[(4-chloro-2-methylphenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	469	Intermediate 182
69	Ethyl 4-[(3-chloro-2-methylphenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	463	Intermediate 183
70	Ethyl 4-[(3-chloro-2-fluorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	486	Intermediate 178
71	Ethyl 7-ethoxy-4-[(3-ethylphenyl)amino]-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	462	Intermediate 184
72	Ethyl 4-[(3-chlorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	469	Intermediate 185

Int	Compound	M/z/NMR	SM
73	Ethyl 4-[(2-chloro-4-fluorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	486	Intermediate 186
74	Ethyl 4-[(4-chloro-2-fluorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	486	Intermediate 187
75	Ethyl 7-ethoxy-4-[(3-methylphenyl)amino]-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	448	Intermediate 188
76	Ethyl 4-[(2-chloro-3-methylphenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	482	Intermediate 189
77	Ethyl 7-ethoxy-4-[(3-fluoro-2-methylphenyl)amino]-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	466	Intermediate 190
78	Ethyl 4-[(3,4-difluorophenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	457	Intermediate 191
79	Ethyl 7-methoxy-6-(4-methylpiperazin-1-yl)-4-{{[2-methyl-3-(trifluoromethyl)phenyl]amino} quinoline-3-carboxylate		Intermediate 192
80	Ethyl 4-[(4-chlorophenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	455	Intermediate 193
81	Ethyl 4-[(2-fluoro-4-methylphenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	453	Intermediate 194
82	Ethyl 7-methoxy-6-(4-methylpiperazin-1-yl)-4-{{[3-(trifluoromethyl)phenyl]amino} quinoline-3-carboxylate	489	Intermediate 195

Int	Compound	M/z/NMR	SM
83	Ethyl 7-ethoxy-4-[(2-fluoro-5-methylphenyl)amino]-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	467	Intermediate 179
84	Ethyl 4-[(3-chloro-2-methylphenyl)amino]-7-ethoxy-6-(4-ethylpiperazin-1-yl)quinoline-3-carboxylate	496	Intermediate 183
85	Ethyl 4-[(3-chloro-2-methylphenyl)amino]-7-ethoxy-6-(4-methyl-1,4-diazepan-1-yl)quinoline-3-carboxylate	496	Intermediate 183
86	Ethyl 7-ethoxy-6-(4-ethylpiperazin-1-yl)-4-[(3-fluoro-2-methylphenyl)amino]quinoline-3-carboxylate	480	Intermediate 190
87	Ethyl 7-ethoxy-4-[(3-fluoro-2-methylphenyl)amino]-6-(4-methyl-1,4-diazepan-1-yl)quinoline-3-carboxylate	480	Intermediate 190
88	Ethyl 7-ethoxy-4-[(2-fluoro-4-methylphenyl)amino]-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	467	Intermediate 196
89	Ethyl 7-ethoxy-4-[(3-methoxy-2-methylphenyl)amino]-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	479	Intermediate 197
90	Ethyl 4-[(2,5-difluorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	471	Intermediate 198
91	Ethyl 4-[(2,5-difluorophenyl)amino]-7-ethoxy-6-(4-ethylpiperazin-1-yl)quinoline-3-carboxylate	485	Intermediate 198
92	Ethyl 4-[(2,5-difluorophenyl)amino]-7-ethoxy-6-(4-methyl-1,4-diazepan-1-yl)quinoline-3-carboxylate	485	Intermediate 198

Int	Compound	M/z/NMR	SM
93	Ethyl 7-ethoxy-6-(4-ethylpiperazin-1-yl)-4-[(2-fluoro-4-methylphenyl)amino]quinoline-3-carboxylate	481	Intermediate 196
94	Ethyl 4-[(3,4-dimethylphenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	463	Intermediate 199
95	Ethyl 4-[(2,4-difluorophenyl)amino]-6-ethoxy-7-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	471	Intermediate 200
96	Ethyl 4-[(2,3-dichlorophenyl)amino]-6-ethoxy-7-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	503	Intermediate 201
97	Ethyl 4-[(2,3-difluorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	471	Intermediate 202
98	Ethyl 4-[(2,3-dimethylphenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	463	Intermediate 203
99	Ethyl 4-[(4-chloro-3-fluorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	488	Intermediate 204
100	Ethyl 4-[(2,3-dichlorophenyl)amino]-6-ethoxy-7-(4-ethylpiperazin-1-yl)quinoline-3-carboxylate	517	Intermediate 201
101	Ethyl 4-[(2,4-difluorophenyl)amino]-6-ethoxy-7-(4-ethylpiperazin-1-yl)quinoline-3-carboxylate	485	Intermediate 200
102	Ethyl 4-[(3-chloro-2,4-difluorophenyl)amino]-7-ethoxy-6-(4-ethylpiperazin-1-yl)quinoline-3-carboxylate	518	Intermediate 205

Int	Compound	M/z/NMR	SM
103	Ethyl 4-[(3-chloro-2,4-difluorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	504	Intermediate 205
104	Ethyl 4-[(3-chloro-4-fluorophenyl)amino]-6-ethoxy-7-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	487	Intermediate 206
105	Ethyl 4-[(3-chloro-4-fluorophenyl)amino]-6-ethoxy-7-(4-ethylpiperazin-1-yl)quinoline-3-carboxylate	501	Intermediate 206
106	Ethyl 4-[[4-fluoro-2-(trifluoromethyl)phenyl]amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate		Intermediate 207
107	Ethyl 4-[(2-chloro-4-fluorophenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	473	Intermediate 208
108	Ethyl 7-methoxy-6-(4-methylpiperazin-1-yl)-4-[[3-(trifluoromethoxy)phenyl]amino]quinoline-3-carboxylate	505	Intermediate 209
109	Ethyl 4-[(2,6-dimethylphenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	449	Intermediate 210
110	Ethyl 4-[(2,4-difluorophenyl)amino]-7-ethoxy-6-(4-ethyl-1,4-diazepan-1-yl)quinoline-3-carboxylate	498	Intermediate 170 and Intermediate 252
111	Ethyl 4-[(2,3-dichlorophenyl)amino]-6-(4-ethyl-1,4-diazepan-1-yl)-7-methoxyquinoline-3-carboxylate	516	Intermediate 155 and Intermediate 252

Int	Compound	M/z/NMR	SM
112	Ethyl 4-[(2,3-dichlorophenyl)amino]-7-ethoxy-6-(4-ethyl-1,4-diazepan-1-yl)quinoline-3-carboxylate	530	Intermediate 171 and Intermediate 252
113	Ethyl 6-[4-(tert-butoxycarbonyl)piperazin-1-yl]-4-[(2,3-dichlorophenyl)amino]-7-ethoxyquinoline-3-carboxylate	589	Intermediate 171
114	Ethyl 6-[4-(tert-butoxycarbonyl)piperazin-1-yl]-4-[(2,4-difluorophenyl)amino]-7-methoxyquinoline-3-carboxylate	542	Intermediate 167
115	Ethyl 6-[4-(tert-butoxycarbonyl)-1,4-diazepan-1-yl]-4-[(2,4-difluorophenyl)amino]-7-methoxyquinoline-3-carboxylate	556	Intermediate 167
116	Ethyl 6-[4-(tert-butoxycarbonyl)-1,4-diazepan-1-yl]-4-[(2,3-dichlorophenyl)amino]-7-ethoxyquinoline-3-carboxylate	602	Intermediate 171
117	Ethyl 6-[4-(tert-butoxycarbonyl)piperazin-1-yl]-4-[(2,4-difluorophenyl)amino]-7-ethoxyquinoline-3-carboxylate	556	Intermediate 170
118	Ethyl 6-[4-(tert-butoxycarbonyl)-1,4-diazepan-1-yl]-4-[(2,4-difluorophenyl)amino]-7-ethoxyquinoline-3-carboxylate	570	Intermediate 170
119	Ethyl 6-[4-(tert-butoxycarbonyl)-1,4-diazepan-1-yl]-4-[(2,3-dichlorophenyl)amino]-7-methoxyquinoline-3-carboxylate	589	Intermediate 155
120	Ethyl 4-[(2-fluoro-5-methylphenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	453	Intermediate 211
121	Ethyl 4-[(2,5-difluorophenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	457	Intermediate 212

Int	Compound	M/z/NMR	SM
122	Ethyl 4-[(3-chloro-2-methylphenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	470	Intermediate 213
123	Ethyl 4-[(2-chloro-3-methylphenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	469	Intermediate 214
124	Ethyl 4-[(2,4-difluorophenyl)amino]-6-[3-(dimethylamino)pyrrolidin-1-yl]-7-methoxyquinoline-3-carboxylate	471	Intermediate 167
125	Ethyl 4-[(3-chloro-2-fluorophenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	473	Intermediate 215
126	Ethyl 4-[(3-chloro-5-fluorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	488	Intermediate 216
127	Ethyl 7-ethoxy-6-(4-methylpiperazin-1-yl)-4-[(2,3,4-trifluorophenyl)amino]quinoline-3-carboxylate	489	Intermediate 217
128	Ethyl 4-[(5-chloro-2-methylphenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	484	Intermediate 218
129	Ethyl 7-ethoxy-4-[(4-methoxy-2-methylphenyl)amino]-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	479	Intermediate 219
130	Ethyl 4-{{2-chloro-5-(trifluoromethyl)phenyl}amino}-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	538	Intermediate 220
131	Ethyl 4-[(2,4-difluorophenyl)amino]-7-ethoxy-6-(4-methyl-3-oxopiperazin-1-yl)quinoline-3-carboxylate	485	Intermediate 170

Int	Compound	M/z/NMR	SM
132	Ethyl 4-[(2,3-dichlorophenyl)amino]-7-(4-ethylpiperazin-1-yl)-6-methoxyquinoline-3-carboxylate	474	Intermediate 168
133	Ethyl 4-[(2-fluoro-5-methylphenyl)amino]-6-methoxy-7-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	454	Intermediate 221
134	Ethyl 7-(4-ethylpiperazin-1-yl)-4-[(2-fluoro-5-methylphenyl)amino]-6-methoxyquinoline-3-carboxylate	467	Intermediate 221
135	Ethyl 4-[(3-chloro-2-fluorophenyl)amino]-6-methoxy-7-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	473	Intermediate 222
136	Ethyl 4-[(3-chloro-2-fluorophenyl)amino]-7-(4-ethylpiperazin-1-yl)-6-methoxyquinoline-3-carboxylate	487	Intermediate 222
137	Ethyl 4-[(2-fluoro-5-methylphenyl)amino]-6-methoxy-7-(4-methyl-1,4-diazepan-1-yl)quinoline-3-carboxylate	467	Intermediate 221
138	Ethyl 4-[(2,4-difluorophenyl)amino]-6-methoxy-7-(4-methyl-1,4-diazepan-1-yl)quinoline-3-carboxylate	471	Intermediate 223
139	Ethyl 4-[(2-chloro-3-fluorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	487	Intermediate 224
140	Ethyl 4-[(2-chloro-3-fluorophenyl)amino]-7-ethoxy-6-(4-ethylpiperazin-1-yl)quinoline-3-carboxylate	501	Intermediate 224
141	Ethyl 4-[(2-chloro-3-fluorophenyl)amino]-7-ethoxy-6-(4-isopropylpiperazin-1-yl)quinoline-3-carboxylate		Intermediate 224

Int	Compound	M/z/NMR	SM
142	Ethyl 6-[4-(tert-butoxycarbonyl)piperazin-1-yl]-7-ethoxy-4-[(2-fluoro-4-methylphenyl)amino]quinoline-3-carboxylate	553	Intermediate 196
143	Ethyl 4-[(2,3-dichlorophenyl)amino]-7-ethoxy-6-(3-oxopiperazin-1-yl)quinoline-3-carboxylate	504	Intermediate 171
144	Ethyl 7-ethoxy-4-[(2-fluoro-5-methylphenyl)amino]-6-(3-oxopiperazin-1-yl)quinoline-3-carboxylate	467	Intermediate 179
145	Ethyl 4-[(2,4-difluorophenyl)amino]-7-ethoxy-6-(3-oxopiperazin-1-yl)quinoline-3-carboxylate	471	Intermediate 170
146	Ethyl 4-[(2-chloro-4-methylphenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	9.98 (s, 1 H), 8.99 (s, 1 H), 7.50 (s, 1 H), 7.30 (s, 1 H), 7.10 (d, 1 H), 6.90 (d, 1 H), 6.77 (s, 1 H), 4.35 (q, 2 H), 4.20 (q, 2 H), 2.70 (s, 4 H), 2.40 (s, 4 H), 2.30 (s, 3 H), 2.20 (s, 3 H), 1.40 (m, 6 H)	Intermediate 225
147	Ethyl 7-ethoxy-4-{[2-fluoro-3-(trifluoromethyl)phenyl]amino}-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	9.55 (s, 1 H), 8.87 (s, 1 H), 7.45-7.15 (m, 5 H), 4.28 (q, 2 H), 4.12 (q, 2 H), 3.90 (s, 4 H), 2.42 (s, 4 H), 2.22 (s, 3 H), 1.45 (t, 3 H), 1.21 (t, 3 H)	Intermediate 226

Int	Compound	M/z/NMR	SM
148	Ethyl 4-[(2,4-dimethoxyphenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	9.98 (s, 1 H), 8.90 (s, 1 H), 7.20 (s, 1 H), 7.00 (m, 1 H), 6.91 (s, 1 H), 6.70 (s, 1 H), 6.52 (t, 1 H), 4.35 (q, 2 H), 4.19 (q, 2 H), 3.80 (s, 3 H), 3.75 (s, 3 H), 2.68 (s, 4 H), 2.35 (s, 4 H), 2.20 (s, 3 H), 2.35 (m, 6 H)	Intermediate 227
149	Ethyl 4-[(2-chloro-4-fluoro-5-methylphenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	9.89 (s, 1 H), 8.91 (s, 1 H), 7.57 (d, 1 H), 7.29 (s, 1 H), 7.00 (d, 1 H), 6.75 (s, 1 H), 4.32 (q, 2 H), 4.20 (q, 2 H), 2.75 (s, 4 H), 2.40 (s, 4 H), 2.21 (s, 3 H), 2.10 (s, 3 H), 1.45 (t, 3 H), 1.37 (t, 3 H)	Intermediate 228
150	Ethyl 4-[(5-chloro-2-fluorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	9.60 (s, 1 H), 8.89 (s, 1 H), 7.35 (m, 2 H), 7.15-7.05 (m, 3 H), 4.20 (q, 4 H), 2.90 (s, 4 H), 2.42 (s, 4 H), 2.20 (s, 3 H), 1.40 (t, 3 H), 1.25 (t, 3 H)	Intermediate 229

Int	Compound	M/z/NMR	SM
151	Ethyl 7-ethoxy-4-{[2-methoxy-5-(trifluoromethyl)phenyl]amino}-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	9.85 (s, 1 H), 8.90 (s, 1 H), 7.40 (m, 1 H), 7.30 (m, 2 H), 6.95 (s, 1 H), 6.85 (s, 1 H), 4.30 (q, 2 H), 4.20 (q, 2 H), 3.90 (s, 3 H), 2.80 (s, 4 H), 2.40 (s, 4 H), 2.20 (s, 3 H), 1.40 (t, 3 H), 1.30 (t, 3 H)	Intermediate 230
152	Ethyl 4-[(2-fluoro-4-methylphenyl)amino]-7-(2-methoxyethoxy)-6-morpholin-4-ylquinoline-3-carboxylate	484	Intermediate 231
153	Ethyl 4-[(2-fluoro-4-methylphenyl)amino]-6-(4-isopropylpiperazin-1-yl)-7-(2-methoxyethoxy)quinoline-3-carboxylate	525	Intermediate 231
154	Ethyl 4-[(2-fluoro-5-methylphenyl)amino]-6-(4-isopropylpiperazin-1-yl)-7-(2-methoxyethoxy)quinoline-3-carboxylate	525	Intermediate 232

Intermediate 155**Ethyl 6-bromo-4-[(2,3-dichlorophenyl)amino]-7-methoxyquinoline-3-carboxylate**

A mixture of ethyl 6-bromo-4-chloro-7-methoxyquinoline-3-carboxylate (Intermediate 233; 1.0 g, 2.9 mmol), 2,3-dichloroaniline (535 mg, 3.2 mmol), acetic acid (900 μ L) and DMF (8 mL) was heated to 100°C for 2 hours. The reaction mixture was poured into ice water, the pH adjusted to 9 with 0.1 N NaOH and the resulting precipitate filtered to give 900 mg of a solid; *m/z*: 471.

10 Intermediates 156-232

The following compounds were prepared by a method similar to Intermediate 155 using the appropriate starting materials.

Int	Compound	M/z / NMR	SM
156	Ethyl 4-[(2-fluoro-5-methylphenyl)amino]-7-(2-methoxyethoxy)-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	497	Intermediate 277
157	Ethyl 4-[(2,5-difluorophenyl)amino]-7-(2-methoxyethoxy)-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	501	Intermediate 277
158	Ethyl 4-[(3-chloro-2-fluorophenyl)amino]-7-(2-methoxyethoxy)-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	517	Intermediate 277
159	Ethyl 4-[(2,3-dichlorophenyl)amino]-7-(2-methoxyethoxy)-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	534	Intermediate 277
160	Ethyl 4-[(2,4-difluorophenyl)amino]-7-(2-methoxyethoxy)-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	501	Intermediate 277
161	Ethyl 4-[(2-fluoro-4-methylphenyl)amino]-7-(2-methoxyethoxy)-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	497	Intermediate 277
162	Ethyl 7-(2-{{tert-butyl(dimethyl)silyl}oxy}ethoxy)-4-[(2,4-difluorophenyl)amino]-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	601	Intermediate 284
163	Ethyl 7-(2-{{tert-butyl(dimethyl)silyl}oxy}ethoxy)-4-[(3-chloro-2-fluorophenyl)amino]-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	617	Intermediate 284
164	Ethyl 4-[(2-chloro-3-fluorophenyl)amino]-7-(2-methoxyethoxy)-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	517	Intermediate 277
165	Ethyl 6-bromo-4-[(2,4-dichlorophenyl)amino]-7-methoxyquinoline-3-carboxylate		Intermediate 233

Int	Compound	M/z / NMR	SM
166	Ethyl 6-bromo-4-[(3,4-dichlorophenyl)amino]-7-methoxyquinoline-3-carboxylate		Intermediate 233
167	Ethyl 6-bromo-4-[(2,4-difluorophenyl)amino]-7-methoxyquinoline-3-carboxylate	438	Intermediate 233
168	Ethyl 7-bromo-4-[(2,3-dichlorophenyl)amino]-6-methoxyquinoline-3-carboxylate		Intermediate 236
169	Ethyl 7-bromo-4-[(3,4-dichlorophenyl)amino]-6-methoxyquinoline-3-carboxylate		Intermediate 236
170	Ethyl 6-bromo-4-[(2,4-difluorophenyl)amino]-7-ethoxyquinoline-3-carboxylate	452	Intermediate 240
171	Ethyl 6-bromo-4-[(2,3-dichlorophenyl)amino]-7-ethoxyquinoline-3-carboxylate	485	Intermediate 240
172	Ethyl 6-bromo-4-[(3,4-dichlorophenyl)amino]-7-ethoxyquinoline-3-carboxylate		Intermediate 240
173	Ethyl 6-bromo-4-[(2,4-difluorophenyl)amino]-7-fluoroquinoline-3-carboxylate		Intermediate 243
174	Ethyl 6-bromo-4-[(2,3-dichlorophenyl)amino]-7-fluoroquinoline-3-carboxylate		Intermediate 243
175	Ethyl 6-bromo-4-[(2,3-dichlorophenyl)amino]-5-fluoroquinoline-3-carboxylate		Intermediate 243
176	Ethyl 6-bromo-7-ethoxy-4-[(4-ethylphenyl)amino]quinoline-3-carboxylate	445	Intermediate 240
177	Ethyl 6-bromo-4-[(3-chloro-4-fluorophenyl)amino]-7-ethoxyquinoline-3-carboxylate		Intermediate 240
178	Ethyl 6-bromo-4-[(3-chloro-2-fluorophenyl)amino]-7-ethoxyquinoline-3-carboxylate	469	Intermediate 240
179	Ethyl 6-bromo-7-ethoxy-4-[(2-fluoro-5-methylphenyl)amino]quinoline-3-carboxylate	449	Intermediate 240

Int	Compound	M/z / NMR	SM
180	Ethyl 6-bromo-4-[(2-fluorophenyl)amino]-7-methoxyquinoline-3-carboxylate	420	Intermediate 233
181	Ethyl 6-bromo-7-methoxy-4-[(3-methoxy-2-methylphenyl)amino]quinoline-3-carboxylate	445	Intermediate 233
182	Ethyl 6-bromo-4-[(4-chloro-2-methylphenyl)amino]-7-methoxyquinoline-3-carboxylate	449	Intermediate 233
183	Ethyl 6-bromo-4-[(3-chloro-2-methylphenyl)amino]-7-ethoxyquinoline-3-carboxylate	463	Intermediate 240
184	Ethyl 6-bromo-7-ethoxy-4-[(3-ethylphenyl)amino]quinoline-3-carboxylate	443	Intermediate 240
185	Ethyl 6-bromo-4-[(3-chlorophenyl)amino]-7-ethoxyquinoline-3-carboxylate	449	Intermediate 240
186	Ethyl 6-bromo-4-[(2-chloro-4-fluorophenyl)amino]-7-ethoxyquinoline-3-carboxylate	467	Intermediate 240
187	Ethyl 6-bromo-4-[(4-chloro-2-fluorophenyl)amino]-7-ethoxyquinoline-3-carboxylate	467	Intermediate 240
188	Ethyl 6-bromo-7-ethoxy-4-[(3-methylphenyl)amino]quinoline-3-carboxylate	429	Intermediate 240
189	Ethyl 6-bromo-4-[(2-chloro-3-methylphenyl)amino]-7-ethoxyquinoline-3-carboxylate	463	Intermediate 240
190	Ethyl 6-bromo-7-ethoxy-4-[(3-fluoro-2-methylphenyl)amino]quinoline-3-carboxylate	447	Intermediate 240
191	Ethyl 6-bromo-4-[(3,4-difluorophenyl)amino]-7-methoxyquinoline-3-carboxylate	437	Intermediate 233

Int	Compound	M/z / NMR	SM
192	Ethyl 6-bromo-7-methoxy-4-{{[2-methyl-3-(trifluoromethyl)phenyl]amino} quinoline-3-carboxylate	484	Intermediate 233
193	Ethyl 6-bromo-4-[(4-chlorophenyl)amino]-7-methoxyquinoline-3-carboxylate	435	Intermediate 233
194	Ethyl 6-bromo-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxyquinoline-3-carboxylate	434	Intermediate 233
195	Ethyl 6-bromo-7-methoxy-4-{{[3-(trifluoromethyl)phenyl]amino} quinoline-3-carboxylate	469	Intermediate 233
196	Ethyl 6-bromo-7-ethoxy-4-[(2-fluoro-4-methylphenyl)amino]quinoline-3-carboxylate	447	Intermediate 240
197	Ethyl 6-bromo-7-ethoxy-4-[(3-methoxy-2-methylphenyl)amino]quinoline-3-carboxylate	459	Intermediate 240
198	Ethyl 6-bromo-4-[(2,5-difluorophenyl)amino]-7-ethoxyquinoline-3-carboxylate	454	Intermediate 240
199	Ethyl 6-bromo-4-[(3,4-dimethylphenyl)amino]-7-ethoxyquinoline-3-carboxylate	444	Intermediate 240
200	Ethyl 7-bromo-4-[(2,4-difluorophenyl)amino]-6-ethoxyquinoline-3-carboxylate	453	Intermediate 246
201	Ethyl 7-bromo-4-[(2,3-dichlorophenyl)amino]-6-ethoxyquinoline-3-carboxylate	485	Intermediate 246
202	Ethyl 6-bromo-4-[(2,3-difluorophenyl)amino]-7-ethoxyquinoline-3-carboxylate	452	Intermediate 240
203	Ethyl 6-bromo-4-[(2,3-dimethylphenyl)amino]-7-ethoxyquinoline-3-carboxylate	444	Intermediate 240

Int	Compound	M/z / NMR	SM
204	Ethyl 6-bromo-4-[(4-chloro-3-fluorophenyl)amino]-7-ethoxyquinoline-3-carboxylate	468	Intermediate 240
205	Ethyl 6-bromo-4-[(3-chloro-2,4-difluorophenyl)amino]-7-ethoxyquinoline-3-carboxylate	485	Intermediate 240
206	Ethyl 7-bromo-4-[(3-chloro-4-fluorophenyl)amino]-6-ethoxyquinoline-3-carboxylate	467	Intermediate 246
207	Ethyl 6-bromo-4-{[4-fluoro-2-(trifluoromethyl)phenyl]amino}-7-methoxyquinoline-3-carboxylate	487	Intermediate 233
208	Ethyl 6-bromo-4-[(2-chloro-4-fluorophenyl)amino]-7-methoxyquinoline-3-carboxylate	453	Intermediate 233
209	Ethyl 6-bromo-7-methoxy-4-{[3-(trifluoromethoxy)phenyl]amino}quinoline-3-carboxylate	485	Intermediate 233
210	Ethyl 6-bromo-4-[(2,6-dimethylphenyl)amino]-7-methoxyquinoline-3-carboxylate	429	Intermediate 233
211	Ethyl 6-bromo-4-[(2-fluoro-5-methylphenyl)amino]-7-methoxyquinoline-3-carboxylate	433	Intermediate 233
212	Ethyl 6-bromo-4-[(2,5-difluorophenyl)amino]-7-methoxyquinoline-3-carboxylate	437	Intermediate 233
213	Ethyl 6-bromo-4-[(3-chloro-2-methylphenyl)amino]-7-methoxyquinoline-3-carboxylate	449	Intermediate 233

Int	Compound	M/z / NMR	SM
214	Ethyl 6-bromo-4-[(2-chloro-3-methylphenyl)amino]-7-methoxyquinoline-3-carboxylate	450	Intermediate 233
215	Ethyl 6-bromo-4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinoline-3-carboxylate	453	Intermediate 233
216	Ethyl 6-bromo-4-[(3-chloro-5-fluorophenyl)amino]-7-ethoxyquinoline-3-carboxylate	469	Intermediate 240
217	Ethyl 6-bromo-7-ethoxy-4-[(2,3,4-trifluorophenyl)amino]quinoline-3-carboxylate	470	Intermediate 240
218	Ethyl 6-bromo-4-[(5-chloro-2-methylphenyl)amino]-7-ethoxyquinoline-3-carboxylate	465	Intermediate 240
219	Ethyl 6-bromo-7-ethoxy-4-[(4-methoxy-2-methylphenyl)amino]quinoline-3-carboxylate	460	Intermediate 240
220	Ethyl 6-bromo-4-[[2-chloro-5-(trifluoromethyl)phenyl]amino]-7-ethoxyquinoline-3-carboxylate	519	Intermediate 240
221	Ethyl 7-bromo-4-[(2-fluoro-5-methylphenyl)amino]-6-methoxyquinoline-3-carboxylate	435	Intermediate 236
222	Ethyl 7-bromo-4-[(3-chloro-2-fluorophenyl)amino]-6-methoxyquinoline-3-carboxylate	455	Intermediate 236
223	Ethyl 7-bromo-4-[(2,4-difluorophenyl)amino]-6-methoxyquinoline-3-carboxylate	439	Intermediate 236
224	Ethyl 6-bromo-4-[(2-chloro-3-fluorophenyl)amino]-7-ethoxyquinoline-3-carboxylate	469	Intermediate 240

Int	Compound	M/z / NMR	SM
225	Ethyl 6-bromo-4-[(2-chloro-4-methylphenyl)amino]-7-ethoxyquinoline-3-carboxylate	9.90 (s, 1 H), 9.00 (s, 1 H), 7.92 (s, 1 H), 7.40 (m, 2 H), 7.10 (m, 1 H), 7.00 (m, 1 H), 4.29 (q, 2 H), 4.20 (q, 2 H), 2.31 (s, 3 H), 1.40 (t, 3 H), 1.30 (t, 3 H)	Intermediate 240
226	Ethyl 6-bromo-7-ethoxy-4-{[2-fluoro-3-(trifluoromethyl)phenyl]amino}quinoline-3-carboxylate	9.56 (s, 1 H), 8.88 (s, 1 H), 8.51 (s, 1 H), 7.50-7.30 (m, 4 H), 4.31 (q, 2 H), 3.91 (q, 2 H), 1.32 (t, 3 H), 1.10 (t, 3 H)	Intermediate 240
227	Ethyl 6-bromo-4-[(2,4-dimethoxyphenyl)amino]-7-ethoxyquinoline-3-carboxylate	10.05 (s, 1 H), 8.92 (s, 1 H), 7.89 (s, 1 H), 7.32 (s, 1 H), 7.05 (d, 1 H), 6.71 (s, 1 H), 6.52 (d, 1 H), 4.21 (q, 4 H), 3.79 (s, 3 H), 3.70 (s, 3 H), 1.40 (t, 3 H), 1.30 (t, 3 H)	Intermediate 240
228	Ethyl 6-bromo-4-[(2-chloro-4-fluoro-5-methylphenyl)amino]-7-ethoxyquinoline-3-carboxylate	9.80 (s, 1 H), 8.95 (s, 1 H), 8.05 (s, 1 H), 7.55 (m, 1 H), 7.45 (s, 1 H), 7.15 (m, 1 H), 4.30 (q, 2 H), 4.18 (q, 2 H), 2.15 (s, 3 H), 1.45 (t, 3 H), 1.28 (t, 3 H)	Intermediate 240

Int	Compound	M/z / NMR	SM
229	Ethyl 6-bromo-4-[(5-chloro-2-fluorophenyl)amino]-7-ethoxyquinoline-3-carboxylate	9.55 (s, 1 H), 8.87 (s, 1 H), 8.45 (s, 1 H), 7.50 (s, 1 H), 7.35 (m, 1 H), 7.17 (m, 2 H), 4.32 (q, 2 H), 4.00 (q, 2 H), 1.46 (t, 3 H), 1.19 (t, 3 H)	Intermediate 240
230	Ethyl 6-bromo-7-ethoxy-4-{[2-methoxy-5-(trifluoromethyl)phenyl]amino}quinoline-3-carboxylate	9.80 (s, 1 H), 8.96 (s, 1 H), 8.15 (s, 1 H), 7.45 (m, 2 H), 7.30 (m, 1 H), 7.18 (s, 1 H), 4.30 (q, 2 H), 4.10 (q, 2 H), 3.85 (s, 3 H), 1.40 (t, 3 H), 1.20 (t, 3 H)	Intermediate 240
231	Ethyl 6-chloro-4-[(2-fluoro-4-methylphenyl)amino]-7-(2-methoxyethoxy)quinoline-3-carboxylate	433	Intermediate 281
232	Ethyl 6-chloro-4-[(2-fluoro-5-methylphenyl)amino]-7-(2-methoxyethoxy)quinoline-3-carboxylate	433	Intermediate 281

Intermediate 233

Ethyl 6-bromo-4-chloro-7-methoxyquinoline-3-carboxylate

This compound was described in WO 2002092571, and prepared in accordance with the procedures described in Burke T.R. et al., *J. Med. Chem.*, 36 (1993) 425-432.

A solution of ethyl 6-bromo-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (Intermediate 234; 8.0 g, 0.025) in phosphorous oxychloride (100 mL) was heated under reflux overnight. After cooling, the solution was carefully poured into ~400 mL of ice water with stirring. The resulting mixture was made just basic with 2N NaOH and extracted with EtOAc. The organic layer was washed with water, dried (Na₂SO₄), and concentrated under

- 110 -

reduced pressure to give 8.0 g (93%) of a white solid. ¹H NMR: 9.14 (s, 1 H), 8.55 (s, 1 H), 7.66 (s, 1 H), 4.42 (d, 2 H), 4.09 (s, 3 H), 1.38 (t, 3 H); *m/z*: 344.

Intermediate 2345 **Ethyl 6-bromo-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate**

A solution of diethyl {[(4-bromo-3-methoxyphenyl)amino]methylene}malonate (Intermediate 235; 11 g, 0.029 mol) in warm diphenyl ether (20 mL) was added dropwise over 15 minutes to refluxing diphenyl ether (180 mL). After 3 hours, the solution was cooled, diluted with hexane (200 mL), and the resulting precipitate collected to give 8.9 g (93%) of a
10 white solid.

Intermediate 235**Diethyl {[(4-bromo-3-methoxyphenyl)amino]methylene}malonate**

To a solution of 4-bromo-3-methoxyaniline (25 g, 0.12 mol) in CH₃CN (150 mL) was
15 added diethylethoxymethylene malonate (27 mL, 0.13 mol). After 20 hours, the solvent was removed under reduced pressure and the residue dissolved in EtOAc. Hexane was added, and the resulting precipitate collected to give 37 g (80%) off-white solid. ¹H NMR: 10.68 (d, 1 H), 8.38 (d, 1 H), 7.52 (d, 1 H), 7.20 (d, 1 H), 6.91 (dd, 1 H), 4.20 (q, 2 H), 4.11 (q, 2 H), 3.86 (s, 3 H), 1.23 (m, 6 H); *m/z*: 372.
20

Intermediate 236**Ethyl 7-bromo-4-chloro-6-methoxyquinoline-3-carboxylate**

A mixture of ethyl 7-bromo-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (Intermediate 237; 4.0 g, 11.6 mmol) and phosphorous oxychloride (80 mL) was heated at
25 reflux for 2.5 hours. The solution was cooled, and poured carefully onto ice (800 g) with stirring. The mixture was carefully neutralized with 2N NaOH, and the resulting precipitate was filtered, washed with water and dried to give 3.8 g white solid. ¹H NMR (CDCl₃): 9.00 (s, 1 H), 8.32 (s, 1 H), 7.54 (s, 1 H), 4.43 (q, 2 H), 4.02 (s, 3 H), 1.39 (t, 3 H).

30 **Intermediate 237****Ethyl 7-bromo-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate**

A solution of diethyl {[(3-bromo-4-methoxyphenyl)amino]methylene}malonate (Intermediate 238; 10 g, 0.027 mol) in warm diphenyl ether (100 mL) was added dropwise

over 15 minutes to refluxing diphenyl ether (100 mL). After 3 hours, the reaction mixture was cooled, and petroleum ether (120 mL) was added to the solid material, which was filtered and washed with hexane to give 8 g white solid. ¹H NMR: 8.54 (s, 1 H), 7.92 (s, 1 H), 7.65 (s, 1 H), 4.22 (q, 2 H), 3.95 (s, 3 H), 1.28 (t, 3 H).

5

Intermediate 238

Diethyl {[3-bromo-4-methoxyphenyl]amino}methylene}malonate

A solution of 3-bromo-4-methoxyaniline (Intermediate 239; 8.3 g, 40.9 mmol) and diethyl ethoxymethylenemalonate (8.85 mL, 44.2 mmol) in CH₃CN (60 mL) was stirred for 2
10 hours. The solvent was removed under reduced pressure. Recrystallization of the residue from hexane gave 11 g white solid. ¹H NMR (CDCl₃): 10.98 (d, 1 H), 8.40 (d, 1 H), 7.40 (d, 1 H), 7.08 (dd, 1 H), 6.91 (d, 1 H), 4.29 (m, 4 H), 3.91 (s, 3 H), 1.37 (m, 6 H).

Intermediate 239

15 3-Bromo-4-methoxyaniline

The title compound was prepared according to the procedure in Liu Y.-Y. and Munich, M., *J. Label Compd Radiopharm.*, 18 (1981), 791-797.

Intermediate 240

20 Ethyl 6-bromo-4-chloro-7-ethoxyquinoline-3-carboxylate

Preparation a)

A mixture of ethyl 6-bromo-7-ethoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (Intermediate 241; 16.8 g, 49 mmol) and phosphorous oxychloride (40 mL) was heated at
25 reflux for 16 hours. The solution was cooled, and poured carefully into ice water (~500 mL) with stirring. The resulting solid was filtered, washed with water and dried to give 17.1 g of a light brown solid. ¹H NMR: 9.13 (s, 1 H), 8.54 (s, 1 H), 7.63 (s, 1 H), 4.39 (m, 4 H), 1.46 (t, 3 H), 1.38 (t, 3 H).

30 Alternative preparation b)

To a solution of diethyl {[4-bromo-3-ethoxyphenyl]amino}methyl}malonate (Intermediate 242; 52.9 g, 0.137 mol) in toluene (125 mL) was added POCl₃ (209.9 g, 125 mL, 1.37 mol). The reaction mixture was stirred at 110°C for 48 hours, cooled and concentrated

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under reduced pressure. The residue was carefully treated with sat. NaHCO_3 solution until no more gas was evolved, and the resulting solid was filtered, washed with sat. NaHCO_3 and water, and then slurried in hot MeOH (~200 mL), cooled and filtered to give 42 g of an orange solid.

5

Alternative preparation c)

Triethylamine (12.8 kg, 126 mol) was added to a suspension of 4-bromo-3-ethoxyaniline hydrochloride (29.94 kg, 118 mol) in toluene (119 L) and water (60 L) at ambient temperature. The suspension was stirred until a solution was obtained. The biphasic
10 mixture was filtered through diatomaceous earth (4 kg) washing the cake with toluene (10 L) and the aqueous layer separated and discarded. Toluene was distilled out (13 L) to dry the mixture. Diethylethoxymethylene malonate (25.60 kg, 118 mol) was added slowly to the toluene solution at 70-80 °C, at a rate that maintained gentle reflux. Toluene and ethanol (70 L) were distilled out under reduced pressure (400 mbar, 85 °C). The reaction temperature
15 was reduced to 60 °C and the reaction analysed by HPLC. Phosphorous oxychloride (45.6 kg, 297 mol) added over 45 minutes. The reaction was heated to 110 °C over 2 hours and held for at least 5 hours. The reaction was cooled to 70 °C and analysed by HPLC. Phosphorous oxychloride and toluene (50 L) were removed by distillation at reduced pressure (100-150 mbar, 50-67 °C). Toluene (40 L) was added and the mixture redistilled (40 L of distillate
20 collected). Tetrahydrofuran (THF) (36 L) was added and the resulting mixture cooled to 20-25 °C. The resulting red solution was added slowly (over ~50 minutes to control gas evolution) to a mixture of potassium bicarbonate (99 kg, 989 mol) in water (296 L) at ambient temperature. The reaction mixture was washed with further THF (3.6 L). The resulting suspension was stirred for 1 hour before isolating on a centrifuge. The wet product was
25 slurried in ethanol (119 L) and heated to 70 °C. The slurry was cooled to ambient temperature and the product collected by centrifuge, washed with ethanol (40 L) and dried under reduced pressure (30 °C at 2 mbar) to give the title compound (30.8 kg, 86 mol, 73%).

Intermediate 241

30 Ethyl 6-bromo-7-ethoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate

A solution of diethyl {[(4-bromo-3-ethoxyphenyl)amino]methyl}malonate (Intermediate 242; 25 g, 64 mmol) in warm diphenyl ether (150 mL) was added dropwise over 15 minutes to refluxing diphenyl ether (~250 mL). After 3 hours the reaction mixture

was cooled, and hexane (~250 mL) added to the solid, which was filtered to give 16.8 g of a white crystalline solid, used without further purification.

Intermediate 242

5 Diethyl {[4-bromo-3-ethoxyphenyl]amino}methyl}malonate

A solution of 4-bromo-3-ethoxyaniline (21 g, 0.1 mol) and diethyl ethoxymethylenemalonate (19 mL, 0.1 mol) in CH₃CN (150 mL) was stirred for 2 hours and then heated to 75°C for 16 hours. The solvent was removed under reduced pressure and the residue recrystallized from hexane to give 25 g of white solid, which was used without further
10 purification.

Intermediate 243

Ethyl 6-bromo-4-chloro-7-fluoroquinoline-3-carboxylate and ethyl 6-bromo-4-chloro-5-fluoroquinoline-3-carboxylate

15 A mixture of ethyl 6-bromo-7-fluoro-4-hydroxyquinoline-3-carboxylate and ethyl 6-bromo-5-fluoro-4-hydroxyquinoline-3-carboxylate (Intermediate 244; 3.2 g, 10.19 mmol) was stirred in refluxing phosphorous oxychloride (4.6 ml, 50.96 mmol) for 3 hours. After cooling, the mixture was concentrated under reduced pressure, and CH₃CN (10 mL) was added. The mixture was poured slowly into NaHCO₃ solution and the resulting slurry extracted with
20 EtOAc. The organic layer was dried (MgSO₄), filtered, concentrated under reduced pressure, and the residue purified by column chromatography (EtOAc/hexanes gradient) to give 0.15 g (4.7%) of ethyl 6-bromo-4-chloro-5-fluoroquinoline-3-carboxylate. ¹H NMR: 9.17 (s, 1 H), 8.64 (d, 1 H), 8.12 (d, 1 H), 4.48 (q, 2 H), 1.40 (t, 3 H); *m/z*: 334, and 1.4 g (44%) of ethyl 6-bromo-7-fluoro-4-hydroxyquinoline-3-carboxylate ¹H NMR: 9.11 (s, 1 H), 8.22 (t, 1 H), 7.96
25 (d, 1 H), 4.48 (q, 2 H), 1.40 (t, 3 H); *m/z*: 334.

Intermediate 244

Ethyl 6-bromo-7-fluoro-4-hydroxyquinoline-3-carboxylate and ethyl 6-bromo-5-fluoro-4-hydroxyquinoline-3-carboxylate

30 A solution of diethyl {[4-bromo-3-fluorophenyl]amino}methylene}malonate (Intermediate 245; 6.00 g, 16.66 mmol) and diphenyl ether (10 mL) was heated to 250°C for 40 minutes. After cooling, hexane (10 mL) was added, and the resulting precipitate filtered

and washed with acetone (20 mL), to give 3.2 g (61%) of a light brown solid, an insoluble mixture of isomers.

Intermediate 245

5 **Diethyl {[(4-bromo-3-fluorophenyl)amino]methylene}malonate**

A solution of 4-bromo-3-fluoroaniline (5.00 g, 28.3 mmol) and diethyl ethoxymethylenemalonate (5.7 mL, 28.4 mmol) in CH₃CN (15 mL) was stirred for 6 days. The reaction mixture was filtered to give 6.2 grams (65 %) of a white solid. ¹H NMR: 10.65 (d, 1 H), 8.36 (d, 1 H), 7.67 (t, 1 H), 7.59 (dd, 1 H), 7.24 (d, 1 H), 4.18 (m, 4 H), 1.29 (m, 6
10 H).

Intermediate 246

Ethyl 7-bromo-4-chloro-6-ethoxyquinoline-3-carboxylate

A suspension of ethyl 7-bromo-6-ethoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate
15 (Intermediate 247; 21 g, 0.06 mol) in phosphorous oxychloride was heated under reflux for 2.5 hours. After cooling, the reaction mixture was poured carefully into 2 L of ice water and neutralized with concentrated aqueous ammonia. The precipitate was collected, washed with water, dried, and recrystallized from EtOAc to give 17 g of an off-white solid. ¹H NMR: 9.01 (s, 1 H), 8.45 (s, 1 H), 7.63 (s, 1 H), 4.43 (q, 2 H), 4.34 (q, 2 H), 1.48 (t, 3 H), 1.38 (t, 3 H);
20 *m/z*: 359.

Intermediate 247

Ethyl 7-bromo-6-ethoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate

A solution of diethyl {[(3-bromo-4-ethoxyphenyl)amino]methylene}malonate
25 (Intermediate 248; 33 g, 0.085 mol) in warm diphenyl ether (200 mL) was added dropwise over 30 minutes to refluxing diphenyl ether (400 mL). After 3 hours at reflux, the reaction was cooled. To the resulting gelatinous solid was added hexane, cyclohexane, and petroleum ether (~150 mL of each) and the mixture filtered. The crude material was triturated with hot hexane for 20 minutes to give 21g of a solid. ¹H NMR: 12.26 (s, 1 H), 8.52 (s, 1 H), 7.91 (s, 1
30 H), 7.62 (s, 1 H), 4.21 (m, 4 H), 1.41 (t, 3 H), 1.28 (t, 3 H); *m/z*: 342.

Intermediate 248**Diethyl {[(3-bromo-4-ethoxyphenyl)amino]methylene} malonate**

A solution of (3-bromo-4-ethoxyphenyl)amine (Intermediate 249; 22 g, 0.1 mol) and diethylethoxymethylene malonate (23 mL, 0.11 mol) in acetonitrile (150 mL) was stirred for 2 hours. The precipitate was collected and recrystallized/triturated with hexane to give 33 g of a solid, used without further purification. ¹H NMR (MeOD): 8.42 (s, 1 H), 7.51 (d, 1 H), 7.20 (m, 1 H), 7.05 (d, 1 H), 4.29 (q, 2 H), 4.22 (q, 2 H), 4.11 (q, 2 H), 1.44 (t, 3 H), 1.34 (m, 6 H); *m/z*: 384.

10 Intermediate 249**(3-Bromo-4-ethoxyphenyl)amine**

To a stirred suspension of 2-bromo-1-ethoxy-4-nitrobenzene (Intermediate 250; 27 g, 0.11 mol), iron powder (50 g, 0.89 mol), and 50% aqueous ethanol (200 mL), was added dropwise over 30 minutes a solution of concentrated HCl (2 mL) in 50% aqueous ethanol (20 mL). Heating was applied after half the acidic solution was added to initiate the reaction. Thereafter, the reaction mixture was kept at reflux by adjusting the rate of addition of the acid. Reflux was maintained for 1.5 hours subsequent to the acid addition via external heating mantle. The reaction mixture was filtered hot through a bed of diatomaceous earth. After cooling, the aqueous filtrate was extracted with chloroform (2 x 300 mL) and EtOAc (2 x 300 mL). The organic extracts were combined, dried (Na₂SO₄), and concentrated under reduced pressure to give 22 g of a solid. ¹H NMR: 6.82 (m, 1 H), 6.53 (d, 1 H), 6.51 (s, 1 H), 3.91 (q, 2 H), 1.28 (t, 3 H); *m/z*: 216.

Intermediate 250**25 2-Bromo-1-ethoxy-4-nitrobenzene**

A mixture of iodoethane, (22.2 mL, 0.28 mol), 2-bromo-4-nitrophenol (Intermediate 251; 24 g, 0.11 mol) and potassium carbonate (30.6 g, 0.22 mol) in DMF (200 mL) was stirred for 18 hours. The reaction mixture was poured into ice water (2 L) and extracted with EtOAc (3 x 300 mL). The combined organic extracts were dried (Na₂SO₄), filtered, and concentrated under reduced pressure to give 27.1 g of a solid, used without further purification. ¹H NMR: 8.42 (d, 1 H), 8.25 (d, 1 H), 7.31 (d, 1 H), 4.28 (q, 2 H), 1.41 (t, 3 H).

Intermediate 251**2-Bromo-4-nitrophenol**

A mixture of 4-nitrophenol (50 g, 0.36 mol), acetic acid (400 mL), and bromine (27 mL, 0.52 mol) was stirred for 18 hours. Excess solvent was removed under reduced pressure and the residue was crystallized from dichloromethane/hexane to give 60 g of a solid, used without further purification. ¹H NMR (MeOD): 8.40 (d, 1 H), 8.12 (dd, 1 H), 7.02 (d, 1 H); *m/z*: 216.

Intermediate 25210 **1-Ethyl-1,4-diazepane**

A mixture of *tert*-butyl 4-ethyl-1,4-diazepane-1-carboxylate (Intermediate 253; 700 mg, 3.07 mmol) in 2M HCl in ether (10 mL) was stirred at room temperature for 2 hours. The white solid was filtered, washed with diethyl ether. The solid was dissolved in 20 ml of MeOH, about 2 g of MP-carbonate (3.1 mmol/g) was added to the solution. The resulting mixture was stirred at room temperature for 30 minutes, filtered, washed with MeOH, and the filtrate was concentrated to give 390 mg light yellow oil. ¹H NMR (CD₂Cl₂): 3.00 (m, 6 H), 2.75 (m, 2 H), 2.62 (m, 2 H), 1.90 (m, 2 H), 1.10 (t, 3 H); *m/z*: 128.

Intermediate 25320 ***tert*-Butyl 4-ethyl-1,4-diazepane-1-carboxylate**

A mixture of *tert*-butyl 1,4-diazepane-1-carboxylate (3 g, 15 mmol), iodoethane (3.51 g, 22.5 mmol) and potassium carbonate (4.14 g, 30 mmol) in acetonitrile (15 ml) was heated to reflux for 20 hours. The reaction mixture was cooled and filtered, washing with dichloromethane. The filtrate was concentrated and the residue purified with an ISCO chromatography system to give 700 mg oil. ¹H NMR (CD₂Cl₂): 3.60 (m, 4 H), 2.70 (m, 6 H), 1.95 (m, 2 H), 1.61 (s, 9 H), 1.20 (t, 3 H); *m/z*: 228.

Intermediate 25430 **Ethyl 4-[(2,4-difluorophenyl)amino]-7-isopropoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate**

A solution of ethyl 4-chloro-7-isopropoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate (Intermediate 266; 0.25 g, 0.64 mmol), 2,4-difluoroaniline (0.22 mL, 1.91 mmol), and glacial acetic acid (0.1 mL) in EtOAc (5 mL) was heated at 77°C for 16 hours. The

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reaction mixture was cooled, NaHCO₃ solution (3 mL) was added, and the mixture was extracted with EtOAc (3 x 3 mL). The combined organic extracts were concentrated, and the residue purified by column chromatography (hexanes/EtOAc) to give 80 mg (53%) of a yellow solid. ¹H NMR: 9.69 (s, 1 H), 8.84 (s, 1 H), 7.39 (m, 1 H), 7.26 (s, 1 H), 7.19 (m, 1 H), 5 7.07 (m, 1 H), 6.96 (s, 1 H), 4.83 (m, 1 H), 4.39 (q, 2 H), 2.75 (s, 4 H), 2.37 (s, 4 H), 2.17 (s, 3 H), 1.34 (d, 6 H), 1.28 (t, 3 H); *m/z*: 485.

Intermediates 255-265

The following compounds were prepared by a method similar to Intermediate 254

Int	Compound	M/z	SM
255	Ethyl 4-[(3,4-dichlorophenyl)amino]-7-isopropoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	517	Intermediate 266
256	Ethyl 4-[(3-chloro-2-fluorophenyl)amino]-7-isopropoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	501	Intermediate 266
257	Ethyl 4-[(2,3-dichlorophenyl)amino]-7-isopropoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	517	Intermediate 266
258	Ethyl 4-[(3-chloro-4-fluorophenyl)amino]-7-isopropoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	501	Intermediate 266
259	Ethyl 4-[(2,4-difluorophenyl)amino]-6-morpholin-4-ylquinoline-3-carboxylate	415	Intermediate 271
260	Ethyl 4-[(3-chloro-4-fluorophenyl)amino]-6-morpholin-4-ylquinoline-3-carboxylate	432	Intermediate 271
261	Ethyl 4-[(2,3-dichlorophenyl)amino]-6-morpholin-4-ylquinoline-3-carboxylate	446	Intermediate 271
262	Ethyl 4-[(2,4-difluorophenyl)amino]-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate	427	Intermediate 274
263	Ethyl 4-[(2,4-dichlorophenyl)amino]-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate		Intermediate 274
264	Ethyl 4-[(3,4-dichlorophenyl)amino]-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate		Intermediate 274
265	Ethyl 4-[(2,3-dichlorophenyl)amino]-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate		Intermediate 274

Intermediate 266**Ethyl 4-chloro-7-isopropoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate**

A mixture of diethyl ({[3-isopropoxy-4-(4-methylpiperazin-1-yl)phenyl]amino}methylene)malonate (Intermediate 267; 5.7 g, 13.6 mmol) and phosphorus
5 oxychloride (12.4 g, 20.8 mmol) was heated at 108°C for 16 hours. The reaction mixture was cooled and concentrated under reduced pressure. The resulting dark oil was diluted with acetonitrile (20 mL), added to a stirred solution of NaHCO₃, and extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried (Na₂SO₄), filtered, and concentrated under reduced pressure. Hexanes (30 mL) was added and after 15 minutes of sonication, the
10 mixture was filtered to give 3.1 g (58%) of a brown solid. ¹H NMR: 8.89 (s, 1 H), 7.45 (s, 1 H), 7.42 (s, 1 H), 4.91 (m, 1 H), 4.39 (q, 2 H), 3.16 (s, 4 H), 2.50 (s, 4 H), 2.23 (s, 3 H), 1.37 (m, 9 H); *m/z*: 392.

Intermediate 267**Diethyl ({[3-isopropoxy-4-(4-methylpiperazin-1-yl)phenyl]amino}methylene)malonate**

A solution of [3-isopropoxy-4-(4-methylpiperazin-1-yl)phenyl]amine (Intermediate 268; 5.0 g, 21.5 mmol) and diethyl ethoxymethylenemalonate (4.65 mL, 23.24 mL) in acetonitrile (20 mL) was stirred for 16 hours. The reaction mixture was concentrated under reduced pressure and purified via column chromatography (hexanes/EtOAc) to give 6.7 g
20 (74%) of a dark viscous oil. ¹H NMR: 10.68 (d, 1 H), 8.23 (d, 1 H), 6.99 (s, 1 H), 6.84 (s, 2 H), 4.65 (m, 1 H), 4.21-4.00 (m, 4 H), 2.93 (s, 4 H), 2.42 (s, 4 H), 1.27-1.16 (m, 12 H).

Intermediate 268**[3-Isopropoxy-4-(4-methylpiperazin-1-yl)phenyl]amine**

25 1-(2-Isopropoxy-4-nitrophenyl)-4-methylpiperazine (Intermediate 269; 6.0 g, 21.5 mmol) and 10% palladium on carbon (0.6 g) in MeOH (30 mL) was stirred under hydrogen gas (50 psi) for 1 hour, then filtered through a pad of diatomaceous earth. The filtrate was concentrated under reduced pressure to give 5.01 g (94%) of a brown oil. ¹H NMR: 6.59 (d, 1 H), 6.18 (d, 1 H), 6.08 (dd, 1 H), 4.65 (s, 2 H), 4.45 (m, 1 H), 2.79 (s, 4 H), 2.39 (s, 4 H), 2.17
30 (s, 3 H), 1.21 (d, 6 H).

Intermediate 269**1-(2-Isopropoxy-4-nitrophenyl)-4-methylpiperazine**

A mixture of 1-chloro-2-isopropoxy-4-nitrobenzene (Intermediate 270; 5.0 g, 23.2 mmol), 1-methyl piperazine (3.09 mL, 27.82 mmol), and potassium carbonate (3.99 g, 23.19 mmol) in DMF (10 mL) was heated at 135°C for 16 hours. The reaction mixture was cooled, added to water (200 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried (Na₂SO₄), filtered, and concentrated under reduced pressure to give 6.0 grams (93%) of a red solid. ¹H NMR: 7.80 (dd, 1 H), 7.65 (d, 1 H), 7.0 (d, 1 H), 4.71 (m, 1 H), 3.20 (m, 4 H), 2.44 (m, 4 H), 2.21 (s, 3 H), 1.32 (d, 6 H); *m/z*: 280.

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Intermediate 270**1-Chloro-2-isopropoxy-4-nitrobenzene**

A mixture of 2-chloro-5-nitrophenol (10.0 g, 57.6 mmol), 2-iodopropane (6.79 mL, 69.1 mmol), caesium carbonate (1.87g, 5.76 mmol), and potassium carbonate (9.93g, 57.6 mmol) in DMF (50 mL) was heated at 35°C for 24 hours. The reaction mixture was cooled, added to water (200 mL) and extracted with EtOAc (3 x 25 mL). The combined organic extracts were dried (Na₂SO₄), filtered, and concentrated under reduced pressure to give 12.1 grams (97%) of a red solid. ¹H NMR: 7.88 (d, 1 H), 7.80 (dd, 1 H), 7.72 (d, 1 H), 4.87 (m, 1 H), 1.32 (d, 6 H).

20

Intermediate 271**Ethyl 4-chloro-6-morpholinoquinoline-3-carboxylate**

Ethyl 4-hydroxy-6-morpholin-4-ylquinoline-3-carboxylate (Intermediate 272; 2.2 g, 7.28 mmol) was stirred in refluxing phosphorous oxychloride (6.6 mL, 72.8 mmol) for 3 hours. After cooling, the mixture was concentrated under reduced pressure, and CH₃CN (20 mL) added. This mixture was poured slowly into NaHCO₃ solution (150 mL) and the resulting slurry was extracted with EtOAc. The organic layer was dried (MgSO₄), filtered, and concentrated, and the residue purified by column chromatography (EtOAc/hexanes gradient) to give 1.8 g (77%) white solid. ¹H NMR: 8.86 (s, 1 H), 8.00 (d, 1 H), 7.87 (d, 1 H), 7.38 (s, 1 H), 4.45 (q, 2 H), 3.82 (s, 4 H), 3.38 (s, 4 H), 1.38 (t, 3 H); *m/z*: 321.

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Intermediate 272**Ethyl 4-hydroxy-6-morpholin-4-ylquinoline-3-carboxylate**

A solution of diethyl {[(4-morpholin-4-ylphenyl)amino]methylene}malonate (Intermediate 273; 5.00 g, 14.35 mmol) in diphenyl ether (30 mL) was heated to 250°C for 2 hours. After cooling, hexane (20 mL) was added, and the resulting precipitate filtered and washed with acetone (20 mL) to give 2.4 g (55%) of a light brown solid. ¹H NMR: 12.21 (s, 1 H), 8.45 (s, 1 H), 7.50 (m, 3 H), 4.21 (m, 2 H), 3.78 (s, 4 H), 3.17 (s, 4 H), 1.27 (t, 3 H); *m/z*: 303.

10 Intermediate 273**Diethyl {[(4-morpholin-4-ylphenyl)amino]methylene}malonate**

A solution of 4-(4-aminophenyl)morpholine (5.00 g, 28.1 mmol) and diethyl ethoxymethylenemalonate (6.1 mL, 30.5 mmol) in CH₃CN (10 mL) was stirred for 24 hours. The reaction mixture was added to EtOAc (50 mL), washed with brine, dried (MgSO₄), filtered, and concentrated. Hexanes (50 mL) were added to the residue and after 30 minutes sonication, the resulting slurry was filtered to give 7.2 g (74 %) of a brown solid. ¹H NMR: 10.75 (d, 1 H), 8.35 (d, 1 H), 7.27 (d, 2 H), 6.98 (d, 2 H), 4.22 (m, 4 H), 3.73 (s, 4 H), 3.08 (s, 4 H), 1.25 (m, 6 H).

20 Intermediate 274**Ethyl 4-chloro-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate**

Ethyl 4-hydroxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate (Intermediate 275; 0.5 g, 1.5 mmol) was stirred in refluxing phosphorous oxychloride (1.5 mL, 15.9 mmol) for 3 hours. After cooling, the mixture was concentrated under reduced pressure, and dichloromethane (10 mL) added. This mixture was poured slowly into NaHCO₃ solution (50 mL) and the resulting slurry extracted with EtOAc. The organic layer was dried (MgSO₄), filtered, and concentrated, and the residue taken up in hexane and filtered to give 0.4 g (76%) black solid. ¹H NMR: 8.84 (s, 1 H), 7.97 (d, 1 H), 7.85 (d, 1 H), 7.35 (s, 1 H), 4.45 (q, 2 H), 3.40 (m, 4 H), 2.47 (m, 4 H), 2.25 (s, 3 H), 1.38 (t, 3 H); *m/z*: 334.

Intermediate 275**Ethyl 4-hydroxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate**

A solution of diethyl ({[4-(4-methylpiperazin-1-yl)phenyl]amino}methylene)malonate (Intermediate 276; 5.00 g, 13.8 mmol) in diphenyl ether (30 mL) was heated to 250°C for 2 hours. After cooling, hexane (20 mL) was added, and the resulting precipitate was filtered and washed with acetone (20 mL) to give 0.52 g (10%) of a light brown solid. ¹H NMR: 12.19 (s, 1 H), 8.43 (s, 1 H), 7.50 (m, 3 H), 4.23 (m, 2 H), 3.19 (m, 4 H), 2.47 (m, 4 H), 2.23 (s, 3 H), 1.27 (t, 3 H).

10 **Intermediate 276****Diethyl ({[4-(4-methylpiperazin-1-yl)phenyl]amino}methylene)malonate**

A solution of 4-(4-methylpiperazino)aniline (3.0 g, 15.7 mmol) and diethyl ethoxymethylenemalonate (3.4 mL, 16.9 mmol) in CH₃CN (10 mL) was stirred for 24 hours. The reaction mixture was concentrated under reduced pressure, hexane (30 mL) was added to the residue, and the resulting slurry was filtered to give 5.0 g (88 %) of a brown solid. ¹H NMR: 10.74 (d, 1 H), 8.34 (d, 1 H), 7.24 (d, 2 H), 6.97 (d, 2 H), 4.14 (m, 4 H), 3.11 (m, 4 H), 2.44 (m, 4 H), 2.21 (s, 3 H), 1.25 (m, 6 H).

Intermediate 27720 **Ethyl 4-chloro-7-(2-methoxyethoxy)-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate**

A mixture of diethyl ({[3-(2-methoxyethoxy)-4-(4-methylpiperazin-1-yl)phenyl]amino}methylene)malonate (Intermediate 278; 6.6 g, 15.15 mmol) and phosphorus oxychloride (23.24 g, 151.5 mmol) was heated at 110°C for 16 hours. The reaction mixture was cooled and concentrated under reduced pressure. The resulting dark oil was diluted with CH₃CN (20 mL) and added to a stirred solution of NaHCO₃. The resulting mixture was extracted with dichloromethane (3 x 25 mL). The combined organic extracts were dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The resulting oil was purified via silica chromatography (EtOAc) to give 1.25 g (20%) of a pale yellow powder. ¹H NMR: 8.92 (s, 1 H), 7.48 (s, 2 H), 4.41 (q, 2 H), 4.39 (q, 2 H), 4.34 (m, 2 H), 3.78 (m, 2 H), 3.37 (s, 3 H), 3.22 (m, 4 H), 2.53 (s, 4 H), 2.26 (s, 3 H), 1.37 (t, 3 H); *m/z*: 408.

Intermediate 278

Diethyl ({[3-(2-methoxyethoxy)-4-(4-methylpiperazin-1-yl)phenyl]amino}methylene)malonate

1-[2-(2-Methoxyethoxy)-4-nitrophenyl]-4-methylpiperazine (Intermediate 279; 7.0 g, 23.70 mmol), 10% palladium on carbon (0.7g), and MeOH (20 ml) were combined under a nitrogen atmosphere. The nitrogen atmosphere was removed and 50 psi of hydrogen gas was applied for 1 hour while shaking the reaction vessel. The hydrogen gas was removed, and replaced with nitrogen gas. Diethyl ethoxymethylenemalonate (4.84 mL, 24.18 mmol) was added, and the resulting mixture was allowed to stand for 16 hours. The resulting black slurry was filtered through a pad of diatomaceous earth, and the filtrate was concentrated under reduced pressure. The resulting oil was purified via silica chromatography (EtOAc) to give 6.6 grams (64%) of a yellow oil. ¹H NMR: 6.59 (d, 1 H), 6.18 (d, 1 H), 6.08 (dd, 1 H), 4.65 (s, 2 H), (s, 2 H), 4.45 (m, 1 H), 2.79 (s, 4 H), 2.39 (s, 4 H), 2.17 (s, 3 H), 1.22 (s, 3 H), 1.20 (s, 3 H); *m/z*: 436.

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Intermediate 279

1-[2-(2-Methoxyethoxy)-4-nitrophenyl]-4-methylpiperazine

To a solution of 1-chloro-2-(2-methoxyethoxy)-4-nitrobenzene (Intermediate 280; 5.0 g, 23.19 mmol) in DMF (10 mL) at 60°C was added *N*-methyl piperazine (3.09 mL, 27.82 mmol). After heating at 130°C for 26 hours, the reaction mixture was cooled and added to NaHCO₃ solution (50 mL). The mixture was extracted with EtOAc (3 x 100 mL), and the combined organic extracts were dried (Na₂SO₄), filtered, and concentrated under reduced pressure to give 6.1 grams (92.6%) of a red solid. ¹H NMR: 7.80 (dd, 1 H), 7.69 (d, 1 H), 7.0 (d, 1 H), 4.21 (m, 2 H), 3.71 (m, 2 H), 3.34 (s, 3 H), 3.24 (m, 4 H), 2.44 (m, 4 H), 2.22 (s, 3 H); *m/z*: 296.

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Intermediate 280

1-Chloro-2-(2-methoxyethoxy)-4-nitrobenzene

A solution of 2-chloro-5-nitrophenol (10.0 g, 57.62 mmol), 1-bromo-2-methoxyethane (8.4 mL, 69.14 mmol), and potassium carbonate (11.92g, 69.14 mmol) in DMF (40 mL) was heated at 40°C for 48 hours. The reaction mixture was cooled and added to NaHCO₃ solution (100 mL) and dichloromethane (100 mL). The resulting mixture was extracted with dichloromethane (3 x 100 mL). The combined organic extracts were dried with (Na₂SO₄),

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filtered, and concentrated under reduced pressure to give a red solid. The red solid was filtered through a pad of silica gel, eluting with a 9:1 ratio of hexanes:EtOAc. The filtrate was concentrated to give 10.3 g (77%) of a red-orange crystalline solid. ¹H NMR: 7.92 (d, 1 H), 7.85 (dd, 1 H), 7.75 (d, 1 H), 4.35 (m, 2 H), 3.73 (m, 2 H), 3.34 (s, 3 H).

5

Intermediate 281**Ethyl 4,6-dichloro-7-(2-methoxyethoxy)quinoline-3-carboxylate**

A solution of ethyl 6-chloro-4-hydroxy-7-(2-methoxyethoxy)quinoline-3-carboxylate (Intermediate 282; 6.7 g, 20.56 mmol), thionyl chloride (4.5 mL, 61.69 mmol), and DMF (1 drop) in CH₃CN (25 mL) was heated at 60°C for 2 hours. The reaction mixture was cooled and added slowly to NaHCO₃ solution (100 mL). The resulting slurry was extracted with EtOAc (3 x 100 mL), the organic extracts were combined and dried (Na₂SO₄). Purification of the residue via silica chromatography (hexanes/EtOAc gradient) gave 5.5 g (78%) of a white solid. ¹H NMR: 9.10 (s, 1 H), 8.34 (s, 1 H), 7.69 (s, 1 H), 4.44 (m, 4 H), 3.81 (m, 2 H), 3.37 (s, 3 H), 1.38 (t, 3 H).

15

Intermediate 282**Ethyl 6-chloro-4-hydroxy-7-(2-methoxyethoxy)quinoline-3-carboxylate**

To a solution of Dowtherm A (25 mL) at 250°C, was added diethyl ({[4-chloro-3-(2-methoxyethoxy)phenyl]amino}methylene)malonate (Intermediate 283; 12.7 g, 34.16 mmol) and heating continued for 1 hour. The reaction vessel was cooled, hexanes (100 mL) was added and the resulting slurry was filtered and dried to give 10.5 g (94%) of an insoluble grey solid.

20

25 **Intermediate 283****Diethyl ({[4-chloro-3-(2-methoxyethoxy)phenyl]amino}methylene)malonate**

A mixture of 1-chloro-2-(2-methoxyethoxy)-4-nitrobenzene (Intermediate 280; 10.3 g, 44.47 mmol), 5% platinum on carbon (1.0g), and zinc(II)iodide (2.84 g, 8.89 mmol) in EtOAc (40 ml) under nitrogen was evacuated to hydrogen (1 atm) and stirred for 24 hours. The hydrogen was replaced with nitrogen, and diethyl ethoxymethylenemalonate (9.07 mL, 24.18 mmol) and Na₂SO₄ (1 g) were added. After 16 hours, the resulting black slurry was filtered through a pad of diatomaceous earth, and the filtrate was concentrated under reduced pressure. The resulting oil was purified via silica chromatography (hexanes/EtOAc gradient)

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to give 12.7 grams (77%) of an off-white powder. ¹H NMR: 10.70 (d, 1 H), 8.40 (d, 1 H), 7.40 (d, 1 H), 7.26 (s, 1 H), 6.98 (d, 1 H), 4.24 (m, 6 H), 3.72 (m, 2 H), 3.34 (s, 3 H), 1.28 (m, 6 H); *m/z*: 372.

5 **Intermediate 284**

Ethyl 7-(2-([*tert*-butyl(dimethyl)silyl]oxy)ethoxy)-4-chloro-6-(4-methylpiperazin-1-yl)quinoline-3-carboxylate

A solution of diethyl ({[3-(2-([*tert*-butyl(dimethyl)silyl]oxy)ethoxy)-4-(4-methylpiperazin-1-yl)phenyl]amino}methylene)malonate (Intermediate 285; 2.0 g, 3.73 mmol), triethylamine (9.05 g, 89.59 mmol) and phosphorus oxychloride (1.14 g, 7.47 mmol) in toluene (10 mL) was heated at 100°C for 24 hours. The reaction mixture was cooled, acetonitrile (10 mL) was added, and the resulting mixture was added to NaHCO₃ solution. The mixture was extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The resulting oil was purified via silica chromatography (EtOAc/MeOH gradient) to give 0.545 g (29%) of a pale yellow solid. ¹H NMR: 8.84 (s, 1 H), 7.40 (s, 2 H), 4.32 (q, 2 H), 4.22 (m, 2 H), 3.94 (m, 2 H), 3.16 (s, 4 H), 2.45 (s, 4 H), 1.28 (t, 3 H), 0.79 (s, 9 H), 0.00 (s, 6 H); *m/z*: 508.

Intermediate 285

20 Diethyl ({[3-(2-([*tert*-butyl(dimethyl)silyl]oxy)ethoxy)-4-(4-methylpiperazin-1-yl)phenyl]amino}methylene)malonate

A mixture of 1-[2-(2-([*tert*-butyl(dimethyl)silyl]oxy)ethoxy)-4-nitrophenyl]-4-methylpiperazine (Intermediate 286; 1.5 g, 3.79 mmol) and 10% palladium on carbon (0.4g) in EtOAc (10 ml) under nitrogen was evacuated to hydrogen (1 atm) and stirred for 16 hours. The hydrogen gas was removed, and replaced with nitrogen gas. Diethyl ethoxymethylenemalonate (0.774 mL, 3.87 mmol) was added, and after stirring for 24 hours, the resulting black slurry was filtered through a pad of diatomaceous earth. The filtrate was concentrated under reduced pressure to give 2.0 g (99%) of a white solid. ¹H NMR: 10.72 (d, 1 H), 8.37 (d, 1 H), 7.02 (s, 1 H), 6.86 (s, 2 H), 4.23-4.10 (m, 6 H), 3.92 (m, 2 H), 2.97 (m, 4 H), 2.43 (m, 4 H), 2.20 (s, 3 H), 1.25 (m, 6 H), 0.86 (s, 9 H), 0.07 (s, 6 H); *m/z*: 536.

Intermediate 286**1-[2-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethoxy)-4-nitrophenyl]-4-methylpiperazine**

A solution of *tert*-butyl[2-(2-chloro-5-nitrophenoxy)ethoxy]dimethylsilane (Intermediate 287; 6.0 g, 18.08 mmol) and *N*-methylpiperazine (4.41 mL, 39.77 mmol) in DMF (10 mL) was heated at 100°C for 3 days. After cooling, water (20 mL) was added, the mixture was extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried (Na₂SO₄), filtered, and concentrated, and the residue purified via silica chromatography (hexanes/EtOAc gradient) to give 5.0 g (70 %) of a yellow solid. ¹H NMR: 7.84 (dd, 1 H), 7.70 (d, 1 H), 7.02 (d, 1 H), 4.17 (m, 2 H), 3.96 (m, 2 H), 3.26 (m, 4 H), 2.45 (m, 4 H), 2.21 (s, 3 H), 0.86 (s, 9 H), 0.07 (s, 6 H); *m/z*: 396.

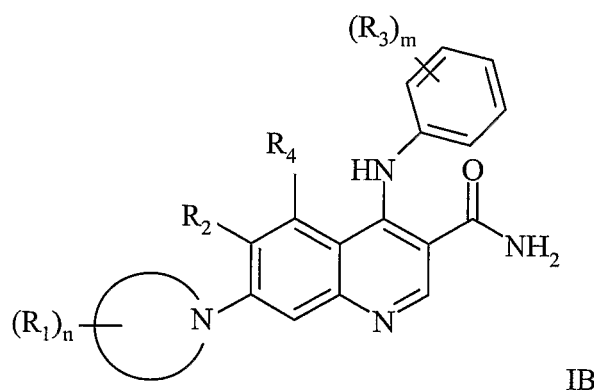
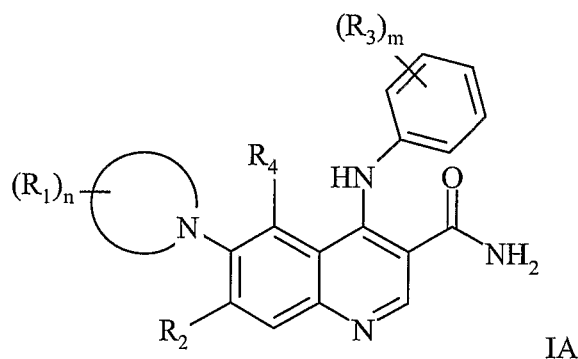
Intermediate 287***tert*-Butyl[2-(2-chloro-5-nitrophenoxy)ethoxy]dimethylsilane**

A mixture of 2-chloro-5-nitrophenol (6.0 g, 34.57 mmol), (2-bromoethoxy)-*tert*-butyldimethylsilane (8.6 mL, 41.5 mmol) and potassium carbonate (7.15 g, 41.5 mmol), in DMF (40 mL) was heated at 40°C for 4 days. The reaction mixture was filtered. Brine (200 mL) was added, and the mixture was extracted with EtOAc (3x 50 mL). The combined organic extracts were concentrated, and the residue purified by silica chromatography (hexanes/EtOAc gradient) to give 6.5 g (57%) of a white solid. ¹H NMR: 7.94 (s, 1 H), 7.84 (dd, 1 H), 7.74 (d, 1 H), 4.325 (m, 2 H), 3.96 (m, 2 H), 0.82 (s, 9 H), 0.04 (s, 6 H).

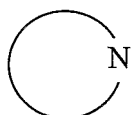
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What is claimed is:

1. A compound of formula IA or IB:



or a pharmaceutically acceptable salt thereof, wherein:



is a 3-10 membered, nitrogen linked, heterocycle or heteroaryl; wherein if said heterocycle or heteroaryl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R₅;

- 10 **R₁** at each occurrence is independently halo, hydroxy, nitro, formyl, cyano, -CO₂H, -SH, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkoxy, -OC(O)-(C₁-C₆)alkyl, -C(O)-(C₁-C₆)alkyl, -CO₂(C₁-C₆)alkyl, -NR'R'', -NR'-C(O)-(C₁-C₆)alkyl, (C₁-C₆)alkylS(O)_a- wherein a is 0 to 2, -NR'-C(O)-O(C₁-C₆)alkyl, -NR'-SO₂-(C₁-C₆)alkyl, -NR'-C(O)NR'R'', -SO₂-NR'R'', -C(O)-NR'R'', carbocyclyl, heterocyclo, heteroaryl or oxo;

R₂ is hydrogen, halo, hydroxy, nitro, formyl, -CO₂H, -SH, cyano, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl, -O-(C₃-C₆)cycloalkyl, -OC(O)-(C₁-C₆)alkyl, -C(O)-(C₁-C₆)alkyl, -CO₂(C₁-C₆)alkyl, -NR'R'', -NR'-C(O)-(C₁-C₆)alkyl, (C₁-C₆)alkylS(O)_a- wherein a is 0 to 2, -NR'-C(O)-O(C₁-C₆)alkyl,

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-NR'-SO₂-(C₁-C₆)alkyl, -NR'-C(O)NR'R'', -SO₂-NR'R'', -C(O)-NR'R'', -OC(O)-NR'R'', carbocyclyl, heterocyclo, heteroaryl or (C₁-C₆)alkoxy;

- R₃** at each occurrence is independently halo, nitro, formyl, cyano, hydroxy, -NR'R'', -CO₂H, -C(O)-(C₁-C₆)alkyl, -CO₂(C₁-C₆)alkyl, -C(O)-NR'R'', -NR'-C(O)-(C₁-C₆)alkyl, 5 -NR'-C(O)NR'R'', -NR'-C(O)-O(C₁-C₆)alkyl, -O-C(O)-(C₁-C₆)alkyl, -SH, -SO₂-NR'R'', (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylS(O)_a wherein a is 0 to 2, -NR'-SO₂-(C₁-C₆)alkyl, carbocyclyl, heterocyclo, or heteroaryl, wherein if said heterocyclo or heteroaryl contains an -NH- moiety that nitrogen may be optionally substituted by (C₁-C₆)alkyl; or
- 10 two **R₃** groups on adjacent carbons may optionally form a 5- or 6-membered saturated, partially unsaturated, unsaturated and/or aromatic ring optionally containing 0, 1, or 2 heteroatoms selected from S, O, or NR_a wherein R_a is absent, H or (C₁-C₆)alkyl;

R₄ is hydrogen or halo;

m is 0-3; wherein the values of **R₃** may be the same or different;

- 15 **n** is 0-3; wherein the values of **R₁** may be the same or different;

p is independently 1 or 2 at each occurrence; and

R₅ is selected from (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, -C(O)-(C₁-C₆)alkyl, -S(O)_p(C₁-C₆)alkyl, -CO₂(C₁-C₆)alkyl, -C(O)-NR'R'', benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

- 20 **R'** and **R''** independently at each occurrence are H, optionally substituted (C₁-C₆)alkyl, or optionally substituted aryl, or taken together with the nitrogen to which they are attached form an optionally substituted 3-6 membered ring saturated or partially unsaturated containing 0 or 1 additional heteroatom selected from NR_a; wherein said optional substituents may be selected from one or more **R₆**;

- 25 **R₆** may be independently (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, halo, nitro, cyano, hydroxy, (C₁-C₆)alkoxy, -NR^xR^y, —COOR^x or —CONR^xR^y; and

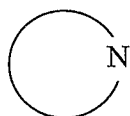
R^x and **R^y** are independently of each other hydrogen or (C₁-C₆)alkyl; and wherein

- each **R_a**, **R₁**, **R₂**, **R₃** and **R₅** may be optionally substituted on carbon by one or more formyl, -SH, azido, halo, nitro, cyano, hydroxy, trifluoromethoxy, -OC(O)-(C₁-C₆)alkyl, 30 -NR'R'', -CO₂H, -C(O)-(C₁-C₆)alkyl, -CO₂(C₁-C₆)alkyl, -C(O)-NR'R'', -S-(C₁-C₆)alkyl, -SO_p-(C₁-C₆)alkyl, -SO_pNR'R'', (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, -NR'-C(O)-(C₁-C₆)alkyl, -NR'-C(O)-O(C₁-C₆)alkyl, -NR'-SO₂-(C₁-C₆)alkyl, -NR'-C(O)NR'R'', (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, or (C₁-C₆)alkoxy.

2. A compound of formula IA as claimed in claim 1 or a pharmaceutically acceptable salt thereof.

3. A compound of formula IB as claimed in claim 1 or a pharmaceutically acceptable salt thereof.

4. A compound of formula IA or IB or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-3 wherein:



is a 5-7 membered, nitrogen linked, heterocycle; wherein if said heterocycle contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R_5 ; wherein

R_5 is selected from (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, $-C(O)-(C_1-C_6)$ alkyl and $-CO_2(C_1-C_6)$ alkyl; and

each R_5 may be optionally substituted on carbon by one or more cyano, hydroxy, $-OC(O)-(C_1-C_6)$ alkyl, $-NR'R''$, (C_3-C_6) cycloalkyl or (C_1-C_6) alkoxy; wherein

R' and R'' independently at each occurrence are (C_1-C_6) alkyl.

5. A compound of formula IA or IB or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-4 wherein R_1 at each occurrence is hydroxy, $-NR'R''$ or oxo; wherein R' and R'' independently at each occurrence are (C_1-C_6) alkyl.

6. A compound of formula IA or IB or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-5 wherein n is 0 or 1.

7. A compound of formula IA or IB or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-6 wherein R_2 is hydrogen, halo or (C_1-C_6) alkoxy; wherein R_2 may be optionally substituted on carbon by one or more (C_1-C_6) alkoxy or hydroxy.

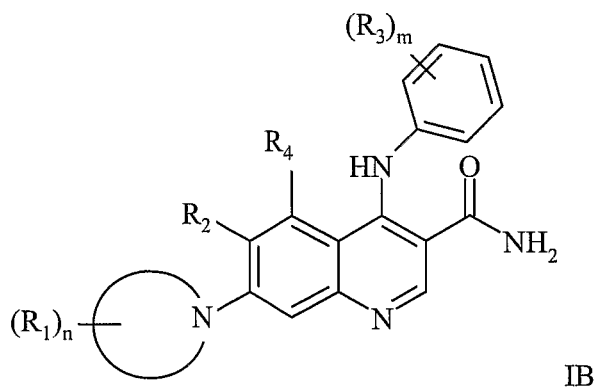
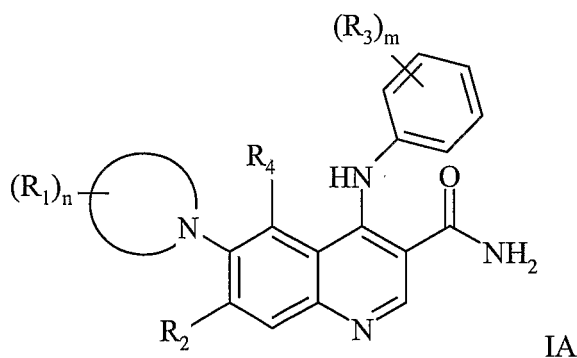
8. A compound of formula IA or IB or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-7 wherein R_3 at each occurrence is independently halo, (C_1-C_6) alkyl or (C_1-C_6) alkoxy; wherein R_3 may be optionally substituted on carbon by halo.

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9. A compound of formula IA or IB or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-8 wherein m is 1-3; wherein the values of R₃ may be the same or different.

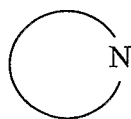
5 10. A compound of formula IA or IB or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-9 wherein R₄ is hydrogen or fluoro.

11. A compound of formula IA or IB:



10

wherein:



is piperazin-1-yl, *N*-methylpiperazin-1-yl, *N*-ethylpiperazin-1-yl, *N*-isopropylpiperazin-1-yl, *N*-acetylpiperazin-1-yl, *N*-(2-hydroxyacetyl)piperazin-1-yl, *N*-(2-dimethylaminoethyl)piperazin-1-yl, *N*-(2-methoxyethyl)piperazin-1-yl, *N*-(2-cyanoethyl)piperazin-1-yl, *N*-(2-hydroxyethyl)piperazin-1-yl, *N*-(cyclopropylmethyl)piperazin-1-yl, *N*-(cyclopropyl)piperazin-1-yl, *N*-((*R*)-2-hydroxypropionyl)piperazin-1-yl, *N*-((*S*)-2-hydroxypropionyl)piperazin-1-yl, *N*-(*t*-butoxycarbonyl)piperazin-1-yl, *N*-(acetoxyacetyl)piperazin-1-yl, piperidin-1-yl, morpholino, homopiperazin-1-yl, *N*-methylhomopiperazin-1-yl, *N*-ethylhomopiperazin-1-yl,

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N-acetylhomopiperazin-1-yl, *N*-isopropylhomopiperazin-1-yl,
N-cyclopropylhomopiperazin-1-yl and pyrrolidin-1-yl;

R_1 at each occurrence is hydroxy, -NMe₂ or oxo;

n is 0 or 1;

5 R_2 is hydrogen, fluoro, methoxy, ethoxy, 2-(methoxy)ethoxy, 2-hydroxyethoxy or
 isopropoxy;

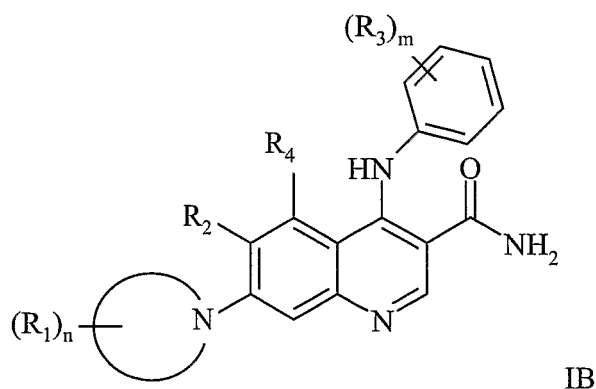
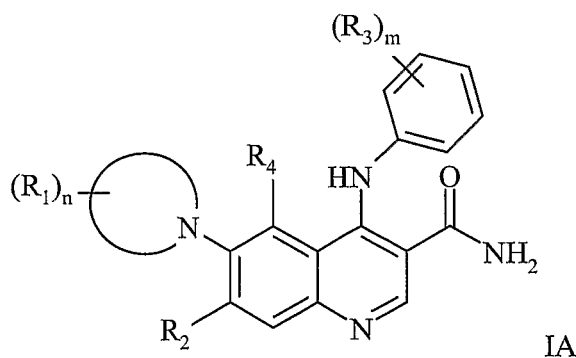
R_3 at each occurrence is independently fluoro, chloro, methyl, trifluoromethyl, ethyl,
 methoxy or trifluoromethoxy;

m is 1-3; wherein the values of R_3 may be the same or different;

10 R_4 is hydrogen or fluoro;

or a pharmaceutically acceptable salt thereof.

12. A compound of formula IA or IB:



15 selected from:

4-[(2,4-difluorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide;

4-[(2,3-dichlorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide;

7-ethoxy-4-[(2-fluoro-5-methylphenyl)amino]-6-(4-isopropylpiperazin-1-yl)quinoline-3-

20 carboxamide;

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4-[(3-chloro-2-fluorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide;

7-ethoxy-4-[(2-fluoro-5-methylphenyl)amino]-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide;

5 7-ethoxy-4-[(2-fluoro-4-methylphenyl)amino]-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide;

4-[(2,4-difluorophenyl)amino]-7-(2-methoxyethoxy)-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide;

4-[(2-fluoro-4-methylphenyl)amino]-7-(2-methoxyethoxy)-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide;

10 y)quinoline-3-carboxamide;

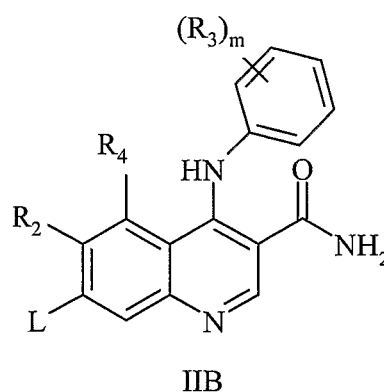
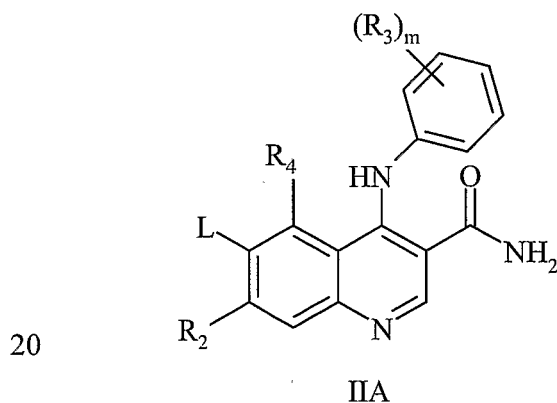
4-[(2-fluoro-5-methylphenyl)amino]-7-(2-methoxyethoxy)-6-(4-methylpiperazin-1-yl)quinoline-3-carboxamide; and

4-[(2-fluoro-4-methylphenyl)amino]-6-(4-isopropylpiperazin-1-yl)-7-(2-methoxyethoxy)quinoline-3-carboxamide.

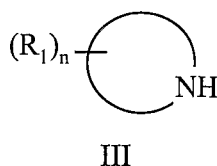
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13. A process for preparing a compound of formula IA or IB or a pharmaceutically acceptable salt thereof, as claimed in claim 1, which process, wherein variable groups are, unless otherwise specified, as defined in claim 1, comprises of:

Process a) reacting a compound of formula IIA or IIB:



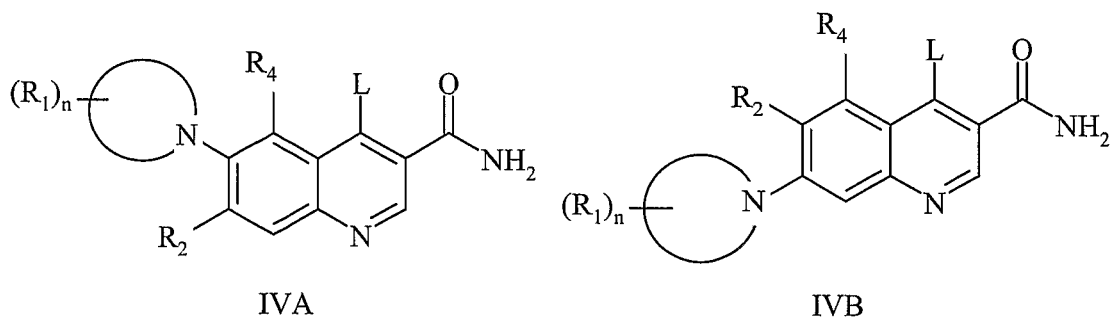
wherein L is a displaceable atom or group; with a compound of formula III:



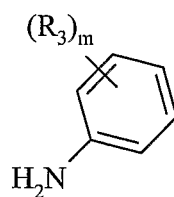
25 or

Process b) reacting a compound of formula IVA or IVB:

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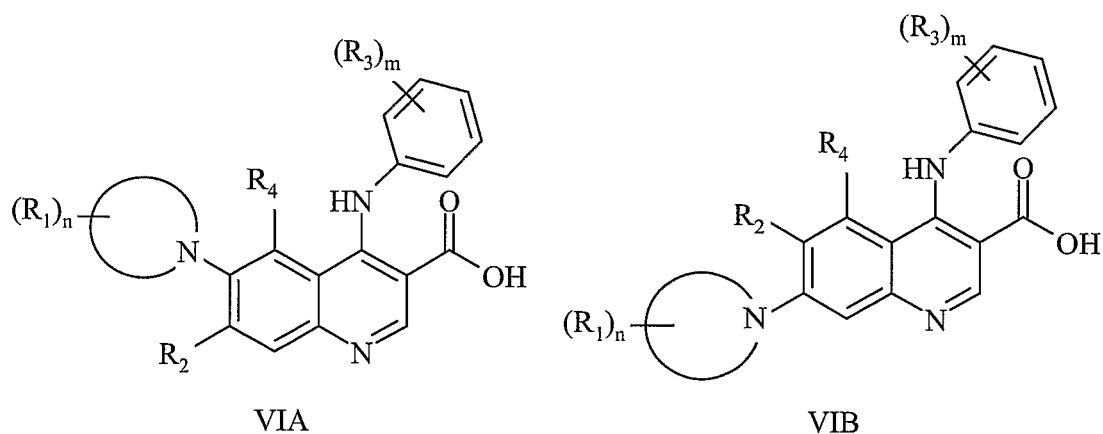
wherein L is a displaceable atom or group; with a compound of formula V:



5

or

Process c) reacting a compound of formula VIA or VIB:

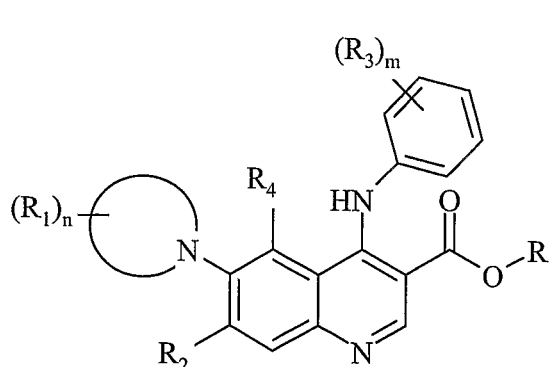


10 or an activated derivative thereof; with ammonia;

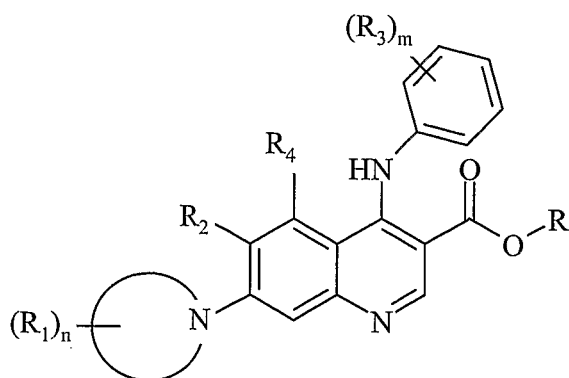
or

Process d) reacting a compound of formula VIIA or VIIB:

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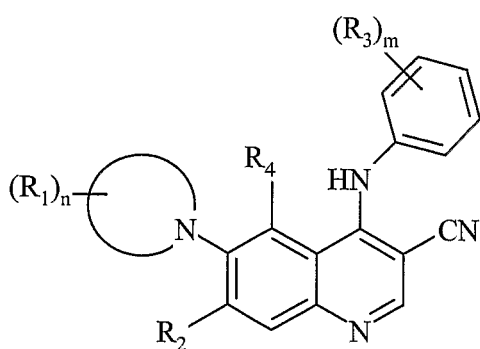
VIIA



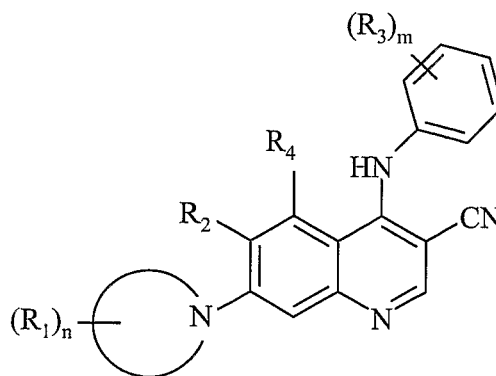
VIIB

wherein R is (C₁-C₆)alkyl, in particular methyl and ethyl; with formamide and a base;
or

5 *Process e)* hydrolysis of a compound of formula VIIA or VIIB:



VIIIA



VIIBB

and thereafter if necessary:

- i) converting a compound of the formula IA or IB into another compound of the formula IA
- 10 or IB;
- ii) removing any protecting groups;
- iii) forming a pharmaceutically acceptable salt.

14. A pharmaceutical composition which comprises a compound of formula IA or IB, or a
15 pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-12, in association
with a pharmaceutically-acceptable diluent or carrier.

15. A compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, as
claimed in any one of claims 1-12, for use as a medicament.

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16. The use of a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-12, in the manufacture of a medicament for use in the production of a CSF-1R kinase inhibitory effect in a warm-blooded animal such as man.

5 17. The use of a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-12, in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as man.

18. The use of a compound of the formula IA or IB, or a pharmaceutically acceptable salt
10 thereof, as claimed in any one of claims 1-12, in the manufacture of a medicament for use in the treatment of melanoma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries.

15

19. The use of a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-12, in the manufacture of a medicament for use in the treatment of breast, ovarian, bladder, cervical, endometrial, prostate, lung, kidney and pancreatic tumors; haematological malignancies including myelodysplastic syndrome, acute
20 myelogenous leukemia, chronic myelogenous leukemia, non Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma and chronic lymphocytic leukemia; and glioma, squamous cell carcinoma of the esophagus, malignant uveal melanoma and follicular lymphoma.

20. The use of a compound of the formula IA or IB, or a pharmaceutically acceptable salt
25 thereof, as claimed in any one of claims 1-12, in the manufacture of a medicament for use in the treatment of tumor-associated osteolysis, osteoporosis including ovariectomy-induced bone loss, orthopedic implant failure, autoimmune disorders including systemic lupus erythematosus, arthritis including rheumatoid arthritis, osteoarthritis, renal inflammation and glomerulonephritis; inflammatory bowel disease; transplant rejection including renal and
30 bone marrow allografts and skin xenograft, atherosclerosis, obesity, Alzheimer's Disease, chronic obstructive pulmonary disease, diabetes and chronic skin disorders including psoriasis and Langerhans cell histiocytosis.

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21. A method for producing a CSF-1R kinase inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula IA or IB, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-12.

5

22. A method for producing an anti-cancer effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula IA or IB, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-12.

10

23. A method of treating melanoma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries, in a warm-blooded
15 animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula IA or IB or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-12.

24. A method of treating breast, ovarian, bladder, cervical, endometrial, prostate, lung,
20 kidney and pancreatic tumors; haematological malignancies including myelodysplastic syndrome, acute myelogenous leukemia, chronic myelogenous leukemia, non Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma and chronic lymphocytic leukemia; and glioma, squamous cell carcinoma of the esophagus, malignant uveal melanoma and follicular lymphoma in a warm-blooded animal, such as man, in need of such treatment which
25 comprises administering to said animal an effective amount of a compound of formula IA or IB or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-12.

25. A method of treating tumor-associated osteolysis, osteoporosis including ovariectomy-induced bone loss, orthopedic implant failure, autoimmune disorders including systemic lupus
30 erythematosus, arthritis including rheumatoid arthritis, osteoarthritis, renal inflammation and glomerulonephritis; inflammatory bowel disease; transplant rejection including renal and bone marrow allografts and skin xenograft, atherosclerosis, obesity, Alzheimer's Disease, chronic obstructive pulmonary disease, diabetes and chronic skin disorders including psoriasis

and Langerhans cell histiocytosis in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula IA or IB or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-12.

5

26. A pharmaceutical composition which comprises a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-12, in association with a pharmaceutically-acceptable diluent or carrier for use in the production of a CSF-1R kinase inhibitory effect in a warm-blooded animal such as man.

10

27. A pharmaceutical composition which comprises a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-12, in association with a pharmaceutically-acceptable diluent or carrier for use in the production of an anti-cancer effect in a warm-blooded animal such as man.

15

28. A pharmaceutical composition which comprises a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-12, in association with a pharmaceutically-acceptable diluent or carrier for use in the treatment of melanoma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer,
20 lung cancer, leukemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries in a warm-blooded animal such as man.

29. A pharmaceutical composition which comprises a compound of the formula IA or IB,
25 or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-12, in association with a pharmaceutically-acceptable diluent or carrier for use in the treatment of breast, ovarian, bladder, cervical, endometrial, prostate, lung, kidney and pancreatic tumors; haematological malignancies including myelodysplastic syndrome, acute myelogenous leukemia, chronic myelogenous leukemia, non Hodgkin's lymphoma, Hodgkin's disease,
30 multiple myeloma and chronic lymphocytic leukemia; and glioma, squamous cell carcinoma of the esophagus, malignant uveal melanoma and follicular lymphoma in a warm-blooded animal such as man.

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30. A pharmaceutical composition which comprises a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-12, in association with a pharmaceutically-acceptable diluent or carrier for use in the treatment of tumor-associated osteolysis, osteoporosis including ovariectomy-induced bone loss,
5 orthopedic implant failure, autoimmune disorders including systemic lupus erythematosus, arthritis including rheumatoid arthritis, osteoarthritis, renal inflammation and glomerulonephritis; inflammatory bowel disease; transplant rejection including renal and bone marrow allografts and skin xenograft, atherosclerosis, obesity, Alzheimer's Disease, chronic obstructive pulmonary disease, diabetes and chronic skin disorders including psoriasis
10 and Langerhans cell histiocytosis in a warm-blooded animal such as man.

31. The use of a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-12, in the production of a CSF-1R kinase inhibitory effect in a warm-blooded animal such as man.

15

32. The use of a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-12, in the production of an anti-cancer effect in a warm-blooded animal such as man.

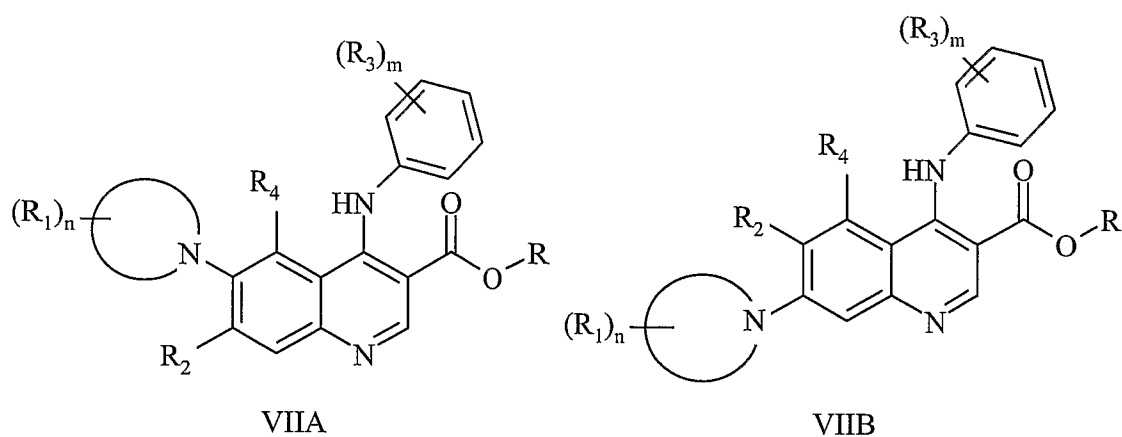
20 33. The use of a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-12, in the treatment of melanoma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs
25 and ovaries.

34. The use of a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-12, in the treatment of breast, ovarian, bladder, cervical, endometrial, prostate, lung, kidney and pancreatic tumors; haematological
30 malignancies including myelodysplastic syndrome, acute myelogenous leukemia, chronic myelogenous leukemia, non Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma and chronic lymphocytic leukemia; and glioma, squamous cell carcinoma of the esophagus, malignant uveal melanoma and follicular lymphoma.

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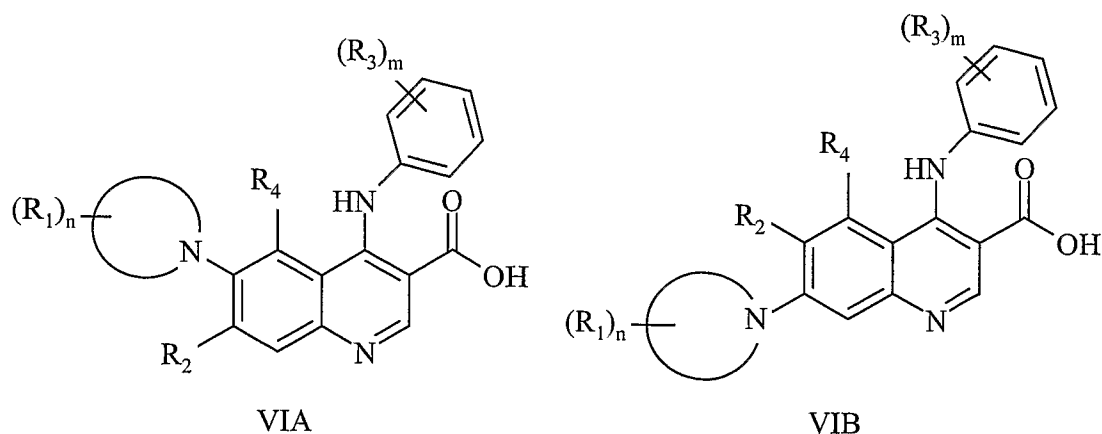
35. The use of a compound of the formula IA or IB, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-12, in the treatment of tumor-associated osteolysis, osteoporosis including ovariectomy-induced bone loss, orthopedic implant failure, autoimmune disorders including systemic lupus erythematosus, arthritis including rheumatoid
 5 arthritis, osteoarthritis, renal inflammation and glomerulonephritis; inflammatory bowel disease; transplant rejection including renal and bone marrow allografts and skin xenograft, atherosclerosis, obesity, Alzheimer's Disease, chronic obstructive pulmonary disease, diabetes and chronic skin disorders including psoriasis and Langerhans cell histiocytosis.

10 36. A compound of formula VIIA and VIIB:



wherein R is (C₁-C₆)alkyl and R₁-R₄, n and m are as defined in any one of claims 1-12.

15 37. A compound of formula VIA and VIB:



wherein R₁-R₄, n and m are as defined in any one of claims 1-12.