

3 - CINNOLINECARBOXAMIDE DERIVATIVES AND THEIR USE FOR TREATING CANCER

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).

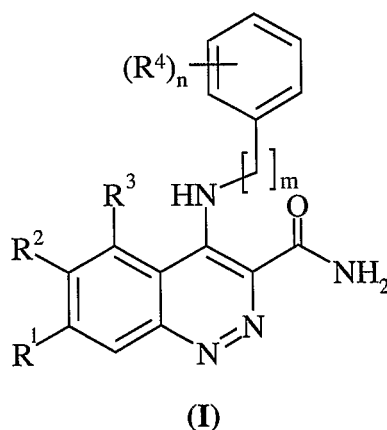
CSF-1R is normally expressed in myeloid cells of the mononuclear phagocytic lineage and their bone-marrow progenitors as well as the epithelial cells of the ducts and alveoli in the lactating, but not normal resting, breast tissue. CSF-1R activation stimulates the proliferation, survival, motility and 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,

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 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 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).

In WO 2006/124996 Supergen Inc discloses certain inhibitors of Polo-Like Kinase-1; in WO/2007045861 Aston et al., and Glaxo Group Limited disclose certain inhibitor of phosphodiesterase type IV, and in WO2006/067445 AstraZeneca discloses certain inhibitors of CSF-1R. The present inventors have found that a novel class of cinnolines are inhibitors of CSF-1R and this forms the basis of the present invention.

Accordingly, the present invention provides a compound of formula (I):



wherein:

R¹ and **R²** are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, C₁₋₆alkanoyl, C₁₋₆alkanoyloxy, *N*-(C₁₋₆alkyl)amino, *N,N*-(C₁₋₆alkyl)₂amino, *N*-(C₁₋₆alkyl)-*N*-(C₁₋₆alkoxy)amino, C₁₋₆alkanoylamino, *N*-(C₁₋₆alkyl)carbamoyl, *N,N*-(C₁₋₆alkyl)₂carbamoyl, C₁₋₆alkylS(O)_a wherein a is 0 to 2, C₁₋₆alkoxycarbonyl, *N*-(C₁₋₆alkyl)sulphamoyl, *N,N*-(C₁₋₆alkyl)₂sulphamoyl,

C₁₋₆alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein R¹ and R² independently of each other may be optionally substituted on carbon by one or more R⁵; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R⁶;

5 R³ is hydrogen or halo;

 m is 0 or 1;

 R⁴ is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, methoxy, ethoxy, acetyl, acetoxyl, methylamino, ethylamino, dimethylamino, diethylamino, 10 *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, phenyl, methylthio, ethylthio, methylsulphanyl, ethylsulphanyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

15 or wherein if two R⁴ groups are on adjacent carbons, they may optionally form a carbocyclic ring or a heterocyclic ring; wherein said carbocyclic ring or heterocyclic ring may be optionally substituted on carbon by one or more R⁷; and wherein if said heterocyclic ring contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R⁸;

20 n is 0-5; wherein the values of R⁴ are the same or different;

 R⁵ is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, C₁₋₆alkanoyl, C₁₋₆alkanoyloxy, *N*-(C₁₋₆alkyl)amino, *N,N*-(C₁₋₆alkyl)₂amino, *N*-(C₁₋₆alkyl)-*N*-(C₁₋₆alkoxy)amino, C₁₋₆alkanoylamino, *N*-(C₁₋₆alkyl)carbamoyl, 25 *N,N*-(C₁₋₆alkyl)₂carbamoyl, C₁₋₆alkylS(O)_a wherein a is 0 to 2, C₁₋₆alkoxycarbonyl, C₁₋₆alkoxycarbonylamino, *N*-(C₁₋₆alkyl)sulphamoyl, *N,N*-(C₁₋₆alkyl)₂sulphamoyl, C₁₋₆alkylsulphonylamino, carbocyclyl-R⁹- or heterocyclyl-R¹⁰-; wherein R⁵ may be optionally substituted on carbon by one or more R¹¹; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R¹²;

30 R⁶ and R¹² are independently selected from C₁₋₆alkyl, C₁₋₆alkanoyl, C₁₋₆alkylsulphonyl, C₁₋₆alkoxycarbonyl, carbamoyl, *N*-(C₁₋₆alkyl)carbamoyl, *N,N*-(C₁₋₆alkyl)₂carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl; wherein

R^6 and R^{12} independently of each other may be optionally substituted on carbon by one or more R^{13} ;

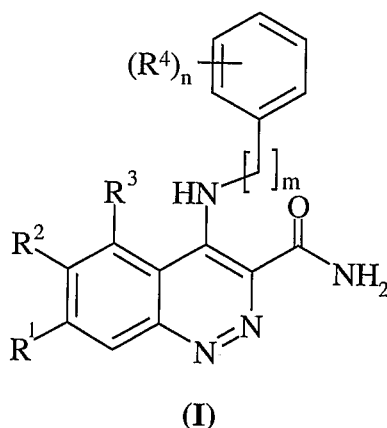
R^{13} is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, N -(C_{1-6} alkyl)amino, N,N -(C_{1-6} alkyl)₂amino, N -(C_{1-6} alkyl)- N -(C_{1-6} alkoxy)amino, C_{1-6} alkanoylamino, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl)₂carbamoyl, C_{1-6} alkylS(O)_a wherein a is 0 to 2, C_{1-6} alkoxycarbonyl, C_{1-6} alkoxycarbonylamino, N -(C_{1-6} alkyl)sulphamoyl, N,N -(C_{1-6} alkyl)₂sulphamoyl, C_{1-6} alkylsulphonylamino, carbocyclyl- R^{14} - or heterocyclyl- R^{15} -; wherein R^{13} may be optionally substituted on carbon by one or more R^{16} ; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{17} ;

R^9 , R^{10} , R^{14} and R^{15} are independently selected from a direct bond, -O-, -N(R^{18})-, -C(O)-, -N(R^{19})C(O)-, -C(O)N(R^{20})-, -S(O)_s-, -SO₂N(R^{21})- or -N(R^{22})SO₂-; wherein R^{18} , R^{19} , R^{20} , R^{21} and R^{22} are independently selected from hydrogen or C_{1-6} alkyl and s is 0-2;

R^8 and R^{17} are independently selected from C_{1-6} alkyl, C_{1-6} alkanoyl, C_{1-6} alkylsulphonyl, C_{1-6} alkoxycarbonyl, carbamoyl, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl)₂carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R^7 , R^{11} and R^{16} are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, methoxy, ethoxy, acetyl, acetoxyl, methylamino, ethylamino, dimethylamino, diethylamino, N -methyl- N -ethylamino, acetylamino, N -methylcarbamoyl, N -ethylcarbamoyl, N,N -dimethylcarbamoyl, N,N -diethylcarbamoyl, N -methyl- N -ethylcarbamoyl, phenyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, N -methylsulphamoyl, N -ethylsulphamoyl, N,N -dimethylsulphamoyl, N,N -diethylsulphamoyl or N -methyl- N -ethylsulphamoyl; or a pharmaceutically acceptable salt thereof.

In some embodiments, the invention relates to a compound of formula (I):



wherein:

R^1 and R^2 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, N -(C_{1-6} alkyl)amino, N,N -(C_{1-6} alkyl) $_2$ amino, N -(C_{1-6} alkyl)- N -(C_{1-6} alkoxy)amino, C_{1-6} alkanoylamino, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl) $_2$ carbamoyl, C_{1-6} alkoxycarbonyl, N -(C_{1-6} alkyl)sulphamoyl, N,N -(C_{1-6} alkyl) $_2$ sulphamoyl, C_{1-6} alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein R^1 and R^2 independently of each other may be optionally substituted on carbon by one or more R^5 ; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^6 ;

R^3 is hydrogen or halo;

m is 0 or 1;

R^4 is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, methoxy, ethoxy, acetyl, acetoxyl, methylamino, ethylamino, dimethylamino, diethylamino, N -methyl- N -ethylamino, acetylamino, N -methylcarbamoyl, N -ethylcarbamoyl, N,N -dimethylcarbamoyl, N,N -diethylcarbamoyl, N -methyl- N -ethylcarbamoyl, phenyl, methylthio, ethylthio, methylsulphanyl, ethylsulphanyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, N -methylsulphamoyl, N -ethylsulphamoyl, N,N -dimethylsulphamoyl, N,N -diethylsulphamoyl or N -methyl- N -ethylsulphamoyl;

or wherein if two R^4 groups are on adjacent carbons, they may optionally form a carbocyclic ring or a heterocyclic ring; wherein said carbocyclic ring or heterocyclic ring may be optionally substituted on carbon by one or more R^7 ; and wherein if said heterocyclic ring contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^8 ;

n is 0-5; wherein the values of R^4 are the same or different;

R^5 is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, N -(C_{1-6} alkyl)amino, N,N -(C_{1-6} alkyl)₂amino, N -(C_{1-6} alkyl)- N -(C_{1-6} alkoxy)amino, C_{1-6} alkanoylamino, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl)₂carbamoyl, C_{1-6} alkylS(O)_a wherein a is 0 to 2, C_{1-6} alkoxycarbonyl, C_{1-6} alkoxycarbonylamino, N -(C_{1-6} alkyl)sulphamoyl, N,N -(C_{1-6} alkyl)₂sulphamoyl, C_{1-6} alkylsulphonylamino, carbocyclyl- R^9 - or heterocyclyl- R^{10} -; wherein R^5 may be optionally substituted on carbon by one or more R^{11} ; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{12} ;

R^6 and R^{12} are independently selected from C_{1-6} alkyl, C_{1-6} alkanoyl, C_{1-6} alkylsulphonyl, C_{1-6} alkoxycarbonyl, carbamoyl, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl)₂carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl; wherein R^6 and R^{12} independently of each other may be optionally substituted on carbon by one or more R^{13} ;

R^{13} is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, N -(C_{1-6} alkyl)amino, N,N -(C_{1-6} alkyl)₂amino, N -(C_{1-6} alkyl)- N -(C_{1-6} alkoxy)amino, C_{1-6} alkanoylamino, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl)₂carbamoyl, C_{1-6} alkylS(O)_a wherein a is 0 to 2, C_{1-6} alkoxycarbonyl, C_{1-6} alkoxycarbonylamino, N -(C_{1-6} alkyl)sulphamoyl, N,N -(C_{1-6} alkyl)₂sulphamoyl, C_{1-6} alkylsulphonylamino, carbocyclyl- R^{14} - or heterocyclyl- R^{15} -; wherein R^{13} may be optionally substituted on carbon by one or more R^{16} ; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{17} ;

R^9 , R^{10} , R^{14} and R^{15} are independently selected from a direct bond, -O-, -N(R^{18})-, -C(O)-, -N(R^{19})C(O)-, -C(O)N(R^{20})-, -S(O)_s-, -SO₂N(R^{21})- or -N(R^{22})SO₂-; wherein R^{18} , R^{19} , R^{20} , R^{21} and R^{22} are independently selected from hydrogen or C_{1-6} alkyl and s is 0-2;

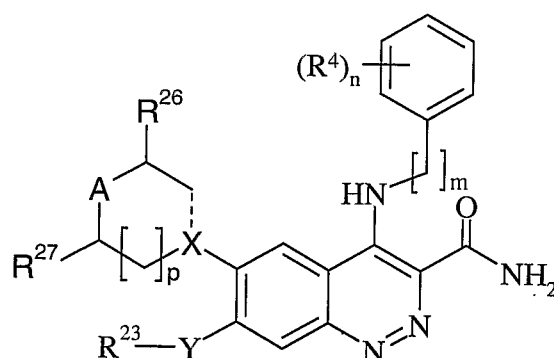
R^8 and R^{17} are independently selected from C_{1-6} alkyl, C_{1-6} alkanoyl, C_{1-6} alkylsulphonyl, C_{1-6} alkoxycarbonyl, carbamoyl, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl)₂carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R^7 , R^{11} and R^{16} are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, methoxy, ethoxy, acetyl, acetoxymethyl, methylamino,

ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, phenyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

or a pharmaceutically acceptable salt thereof.

In some embodiments, the invention relates to a compound of formula (I) having formula (IA):



formula (IA)

or a pharmaceutically acceptable salt thereof, wherein:

--- is selected from a single and double bond;

if --- is a single bond, then X is selected from CR²⁴ and N;

if --- is a double bond, then X is C;

Y is selected from O and S;

A is selected from O, S, NR²⁵, and CR²⁸R²⁹;

p is 0-2;

m is 0 or 1;

R⁴ is independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, phenyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

or wherein if two R^4 groups are on adjacent carbons, they may optionally form a carbocyclic ring or a heterocyclic ring; wherein said carbocyclic ring or heterocyclic ring may be optionally substituted on carbon by one or more R^7 ; and wherein if said heterocyclic ring contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^8 ;

n is 0-5; wherein the values of R^4 are the same or different;

R^7 may be independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, methoxy, ethoxy, acetyl, acetoxyl, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, phenyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

R^8 may be selected from C_{1-6} alkyl, C_{1-6} alkanoyl, C_{1-6} alkylsulphonyl, C_{1-6} alkoxycarbonyl, carbamoyl, *N*-(C_{1-6} alkyl)carbamoyl, *N,N*-(C_{1-6} alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R^{23} is selected from H, and C_{1-6} alkyl wherein C_{1-6} alkyl is optionally substituted with C_{1-6} alkoxy;

R^{24} , R^{26} , R^{27} , R^{28} are each independently selected from hydrogen and C_{1-6} alkyl;

R^{25} may be selected from hydrogen, C_{1-6} alkyl and C_{1-6} alkanoyl, wherein C_{1-6} alkyl and C_{1-6} alkanoyl may be optionally substituted on carbon by one or more R^{30} ;

or R^{25} and R^{27} together with the atom they are attached may optionally form a heterocyclic ring; wherein said heterocyclic ring may be optionally substituted on carbon by one or more R^{35} ; and wherein if said heterocyclic ring contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{36} ;

R^{29} may be selected from hydrogen and amino, wherein amino may be optionally substituted with one or more C_{1-6} alkyl;

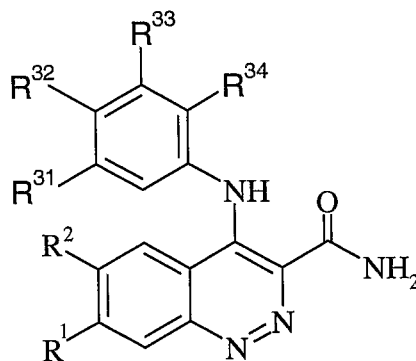
R^{30} may be selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, methoxy, ethoxy, acetyl, acetoxyl, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, phenyl,

methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl and *N*-methyl-*N*-ethylsulphamoyl; and

R^{35} may be independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, methoxy, ethoxy, acetyl, acetoxymethyl, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, phenyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

R^{36} may be selected from C_{1-6} alkyl, C_{1-6} alkanoyl, C_{1-6} alkylsulphonyl, C_{1-6} alkoxycarbonyl, carbamoyl, *N*-(C_{1-6} alkyl)carbamoyl, *N,N*-(C_{1-6} alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl.

In some embodiments, the invention relates to a compound of formula (I) having formula (IB):



formula (IB)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, *N*-(C_{1-6} alkyl)amino, *N,N*-(C_{1-6} alkyl)₂amino, *N*-(C_{1-6} alkyl)-*N*-(C_{1-6} alkoxy)amino, C_{1-6} alkanoylamino, *N*-(C_{1-6} alkyl)carbamoyl, *N,N*-(C_{1-6} alkyl)₂carbamoyl, C_{1-6} alkoxycarbonyl, *N*-(C_{1-6} alkyl)sulphamoyl, *N,N*-(C_{1-6} alkyl)₂sulphamoyl, C_{1-6} alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein R^1 and R^2 independently of each other may be optionally substituted

on carbon by one or more R^5 ; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^6 ;

R^5 is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, N -(C_{1-6} alkyl)amino, N,N -(C_{1-6} alkyl)₂amino, N -(C_{1-6} alkyl)- N -(C_{1-6} alkoxy)amino, C_{1-6} alkanoylamino, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl)₂carbamoyl, C_{1-6} alkylS(O)_a wherein a is 0 to 2, C_{1-6} alkoxycarbonyl, C_{1-6} alkoxycarbonylamino, N -(C_{1-6} alkyl)sulphamoyl, N,N -(C_{1-6} alkyl)₂sulphamoyl, C_{1-6} alkylsulphonylamino, carbocyclyl- R^9 - or heterocyclyl- R^{10} -; wherein R^5 may be optionally substituted on carbon by one or more R^{11} ; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{12} ;

R^6 and R^{12} are independently selected from C_{1-6} alkyl, C_{1-6} alkanoyl, C_{1-6} alkylsulphonyl, C_{1-6} alkoxycarbonyl, carbamoyl, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl; wherein R^6 and R^{12} independently of each other may be optionally substituted on carbon by one or more R^{13} ;

R^{13} is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, N -(C_{1-6} alkyl)amino, N,N -(C_{1-6} alkyl)₂amino, N -(C_{1-6} alkyl)- N -(C_{1-6} alkoxy)amino, C_{1-6} alkanoylamino, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl)₂carbamoyl, C_{1-6} alkylS(O)_a wherein a is 0 to 2, C_{1-6} alkoxycarbonyl, C_{1-6} alkoxycarbonylamino, N -(C_{1-6} alkyl)sulphamoyl, N,N -(C_{1-6} alkyl)₂sulphamoyl, C_{1-6} alkylsulphonylamino, carbocyclyl- R^{14} - or heterocyclyl- R^{15} -; wherein R^{13} may be optionally substituted on carbon by one or more R^{16} ; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{17} ;

R^9 , R^{10} , R^{14} and R^{15} are independently selected from a direct bond, -O-, -N(R^{18})-, -C(O)-, -N(R^{19})C(O)-, -C(O)N(R^{20})-, -S(O)_s-, -SO₂N(R^{21})- or -N(R^{22})SO₂-; wherein R^{18} , R^{19} , R^{20} , R^{21} and R^{22} are independently selected from hydrogen or C_{1-6} alkyl and s is 0-2;

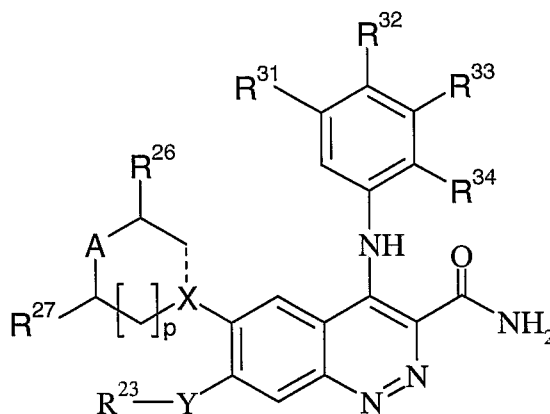
R^{17} are independently selected from C_{1-6} alkyl, C_{1-6} alkanoyl, C_{1-6} alkylsulphonyl, C_{1-6} alkoxycarbonyl, carbamoyl, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R^{11} and R^{16} are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl,

C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, phenyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl; and

R³¹, R³², R³³, and R³⁴ are each independently selected from hydrogen, halo, and C₁₋₄alkyl.

In some embodiments, the invention relates to a compound of formula (I) having formula (IC):



formula (IC)

or a pharmaceutically acceptable salt thereof, wherein:

- is selected from a single and double bond;
- if --- is a single bond, then X is selected from CR²⁴ and N;
- if --- is a double bond, then X is C;
- Y is selected from O and S;
- A is selected from O, S, NR²⁵, and CR²⁸R²⁹;
- p is 0-2;
- R²³ is C₁₋₆alkyl;
- R²⁴, R²⁶, R²⁷, R²⁸ are each independently selected from hydrogen and C₁₋₆alkyl;
- R²⁵ may be selected from hydrogen, C₁₋₆alkyl and C₁₋₆alkanoyl wherein C₁₋₆alkyl and C₁₋₆alkanoyl may be optionally substituted on carbon by one or more R³⁰;
- R²⁹ may be selected from hydrogen and amino optionally substituted with one or more C₁₋₆alkyl;

R^{30} may be selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, phenyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl, and *N*-methyl-*N*-ethylsulphamoyl;

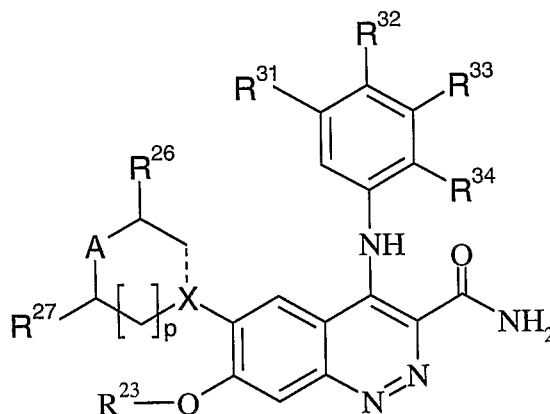
R^{31} is selected from hydrogen and C_{1-4} alkyl;

R^{32} is selected from hydrogen, halo, and C_{1-4} alkyl;

R^{33} is selected from hydrogen and halo; and

R^{34} is selected from halo.

In some embodiments, the invention relates to a compound of formula (I) having formula (ID):



formula (ID)

or a pharmaceutically acceptable salt thereof, wherein:

--- is selected from a single and double bond;

if --- is a single bond, then X is selected from CH and N;

if --- is a double bond, then X is C;

A is selected from O, NR^{25} , and CHR^{29} ;

p is 0-2;

R^{23} is selected from methyl and ethyl;

R^{25} is selected from hydrogen, methyl, ethyl, isopropyl, tert-butyl, 1-methoxy-2-ethyl,

1-hydroxy-2-ethyl, 1,1,1-trifluoro-2-ethyl, 2-hydroxy-1-propionyl, and mesyl;

R^{26} and R^{27} , are each independently selected from hydrogen and methyl;

R^{29} may be dimethylamino;

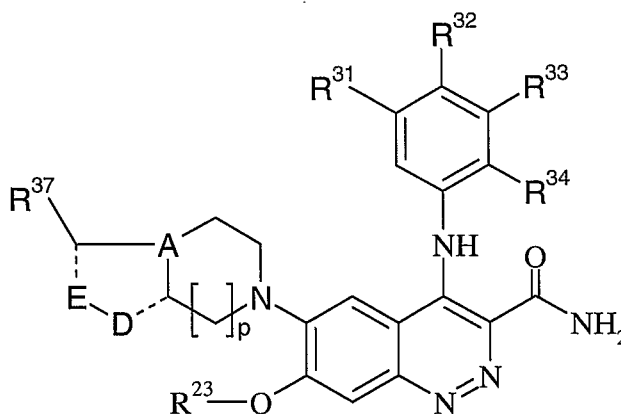
R^{31} is selected from hydrogen and methyl;

R^{32} is selected from hydrogen, fluoro, and methyl;

R^{33} is selected from hydrogen and chloro; and

5 R^{34} is selected from fluoro and chloro.

In some embodiments, the invention relates to a compound of formula (I) having formula (IE):



formula (IE)

10 or a pharmaceutically acceptable salt thereof, wherein:

--- is selected from a single and double bond;

A is selected from N, and CH;

D is selected from N, NH, CH, and CH₂;

E is selected from N, NH, CH, and CH₂;

15 p is 0-1;

R^{23} is selected from C₁₋₆alkyl;

R^{31} is selected from hydrogen and C₁₋₄alkyl;

R^{32} is selected from hydrogen, halo, and C₁₋₄alkyl;

R^{33} is selected from hydrogen and halo; and

20 R^{34} is halo; and

R^{37} is selected from H and OH.

In this specification the term “alkyl” includes both straight and branched chain alkyl groups. References to individual alkyl groups such as “propyl” are specific for the straight chain version only and references to individual branched chain alkyl groups such as ‘isopropyl’ are specific for the branched chain version only. For example, “C₁₋₆alkyl” includes C₁₋₄alkyl, C₁₋₃alkyl, propyl, isopropyl and *t*-butyl. A similar convention applies to other

25

radicals, for example “phenylC₁₋₆alkyl” includes phenylC₁₋₄alkyl, benzyl, 1-phenylethyl and 2-phenylethyl. The term “halo” refers to fluoro, chloro, bromo and iodo.

Where optional substituents are chosen from “one or more” groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups.

A “heterocyclyl” is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 4-12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH₂- group can optionally be replaced by a -C(O)- and a ring sulphur atom may be optionally oxidised to form the S-oxides. Examples and suitable values of the term “heterocyclyl” are morpholino, piperidyl, pyridyl, pyranyl, pyrrolyl, pyrazolyl, isothiazolyl, indolyl, quinolyl, thienyl, 1,3-benzodioxolyl, thiadiazolyl, piperazinyl, thiazolidinyl, pyrrolidinyl, thiomorpholino, pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, tetrahydropyranyl, imidazolyl, pyrimidyl, pyrazinyl, pyridazinyl, isoxazolyl, *N*-methylpyrrolyl, 4-pyridone, 1-isoquinolone, 2-pyrrolidone, 4-thiazolidone, pyridine-*N*-oxide and quinoline-*N*-oxide. A particular example of the term “heterocyclyl” is pyrazolyl. In one aspect of the invention a “heterocyclyl” is a saturated, partially saturated or unsaturated, monocyclic ring containing 5 or 6 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, it may, unless otherwise specified, be carbon or nitrogen linked, a -CH₂- group can optionally be replaced by a -C(O)- and a ring sulphur atom may be optionally oxidised to form the S-oxides.

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 -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.

“If two R⁴ groups are on adjacent carbons, they may optionally form a carbocyclic ring or a heterocyclic ring”. Said “carbocyclic ring” or a “heterocyclic ring” is therefore fused to the phenyl ring of formula (I).

A “carbocyclic ring” is a partially saturated or totally unsaturated, monocyclic ring that contains 3-8 carbon atoms of which two are shared with the phenyl ring in formula (I); wherein a -CH₂- group can optionally be replaced by a -C(O)-. Suitable examples of a “carbocyclic ring” fused to the phenyl ring in formula (I) include indanyl (carbocyclic ring is

a partially saturated 5 membered ring) and naphthyl (carbocyclic ring is a totally unsaturated 6 membered ring).

A “heterocyclic ring” is a partially saturated or totally unsaturated, monocyclic ring containing 4-8 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen and two atoms are carbon atoms shared with the phenyl ring in formula (I); wherein a -CH₂- group can optionally be replaced by a -C(O)- and a ring sulphur atom may be optionally oxidised to form the S-oxides. Suitable examples of a “heterocyclic ring” fused to the phenyl ring in formula (I) include indoliny (heterocyclic ring is a partially saturated 5 membered ring containing one nitrogen atom) and quinoxaliny (heterocyclic ring is a totally unsaturated 6 membered ring containing two nitrogen atoms).

An example of “C₁₋₆alkanoyloxy” is acetoxy. Examples of “C₁₋₆alkoxycarbonyl” include methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl. Examples of “C₁₋₆alkoxy” include methoxy, ethoxy and propoxy. Examples of “C₁₋₆alkanoylamino” include formamido, acetamido and propionylamino. Examples of “C₁₋₆alkylS(O)_a wherein a is 0 to 2” include methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl. Examples of “C₁₋₆alkanoyl” include propionyl and acetyl. Examples of “N-(C₁₋₆alkyl)amino” include methylamino and ethylamino. Examples of “N,N-(C₁₋₆alkyl)₂amino” include di-*N*-methylamino, di-(*N*-ethyl)amino and *N*-ethyl-*N*-methylamino. Examples of “C₂₋₆alkenyl” are vinyl, allyl and 1-propenyl. Examples of “C₂₋₆alkynyl” are ethynyl, 1-propynyl and 2-propynyl. Examples of “N-(C₁₋₆alkyl)sulphamoyl” are *N*-(methyl)sulphamoyl and *N*-(ethyl)sulphamoyl. Examples of “N-(C₁₋₆alkyl)₂sulphamoyl” are *N,N*-(dimethyl)sulphamoyl and *N*-(methyl)-*N*-(ethyl)sulphamoyl. Examples of “N-(C₁₋₆alkyl)carbamoyl” are *N*-(C₁₋₄alkyl)carbamoyl, methylaminocarbonyl and ethylaminocarbonyl. Examples of “N,N-(C₁₋₆alkyl)₂carbamoyl” are *N,N*-(C₁₋₄alkyl)₂carbamoyl, dimethylaminocarbonyl and methylethylaminocarbonyl. Examples of “C₁₋₆alkylsulphonyl” are mesyl, ethylsulphonyl and isopropylsulphonyl. Examples of “C₁₋₆alkylsulphonylamino” are mesylamino, ethylsulphonylamino and isopropylsulphonylamino. Examples of “C₁₋₆alkoxycarbonylamino” are methoxycarbonylamino and *t*-butoxycarbonylamino. Examples of “C₁₋₆alkoxycarbonylamino” include methoxycarbonylamino and *t*-butoxycarbonylamino.

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 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 (I) 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 (I) that possess CSF-1R kinase inhibitory activity.

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

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.

R^1 and R^2 are independently selected from C_{1-6} alkoxy or heterocyclyl; wherein R^1 and R^2 independently of each other may be optionally substituted on carbon by one or more R^5 ; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^6 ; wherein

R^5 is C_{1-6} alkoxy; and

R^6 is C_{1-6} alkyl.

R^1 and R^2 are independently selected from C_{1-6} alkoxy or heterocyclyl; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^6 ; wherein R^6 is selected from C_{1-6} alkyl.

R^1 and R^2 are independently selected from C_{1-6} alkoxy or piperazinyl; wherein R^1 and R^2 independently of each other may be optionally substituted on carbon by one or more R^5 ; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^6 ; wherein

R^5 is C_{1-6} alkoxy; and

R⁶ is C₁₋₆alkyl.

R¹ and R² are independently selected from C₁₋₆alkoxy or piperazinyl; wherein said piperazinyl may be optionally substituted on nitrogen by a group selected from R⁶; wherein R⁶ is selected from C₁₋₆alkyl.

5 R¹ and R² are independently selected from methoxy, ethoxy or piperazin-1-yl; wherein R¹ and R² independently of each other may be optionally substituted on carbon by one or more R⁵; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R⁶; wherein

R⁵ is methoxy; and

10 R⁶ is methyl, ethyl, isopropyl or *t*-butyl.

R¹ and R² are independently selected from methoxy, ethoxy or piperazinyl; wherein said piperazinyl may be optionally substituted on nitrogen by a group selected from R⁶; wherein R⁶ is selected from methyl, ethyl or isopropyl.

15 R¹ and R² are independently selected from 2-methoxyethoxy, ethoxy, methoxy, 4-ethylpiperazin-1-yl, 4-isopropylpiperazin-1-yl, 4-methylpiperazin-1-yl or 4-*tert*-butylpiperazin-1-yl.

R¹ and R² are independently selected from methoxy, ethoxy, 1-methylpiperazin-4-yl, 1-ethylpiperazin-4-yl or 1-isopropylpiperazin-4-yl.

20 R¹ and R² are both methoxy or R¹ is ethoxy and R² is selected from 1-methylpiperazin-4-yl, 1-ethylpiperazin-4-yl or 1-isopropylpiperazin-4-yl.

R¹ and R² are both methoxy.

R¹ is ethoxy and R² is selected from 1-methylpiperazin-4-yl, 1-ethylpiperazin-4-yl or 1-isopropylpiperazin-4-yl.

R¹ is 2-methoxyethoxy, ethoxy or methoxy.

25 R² is 4-ethylpiperazin-1-yl, 4-isopropylpiperazin-1-yl, 4-methylpiperazin-1-yl, 4-*tert*-butylpiperazin-1-yl or methoxy.

R¹ is 2-methoxyethoxy, ethoxy or methoxy and R² is 4-ethylpiperazin-1-yl, 4-isopropylpiperazin-1-yl, 4-methylpiperazin-1-yl, 4-*tert*-butylpiperazin-1-yl or methoxy.

R³ is hydrogen.

30 m is 0.

m is 1.

R⁴ is selected from halo or methyl.

R⁴ is selected from fluoro, chloro or methyl.

n is 2; wherein the values of R^4 are the same or different.

R^4 , n and the phenyl to which they are attached form 2,3-dichlorophenyl, 2,4-difluorophenyl, 2-fluoro-4-methyl-phenyl, 2-fluoro-5-methyl-phenyl or 3-chloro-2-fluoro-phenyl.

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

R^1 and R^2 are independently selected from C_{1-6} alkoxy or heterocyclyl; wherein R^1 and R^2 independently of each other may be optionally substituted on carbon by one or more R^5 ; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^6 ;

10 R^3 is hydrogen;

m is 0;

R^4 is selected from halo or methyl;

n is 2; wherein the values of R^4 are the same or different;

15 R^5 is C_{1-6} alkoxy; and

R^6 is C_{1-6} alkyl;

or a pharmaceutically acceptable salt thereof.

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

20 R^1 and R^2 are independently selected from C_{1-6} alkoxy or heterocyclyl; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^6 ; wherein R^6 is selected from C_{1-6} alkyl;

R^3 is hydrogen;

m is 0;

25 R^4 is selected from halo or methyl; and

n is 2; wherein the values of R^4 are the same or different;

or a pharmaceutically acceptable salt thereof.

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

30 R^1 and R^2 are independently selected from 2-methoxyethoxy, ethoxy, methoxy, 4-ethylpiperazin-1-yl, 4-isopropylpiperazin-1-yl, 4-methylpiperazin-1-yl or 4-*tert*-butylpiperazin-1-yl;

R^3 is hydrogen;

m is 0;

R⁴ is selected from fluoro, chloro or methyl; and

n is 2; wherein the values of R⁴ are the same or different;

or a pharmaceutically acceptable salt thereof.

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

R¹ and R² are independently selected from methoxy, ethoxy, 1-methylpiperazin-4-yl, 1-ethylpiperazin-4-yl or 1-isopropylpiperazin-4-yl;

R³ is hydrogen;

10 m is 0;

R⁴ is selected from fluoro, chloro or methyl; and

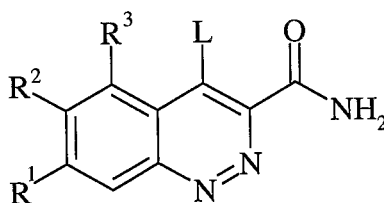
n is 2; wherein the values of R⁴ are the same or different;

or a pharmaceutically acceptable salt thereof.

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

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

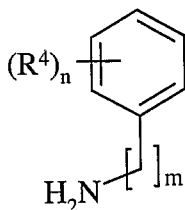
Process a) reacting a compound of formula (II):



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(II)

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

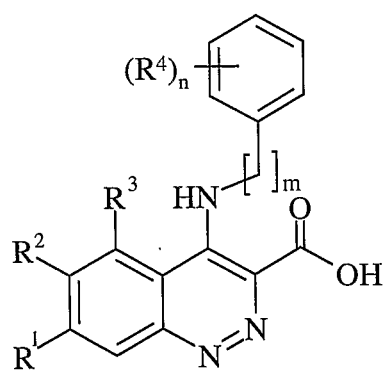


(III)

25 or

Process b) reacting a compound of formula (IV):

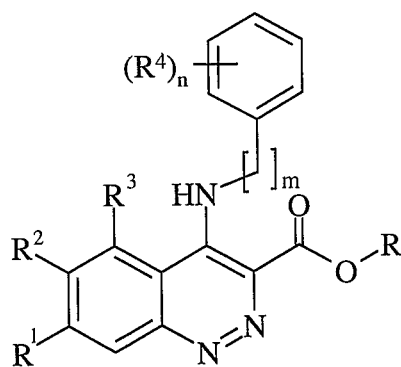
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(IV)

or an activated derivative thereof; with ammonia;

Process c) reacting a compound of formula (V):

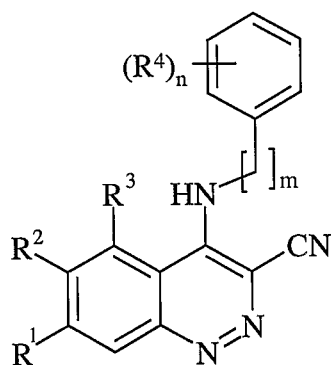


(V)

wherein R is C₁₋₆alkyl, in particular methyl and ethyl; with formamide and a base;

or

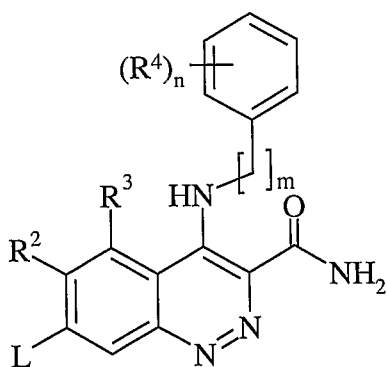
Process d) hydrolysis of a compound of formula (VI):



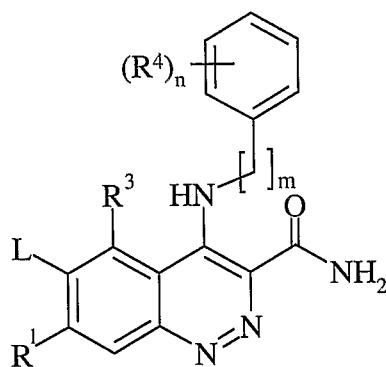
(VI)

or

Process e) for compounds of formula (I) when one of R¹ and R² is a carbon linked group; by reaction of a compound of formula (VIIa) or (VIIb):

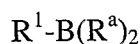


(VIIa)

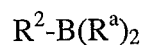


(VIIb)

wherein L is a displaceable group; with a compound of formula (VIIIa) or (VIIIb):



(VIIIa)

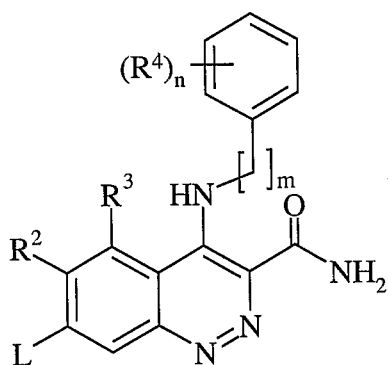


(VIIIb)

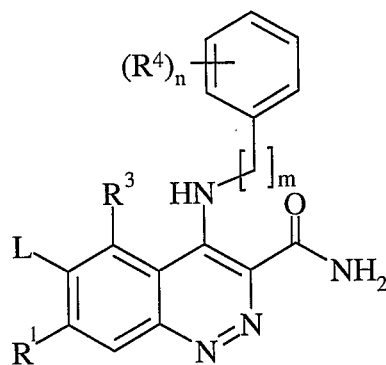
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wherein $-B(R^a)_2$ is a boronic acid derivative or trialkylborane; or

Process f) for compounds of formula (I) when one of R¹ and R² is a nitrogen linked group; by reaction of a compound of formula (IXa) or (IXb):



(IXa)



(IXb)

10

wherein L is a displaceable group; with a compound of formula (Xa) or (Xb):



(Xa)



(Xb)

and thereafter if necessary:

- 15
- i) converting a compound of the formula (I) into another compound of the formula (I);
 - 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.

$-B(R^a)_2$ is a boronic acid derivative, suitable examples of boronic acid derivatives include dihydroxyboryl, 4,4,5,5-tetramethyl-1,3,2-dioxaborolanyl; a suitable example of a trialkylborane is 9-borabicyclo[3.3.1]nonyl.

Specific reaction conditions for the above reactions are as follows.

5 *Process a)* Compounds of formula (II) can be reacted with compounds of formula (III) 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.

Alternatively, compounds of formula (II) can be reacted with compounds of formula (III) using coupling chemistry utilizing an appropriate catalyst and ligand such as $Pd_2(dba)_3$ and BINAP respectively and a suitable base such as sodium *tert*-butoxide or cesium carbonate. The reaction usually requires thermal conditions often in the range of 80 °C to 100 °C.

Compounds of formula (II) may be prepared by a modification of *Scheme 1* or *Scheme 2* (see below).

15 Compounds of formula (III) 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 b) Acids of formula (IV) and ammonia may be coupled together in the presence of a suitable coupling reagent. Standard peptide coupling reagents known in the art can be employed as suitable coupling reagents, for example carbonyldiimidazole and dicyclohexylcarbodiimide, 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.

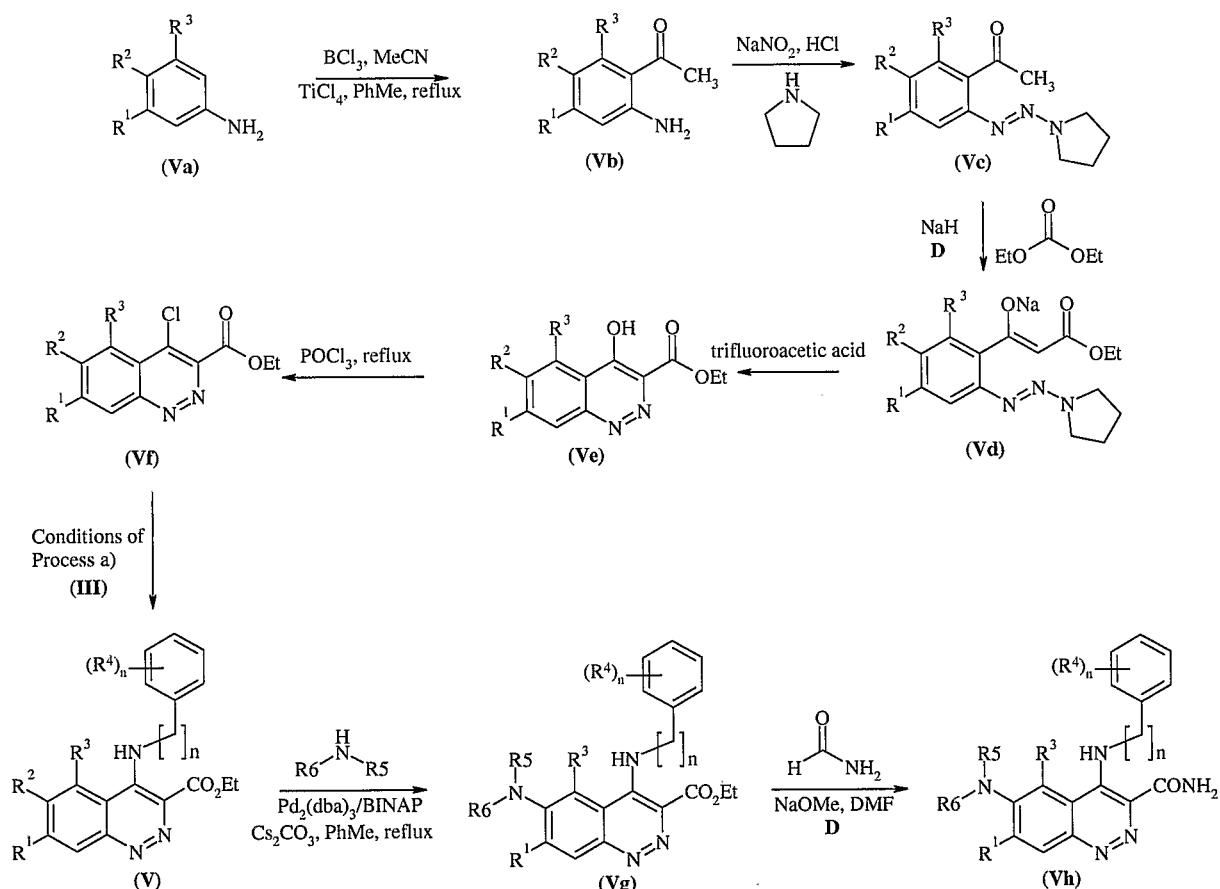
Compounds of formula (IV) may be prepared by a modification of *Scheme 1* or *Scheme 2* (see below).

Process c) Esters of formula (V) 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 (V) may be prepared according to *Scheme 1*.



Scheme 1

Compounds of formula (Va) and (Vb) 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 d) Compounds of formula (VI) can be hydrolysed under standard acidic or basic conditions.

Compounds of formula (VI) may be prepared by a modification of *Scheme 1* or *Scheme 2*.

Process e) Compounds of formula (VIIa) and (VIIb) can be reacted with boronic acid derivatives of formula (VIIIa) and (VIIIb) using a palladium catalyst and a base. A suitable catalyst is $\text{Pd}(\text{PPh}_3)_4$ and a suitable base is potassium carbonate. The reaction is typically performed at a temperature of 100 °C, or under microwave conditions, in a suitable solvent system such as dioxane/water.

Compounds of formula (VIIa) and (VIIb) can be reacted with trialkylboranes of formula (VIIIa) and (VIIIb) under standard Suzuki conditions, for example using a Pd catalyst in the presence of a base in a suitable solvent, for example, DMF typically at 50°C.

Compounds of formula (VIIa) and (VIIb) may be prepared by a modification of *Scheme 1* or *Scheme 2*.

Compounds of formula (VIIIa) and (VIIIb) are commercially available compounds or they are literature compounds or they are readily prepared by processes known to the person skilled in the art.

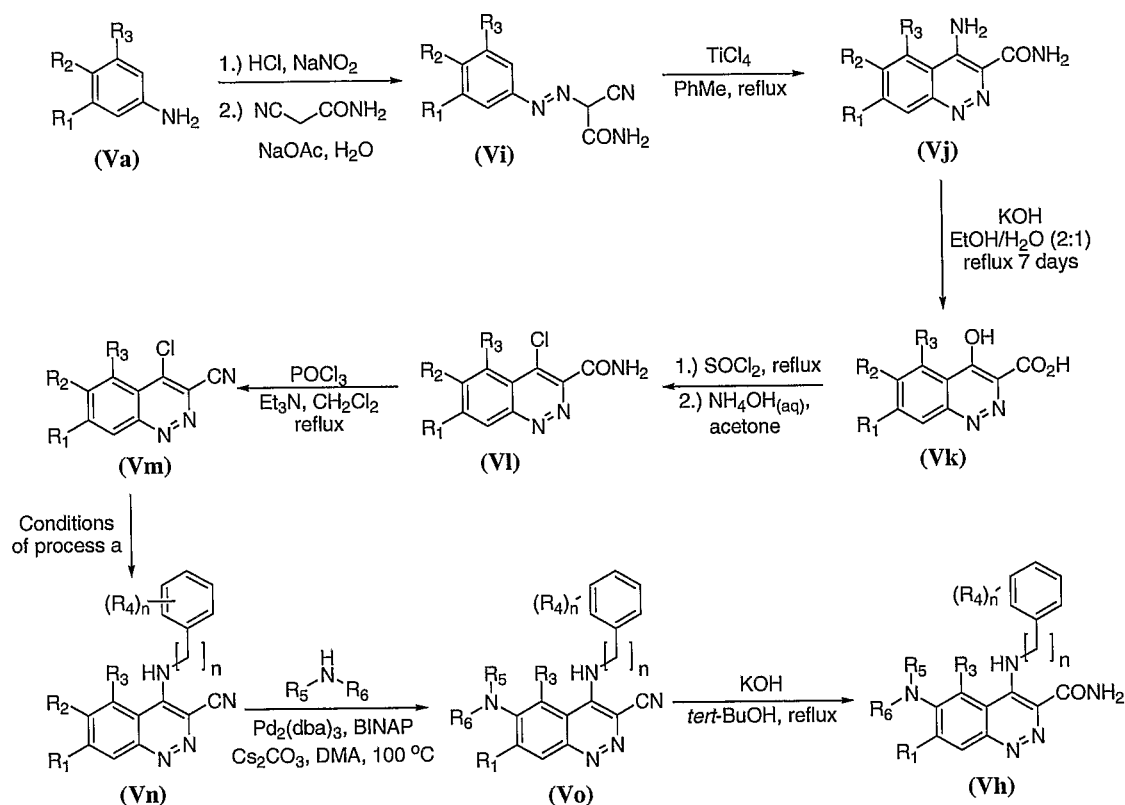
Process f) Compounds of formula (IXa) and (IXb) can be reacted with amines of formula (Xa) and (Xb) using a palladium catalyst a ligand and a base. A suitable catalyst is $\text{Pd}_2(\text{dba})_3$, a suitable ligand is BINAP and a suitable base is caesium carbonate. The reaction is typically performed at a temperature of 100 °C, or under microwave conditions, in a suitable solvent system such as toluene or dimethylacetamide.

Compounds of formula (IXa) and (IXb) may be prepared by a modification of *Scheme 1* or *Scheme 2*.

Compounds of formula (Xa) and (Xb) are commercially available compounds or they are literature compounds or they are readily prepared by processes known to the person skilled in the art.

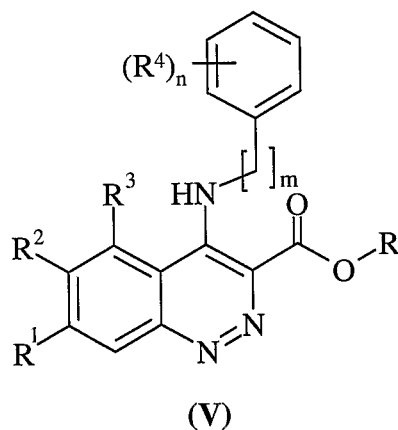
An alternative scheme for preparing certain compounds of formula (I) which can be modified to prepare certain intermediates described herein above is shown in *Scheme 2*:

- 25 -



Scheme 2

In some embodiments, the invention relates to a process of producing a compound of formula (I) as disclosed herein comprising reacting a compound of formula (V):



5

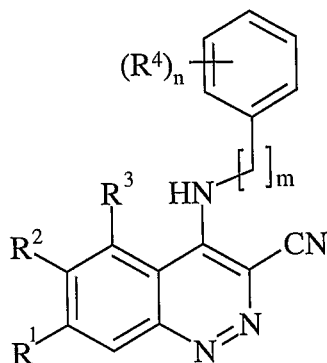
wherein R is C₁₋₆alkyl with formamide and a base, such that a compound of formula (I) is formed;

and optionally thereafter:

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

In further embodiments, R is selected from methyl and ethyl.

In some embodiments, the invention relates to a process of producing a compound of formula (I) as disclosed herein comprising hydrolyzing a compound of formula (VI):



(VI)

such that a compound of formula (I) is formed;

and optionally thereafter:

i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups; or

iii) forming a pharmaceutically acceptable salt.

In further embodiments, hydrolyzing is performed by mixing a compound of formula (VI) with a metal hydroxide and a branched alkyl alcohol.

In further embodiments, said metal hydroxide is potassium hydroxide.

In further embodiments, said branched alkyl alcohol is a tertiary alcohol such as tert-butyl alcohol.

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.

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 these are provided as a further feature of the invention.

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

In some embodiments, the invention relates to a method of treating cancer comprising providing a subject at risk for, diagnosed with, or exhibiting symptoms of cancer and administering a pharmaceutical composition comprising a compound of formula (I) as
20 disclosed herein to said subject.

In some embodiments, the invention relates to a method of inhibiting CSF-1R kinase comprising providing a CSF-1R kinase and a compound of formula (I) as disclosed herein, and mixing under conditions such that CSF-1R kinase is inhibited.

25 **Biological Activity**

Assay 1: CSF-1R *in vitro* AlphaScreen assay

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
30 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 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 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, 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).

Assay 2: CSF1R in-vitro AlphaScreen assay

Activity of purified CSF-1R was determined in-vitro using an Amplified Luminescent Proximity Homogeneous Assay (ALPHA) (Perkin Elmer, MA), which measures phosphorylation of 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) 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 322ug/l of cell pellet at >95% purity.

The phosphorylation of the CSF-1R substrate in the presence and absence of the compound of interest was determined. Briefly, 5ul of Enzyme/Substrate/adenosine triphosphate (ATP) mix consisting of 0.46nM of purified CSF-1R, 12nM pEY substrate, and 12mM ATP in 1.2x buffer was preincubated with 2ul of compound for 20 minutes at 25 °C. Reactions were initiated with 5ul of Metal mix consisting of 24mM MgCl₂ in 1.2x buffer and incubated at 25 °C for 90 minutes and reactions were stopped by addition of 5ul of Detection mix consisting of 20mM HEPES, 102mM ethylenediamine tetraacetic acid, 1.65mg/ml BSA, 136mM NaCl, 40ug/ml Streptavidin donor beads (Perkin Elmer, MA, Catalog #6760002), and 40ug/ml phosphotyrosine-specific antibody coated acceptor beads (Perkin Elmer, MA, Catalog #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).

When tested in one or other of the above *in vitro* assays, the compounds of the present invention generally exhibited activity less than 30 μ M. For example the following results

5 were obtained in an assay substantially similar to one or other of the assays described hereinabove:

Example No		Assay 1 IC ₅₀	Assay 2 IC ₅₀
1		< 3 nM	
2		8 nM	
3		< 3 nM	
4		5 nM	
5		< 3 nM	
6		< 3 nM	
7		< 4 nM	
8		3 nM	
9		< 15 nM	
10		< 3 nM	
11		8 nM	
12		5 nM	
13		< 3 nM	
14		< 3 nM	
15		< 4 nM	
16		9 nM	
17		< 3 nM	
18		< 3 nM	
19		< 3 nM	
20		< 3 nM	
21		< 3 nM	
22		< 3 nM	
23		< 5 nM	
24		< 3 nM	

Example No		Assay 1 IC ₅₀	Assay 2 IC ₅₀
25		< 3 nM	
26		51 nM	
27		< 3 nM	
28		< 3 nM	
29			7 nM
30			10 nM
31			13 nM
32			8 nM
33			12 nM
34			5 nM
35			< 9 nM
36			< 3 nM
37			71 nM
38			< 3 nM
39			< 3 nM
40			< 3 nM
41			< 3 nM
42			7 nM
43			3nM
44			16nM
45			6nM
46			
47			6 nM
48			< 3 nM

Example No		Assay 1 IC ₅₀	Assay 2 IC ₅₀
49			20 nM
50			33 nM
51			

Example No		Assay 1 IC ₅₀	Assay 2 IC ₅₀
52			
53			
54			

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

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

The compound of formula (I) 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 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.

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

We have found that the compounds defined in the present invention, or a pharmaceutically acceptable salt thereof, are effective anti-cancer agents which property is 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.

In a further aspect of the invention, compounds of formula (I) 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 (I), 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 of the formula (I), 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 (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the
5 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 (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of breast, ovarian, bladder,
10 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 chronic lymphocytic leukemia; and glioma, squamous cell carcinoma of the esophagus, malignant uveal melanoma and follicular lymphoma.

15 According to a further feature of the invention, there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore 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
20 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
25 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 (I), or a pharmaceutically acceptable salt thereof, as defined above.

According to a further feature of this aspect of the invention there is provided a
30 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 (I), 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 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 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 (I) or a pharmaceutically acceptable salt thereof as defined herein before.

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 treatment which comprises administering to said animal an effective amount of a compound of formula (I) 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 (I), or a pharmaceutically acceptable salt thereof, as defined herein before 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.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt thereof, as defined herein before 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.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I), 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 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
5 which comprises a compound of the formula (I), 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 ovariectomy-induced bone loss, orthopedic implant failure, autoimmune disorders including systemic lupus erythematosus, arthritis including rheumatoid arthritis, osteoarthritis, renal inflammation and
10 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.

According to a further aspect of the invention there is provided the use of a compound
15 of the formula (I), 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 man.

According to this aspect of the invention there is provided the use of a compound of the formula (I), 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.

20 According to a further feature of the invention, there is provided the use of a compound of the formula (I), 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
25 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 (I), or a pharmaceutically acceptable salt thereof, as defined herein
30 before 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 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.

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 oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside and hydroxyurea; antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);
- (ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and 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 finasteride;
- (iii) Agents which inhibit cancer cell invasion (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);
- (iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies (for example the anti-erbB2 antibody trastuzumab [HerceptinTM] 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;

- 5 (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
- 10 $\alpha v \beta 3$ 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
- 15 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
- 20 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
- 25 cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies;
- (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
- 30 deacetylase inhibitors; and
- (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 employ the compounds of this invention within the dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

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

10 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.

Examples

15 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;

(ii) organic solutions were dried over anhydrous sodium sulphate or magnesium sulphate;

20 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;

25 (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,

30 determined at 400 MHz using perdeuterio dimethyl sulphoxide (DMSO-d₆) as solvent unless otherwise indicated;

(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 are given; generally, only ions which indicate the parent mass are reported; and unless

5 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) "H-Cube" refers to the H-Cube continuous hydrogenation equipment manufactured by Thales Nanotechnology

10 and

(xii) the following abbreviations have been used:

DMA	<i>N,N</i> -dimethylacetamide
DMF	<i>N,N</i> -dimethylformamide;
EtOAc	ethyl acetate;
15 MeOH	methanol;
THF	tetrahydrofuran;
TFA	trifluoroacetic acid;
DMSO	dimethylsulphoxide; and
DCM	dichloromethane.

20

Example 1

4-[(2,4-Difluorophenyl)amino]-6,7-dimethoxycinnoline-3-carboxamide

To a 25 mL round bottom flask charged with a magnetic stir bar was added ethyl 4-[(2,4-difluorophenyl)amino]-6,7-dimethoxycinnoline-3-carboxylate (0.195 g, 0.50 mmol)
25 (Method 27), anhydrous DMF (3 mL), formamide (0.135 g, 3 mmol), and 3 mL of a 0.5 M solution of sodium methoxide in MeOH. The reaction was warmed to 100 °C for 2 h before being allowed to cool to rt. The reaction was poured over water (~ 50 mL) and the crude product precipitated from solution. The solid was collected via vacuum filtration using a Buchner funnel and was purified on 40 g silica using EtOAc/MeOH (4:1) as eluent providing
30 0.174 g (96 %) of the title compound as a white solid. 1H NMR: 11.35 (s, 1 H), 8.86 (s, 1 H), 8.05 (s, 1 H), 7.71 (s, 1 H), 7.48 (m, 1 H), 7.38 (m, 1 H), 7.18 (m, 1 H), 6.69 (s, 1 H), 4.06 (s, 3 H), 3.50 (s, 3 H); m/z 361.

Examples 2-12

The following examples were prepared according to the procedure in Example 1 using the appropriate starting material, and were purified either by silica gel chromatography or semi-preparative reverse phase HPLC.

Ex.	Compound	¹ H NMR (300 MHz)	m/z	Starting Material
2	4-[(2-Fluoro-4-methylphenyl)amino]-6,7-dimethoxycinnoline-3-carboxamide	11.26 (s, 1 H), 8.80 (s, 1 H), 7.95 (s, 1 H), 7.65 (s, 1 H), 7.15 (m, 2 H), 7.05 (d, 1 H), 6.62 (s, 1 H), 4.00 (s, 3 H), 3.37 (s, 3 H), 2.30 (s, 3 H)	357	ethyl 4-[(2-fluoro-4-methylphenyl)amino]-6,7-dimethoxycinnoline-3-carboxylate (Method 29)
3	4-[(3-Chloro-2-fluorophenyl)amino]-6,7-dimethoxycinnoline-3-carboxamide	11.35 (s, 1 H), 8.85 (s, 1 H), 8.05 (s, 1 H), 7.70 (s, 1 H), 7.35 (t, 1 H), 7.17 (t, 1 H), 7.05 (t, 1 H), 6.70 (s, 1 H), 4.05 (s, 3 H), 3.48 (s, 3 H)	378	ethyl 4-[(3-chloro-2-fluorophenyl)amino]-6,7-dimethoxycinnoline-3-carboxylate (Method 30)
4	4-[(2-Fluoro-5-methylphenyl)amino]-6,7-dimethoxycinnoline-3-carboxamide	11.30 (s, 1 H), 8.80 (s, 1 H), 7.98 (s, 1 H), 7.65 (s, 1 H), 7.20 (m, 1 H), 7.03 (m, 2 H), 6.65 (s, 1 H), 4.00 (s, 3 H), 3.40 (s, 3 H), 2.22 (s, 3 H)	357	ethyl 4-[(2-fluoro-5-methylphenyl)amino]-6,7-dimethoxycinnoline-3-carboxylate (Method 31)
5	4-[(2,3-Dichlorophenyl)amino]-6,7-dimethoxycinnoline-3-carboxamide	11.50 (s, 1 H), 8.89 (s, 1 H), 8.05 (s, 1 H), 7.71 (s, 1 H), 7.40 (d, 1 H), 7.25 (t, 1 H), 6.90 (d, 1 H), 6.55 (s, 1 H), 4.00 (s, 3 H), 3.50 (s, 3 H)	394	ethyl 4-[(2,3-dichlorophenyl)amino]-6,7-dimethoxycinnoline-3-carboxylate (Method 32)

Ex.	Compound	¹ H NMR (300 MHz)	m/z	Starting Material
6	7-Ethoxy-4-[(2-fluoro-5-methylphenyl)amino]-6-(4-methylpiperazin-1-yl)cinnoline-3-carboxamide	8.78 (s, 1 H), 7.85 (s, 1 H), 7.56 (s, 1 H), 7.31-7.15 (m, 2 H), 7.03 (d, 2 H), 6.64 (s, 1 H), 4.26 (q, 2 H), 2.76 (s, 4 H), 2.33 (s, 4 H), 2.27 (s, 3 H), 2.12 (s, 3 H), 1.42 (t, 3 H)	440	ethyl 7-ethoxy-4-[(2-fluoro-5-methylphenyl)amino]-6-(4-methylpiperazin-1-yl)cinnoline-3-carboxylate (Method 47)
7	4-[(2,4-Difluorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)cinnoline-3-carboxamide	11.90 (s, br, 1 H), 8.62 (s, 1 H), 8.07 (s, 1 H), 7.60 (s, 1 H), 7.50 (m, 2 H), 7.20 (m, 1 H), 7.00 (s, br, 1 H), 4.30 (q, 2 H), 3.50 (m, 4 H), 3.13 (m, 2 H), 2.90 (m, 2 H), 3.80 (d, 3 H), 1.50 (t, 3 H)	443	ethyl 4-[(2,4-difluorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)cinnoline-3-carboxylate (Method 48)
8	4-[(2,3-Dichlorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)cinnoline-3-carboxamide	11.48 (s, 1 H), 8.84 (s, 1 H), 8.01 (s, 1 H), 7.61 (s, 1 H), 7.41 (s, 1 H), 7.26 (t, 1 H), 6.94 (s, 1 H), 6.45 (s, 1 H), 4.28 (d, 2 H), 2.81 (s, 4 H), 2.33 (s, 4 H), 2.15 (s, 3 H), 1.42 (t, 3 H)	476	ethyl 4-[(2,3-dichlorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)cinnoline-3-carboxylate (Method 49)
9	4-[(3-Chloro-2-fluorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)cinnoline-3-carboxamide	11.36 (s, 1 H), 8.83 (s, 1 H), 8.00 (s, 1 H), 7.60 (s, 1 H), 7.38 (t, 1 H), 7.17 (d, 2 H), 6.58 (s, 1 H), 4.28 (q, 2 H), 2.80 (s, 4 H), 2.32 (s, 4 H), 2.15 (s, 3 H), 1.42 (t, 3 H)	460	ethyl 4-[(3-chloro-2-fluoro-phenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)cinnoline-3-carboxylate (Method 50)

Ex.	Compound	¹ H NMR (300 MHz)	m/z	Starting Material
10	7-Ethoxy-4-[(2-fluoro-4-methyl-phenyl)amino]-6-(4-methylpiperazin-1-yl)cinnoline-3-carboxamide	11.27 (s, 1 H), 8.75 (s, 1 H), 7.91 (s, 1 H), 7.53 (s, 1 H), 7.18 (d, 2 H), 7.05 (s, 1 H), 6.59 (s, 1 H), 4.25 (d, 2 H), 2.74 (s, 4 H), 2.32 (s, 7 H), 2.17 (s, 3 H), 1.41 (t, 3 H)	439	ethyl 7-ethoxy-4-[(2-fluoro-4-methyl-phenyl)amino]-6-(4-methylpiperazin-1-yl)cinnoline-3-carboxylate (Method 51)
11	4-[(2,4-Difluorophenyl)amino]-7-ethoxy-6-(4-propan-2-ylpiperazin-1-yl)cinnoline-3-carboxamide	11.25 (s, 1 H), 8.78 (s, 1 H), 7.94 (s, 1 H), 7.56 (s, 1 H), 7.38 - 7.50 (m, 1 H), 7.24 - 7.38 (m, 1 H), 7.02 - 7.17 (m, 1 H), 6.55 (s, 1 H), 4.26 (q, 2 H), 2.78 (s, 4 H), 2.60-2.64 (m, 1 H), 2.47 (s, 4 H), 1.42 (t, 3 H), 0.96 (d, 6 H)	472	ethyl 4-[(2,4-difluorophenyl)amino]-7-ethoxy-6-(4-propan-2-ylpiperazin-1-yl)cinnoline-3-carboxylate (Method 52)
12	4-[(2,4-Difluorophenyl)amino]-7-ethoxy-6-(4-ethylpiperazin-1-yl)cinnoline-3-carboxamide	11.20 (s, 1 H), 7.90 (s, 1 H), 7.50 (s, 1 H), 7.39 (t, 1 H), 7.25 (t, 1 H), 7.06 (t, 1 H), 6.51 (s, 1 H), 4.25 (q, 2 H), 3.30 (q, 2 H), 2.70 (s, 4 H), 2.30 (s, 4 H), 1.37 (t, 3 H), 0.90 (t, 3 H)	457	ethyl 4-[(2,4-difluorophenyl)amino]-7-ethoxy-6-(4-ethylpiperazin-1-yl)cinnoline-3-carboxylate (Method 53)

Examples 6-12 were in some cases also prepared from the appropriate intermediates according to procedures similar to those described for Example 13 and Methods 47, 27 and 24.

4-(2-Fluoro-4-methylphenylamino)-7-methoxy-6-(4-methylpiperazin-1-yl)cinnoline-3-carboxamide

A 100 mL round bottom flask was charged with 4-(2-fluoro-4-methylphenylamino)-7-methoxy-6-(4-methylpiperazin-1-yl)cinnoline-3-carbonitrile (Method 60) (360 mg, 0.89 mmol) and potassium hydroxide (4.9 g, 88.6 mmol). Anhydrous *tert*-butyl alcohol (30 ml) was added and the reaction was heated at vigorous reflux 1 h before being allowed to cool to rt. The reaction mixture was then poured into a separatory funnel containing water (~ 100 mL) and extracted with EtOAc (2 X 200 mL). The combined organic layer was washed with sat'd aqueous NaCl (~ 100 mL), dried with MgSO₄, filtered, and conc. *in vacuo* to give the crude product which was purified via silica gel chromatography (40 g) using EtOAc/MeOH (1:1) as eluent to give the title compound as a yellow solid. The solid was then recrystallized from 5 mL of MeOH which provided pure title compound (184 mg, 48.9 %) as a pale yellow solid. ¹H NMR: 11.60 (s, 1 H), 8.55 (s, 1 H), 7.85 (s, 1 H), 7.16 (s, 1 H), 7.37 (m, 2 H), 7.10 (m, 1 H), 6.21 (s, 1 H), 4.05 (s, 3 H), 2.46 (s, br, 4 H), 2.70-2.60 (m, 7 H), 2.35 (s, 3 H); *m/z* 425.

Examples 14-46

The following examples were prepared according to the procedure of Example 13 using the appropriate starting material and purified by silica gel chromatography or semi-preparative reverse phase HPLC. The resulting materials were subsequently recrystallized where necessary.

Example	Compound	¹ H NMR (300 MHz)	<i>m/z</i>	Starting Material
14	4-[(3-Chloro-2-fluorophenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)cinnoline-3-carboxamide	11.38 (s, 1 H), 8.84 (s, 1 H), 8.00 (s, 1 H), 7.64 (s, 1 H), 7.39 (s, 1 H), 7.09 - 7.24 (m, 2 H), 6.60 (s, 1 H), 4.02 (s, 3 H), 2.79 (s, 4 H), 2.35 (s, 4 H), 2.17 (s, 3 H)	446	4-[(3-chloro-2-fluorophenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)cinnoline-3-carbonitrile Method 54

Example	Compound	¹ H NMR (300 MHz)	m/z	Starting Material
15	4-[(2-Fluoro-4-methylphenyl)amino]-6-(4-isopropylpiperazin-1-yl)-7-methoxycinnoline-3-carboxamide	11.29 (s, 1 H), 8.77 (s, 1 H), 7.91 (s, 1 H), 7.56 (s, 1 H), 7.17 (t, 2 H), 7.04 (d, 1 H), 6.60 (s, 1 H), 3.99 (s, 3 H), 2.69 (s, 4 H), 2.55 - 2.66 (m, 1 H), 2.42 (s, 4 H), 2.32 (s, 3 H), 0.94 (d, 6 H)	453	4-[(2-fluoro-4-methylphenyl)amino]-6-(4-isopropylpiperazin-1-yl)-7-methoxycinnoline-3-carbonitrile Method 55
16	6-(4- <i>tert</i> -Butylpiperazin-1-yl)-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carboxamide	11.31 (s, 1 H), 8.76 (s, 1 H), 7.90 (s, 1 H), 7.56 (s, 1 H), 7.13 - 7.24 (m, 2 H), 7.06 (s, 1 H), 6.59 (s, 1 H), 3.99 (s, 3 H), 2.69 (s, 4 H), 2.50 (s, 4 H), 2.32 (s, 3 H), 0.99 (s, 9 H)	467	6-(4- <i>tert</i> -butylpiperazin-1-yl)-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile Method 56
17	4-[(2,4-Difluorophenyl)amino]-7-(2-methoxyethoxy)-6-(4-methylpiperazin-1-yl)cinnoline-3-carboxamide	10.65 (s, br, 1 H), 8.60 (s, 1 H), 7.95 (s, 1 H), 7.68 (s, 1 H), 7.39 (m, 2 H), 7.10 (t, 1 H), 6.82 (s, br, 1 H), 4.30 (s, 2 H), 3.75 (s, 2 H), 3.65 (m, 2 H), 3.40 (m, 2 H), 3.30 (s, 3 H), 3.05 (m, 2 H), 2.80 (m, 2 H), 2.72 (s, 3 H)	473	4-[(2,4-difluorophenyl)amino]-7-(2-methoxyethoxy)-6-(4-methylpiperazin-1-yl)cinnoline-3-carbonitrile Method 61

Example	Compound	¹ H NMR (300 MHz)	m/z	Starting Material
18	4-[(2-Fluoro-4-methylphenyl)amino]-7-(2-methoxyethoxy)-6-(4-methylpiperazin-1-yl)cinnoline-3-carboxamide	10.90 (s, br, 1 H), 8.64 (s, 1 H), 8.03 (s, 1 H), 7.58 (s, 1 H), 7.28 (m, 1 H), 7.20 (d, 1 H), 7.05 (d, 1 H), 6.75 (s, br, 1 H), 4.30 (m, 2 H), 3.70 (m, 2 H), 3.35 (m, 4 H), 3.30 (s, 3 H), 3.01 (m, 2 H), 2.75 (m, 5 H), 2.35 (s, 3 H)	469	4-[(2-fluoro-4-methylphenyl)amino]-7-(2-methoxyethoxy)-6-(4-methylpiperazin-1-yl)cinnoline-3-carbonitrile Method 62
19	4-[(2-Fluoro-5-methylphenyl)amino]-7-(2-methoxyethoxy)-6-(4-methylpiperazin-1-yl)cinnoline-3-carboxamide	11.05 (s, br, 1 H), 8.65 (s, 1 H), 8.05 (s, 1 H), 7.60 (s, 1 H), 7.25-7.10 (m, 3 H), 6.81 (s, br, 1 H), 4.30 (m, 2 H), 3.73 (m, 2 H), 3.31 (m, 4 H), 3.30 (s, 3 H), 3.01 (m, 2 H), 2.80 (m, 2 H), 2.70 (s, 3 H), 2.20 (s, 3 H),	469	4-[(2-fluoro-5-methylphenyl)amino]-7-(2-methoxyethoxy)-6-(4-methylpiperazin-1-yl)cinnoline-3-carbonitrile Method 63
20	4-[(2,4-Difluorophenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)cinnoline-3-carboxamide	11.30 (s, 1 H), 8.85 (s, 1 H), 7.97 (s, 1 H), 7.65 (s, 1 H), 7.47 (m, 1 H), 7.36 (m, 1 H), 7.16 (m, 1 H), 6.62 (s, 1 H), 4.08 (s, 3 H), 2.82 (s, 4 H), 2.35 (s, 4 H), 2.20 (s, 3 H)	429	4-[(2,4-difluorophenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)cinnoline-3-carbonitrile Method 57

Example	Compound	¹ H NMR (300 MHz)	m/z	Starting Material
21	4-[(3-Chloro-2-fluorophenyl)amino]-7-(2-methoxyethoxy)-6-(4-methylpiperazin-1-yl)cinnoline-3-carboxamide	11.30 (s, 1 H), 8.85 (s, 1 H), 7.90 (s, 1 H), 7.57 (s, 1 H), 7.30 (m, 1 H), 7.12 (m, 1 H), 7.08 (m, 1 H), 6.52 (s, 1 H), 4.26 (m, 2 H), 3.70 (m, 2 H), 3.25 (s, 3 H), 2.80 (m, 4 H), 2.29 (m, 4 H), 2.12 (s, 3 H)	490	4-[(3-chloro-2-fluorophenyl)amino]-7-(2-methoxyethoxy)-6-(4-methylpiperazin-1-yl)cinnoline-3-carbonitrile Method 64
22	4-[(2-Fluoro-5-methylphenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)cinnoline-3-carboxamide	11.35 (s, 1 H), 8.80 (s, 1 H), 7.95 (s, 1 H), 7.60 (s, 1 H), 7.22 (m, 1 H), 7.05 (m, 2 H), 6.69 (s, 1 H), 4.01 (s, 3 H), 2.76 (s, 4 H), 2.30 (s, 4 H), 2.25 (s, 3 H), 2.16 (s, 3 H)	425	4-[(2-fluoro-5-methylphenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)cinnoline-3-carbonitrile Method 58
23	4-[(2-Fluoro-5-methylphenyl)amino]-6-(4-isopropylpiperazin-1-yl)-7-methoxycinnoline-3-carboxamide	11.38 (s, 1 H), 8.85 (s, 1 H), 8.01 (s, 1 H), 7.69 (s, 1 H), 7.30 (m, 1 H), 7.10 (m, 2 H), 6.72 (s, 1 H), 4.10 (s, 3 H), 2.81 (s, 4 H), 2.70 (m, 1 H), 2.50 (s, 4 H), 2.30 (s, 3 H), 1.02 (d, 6 H)	453	4-[(2-fluoro-5-methylphenyl)amino]-6-(4-isopropylpiperazin-1-yl)-7-methoxycinnoline-3-carbonitrile Method 59

Example	Compound	¹ H NMR (300 MHz)	m/z	Starting Material
24	4-[(2,4-Difluorophenyl)amino]-6-(4-isopropylpiperazin-1-yl)-7-(2-methoxyethoxy)cinnoline-3-carboxamide	11.00 (s, br, 1 H), 8.50 (s, 1 H), 7.99 (s, 1 H), 7.60 (s, 1 H), 7.40 (m, 2 H), 7.10 (m, 2 H), 4.30 (s, 2 H), 3.75 (s, 2 H), 3.60-3.40 (m, 8 H), 3.00 (m, 4 H), 1.21 (d, 6 H)	501	4-[(2,4-difluorophenyl)amino]-6-(4-isopropylpiperazin-1-yl)-7-(2-methoxyethoxy)cinnoline-3-carbonitrile Method 65
25	7-Ethoxy-4-[(2-fluoro-4-methylphenyl)amino]-6-(4-isopropylpiperazin-1-yl)cinnoline-3-carboxamide	11.02 (s, br, 1 H), 8.59 (s, 1 H), 8.05 (s, 1 H), 7.55 (s, 1 H), 7.29 (m, 1 H), 7.20 (d, 1 H), 7.08 (d, 1 H), 6.80 (s, br, 1 H), 4.25 (q, 2 H), 3.60 (m, 1 H), 3.30 (m, 4 H), 2.92 (m, 4 H), 2.30 (s, 3 H), 1.40 (t, 3 H), 1.25 (d, 6 H)	467	7-ethoxy-4-[(2-fluoro-4-methylphenyl)amino]-6-(4-isopropylpiperazin-1-yl)cinnoline-3-carbonitrile Method 66
26	4-[(2-Fluoro-4-methylphenyl)amino]-7-methoxy-6-pyridin-4-ylcinnoline-3-carboxamide	11.64 (s, 1 H), 8.84 (s, 1 H), 8.54 (d, 2 H), 8.00 (s, 1 H), 7.78 (s, 1 H), 7.58 (m, 3 H), 7.29 (m, 2 H), 7.15 (m, 1 H), 4.01 (s, 3 H), 2.37 (s, 3 H)	404	4-[(2-fluoro-4-methylphenyl)amino]-7-methoxy-6-pyridin-4-ylcinnoline-3-carbonitrile Method 84

Example	Compound	¹ H NMR (300 MHz)	m/z	Starting Material
27	7-Ethoxy-4-[(2-fluoro-4-methylphenyl)amino]-6-(4-methyl-1,4-diazepan-1-yl)cinnoline-3-carboxamide	11.14 (s, 1 H), 8.70 (s, 1 H), 7.86 (s, 1 H), 7.48 (s, 1 H), 7.17 (m, 1 H), 7.09 (m, 1 H), 7.01 (m, 1 H), 6.46 (s, 1 H), 4.24 (q, 2 H), 3.17 (m, 2 H), 2.96 (m, 2 H), 2.41 (m, 2 H), 2.31 (s, 3 H), 2.20 (m, 2 H), 1.69 (m, 2 H), 1.42 (t, 3 H)	453	7-ethoxy-4-[(2-fluoro-4-methylphenyl)amino]-6-(4-methyl-1,4-diazepan-1-yl)cinnoline-3-carbonitrile Method 67
28	6-[(3R,5S)-3,5-Dimethylpiperazin-1-yl]-7-ethoxy-4-[(2-fluoro-4-methylphenyl)amino]cinnoline-3-carboxamide	11.30 (s, 1 H), 8.73 (s, 1 H), 7.89 (s, 1 H), 7.51 (s, 1 H), 7.19 (m, 2 H), 7.06 (m, 1 H), 6.58 (s, 1 H), 4.25 (q, 2 H), 3.06 (d, 2 H), 2.75 (m, 2 H), 2.32 (s, 3 H), 1.79 (m, 2 H), 1.40 (t, 3 H), 0.85 (d, 6 H)	453	6-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-7-ethoxy-4-[(2-fluoro-4-methylphenyl)amino]cinnoline-3-carbonitrile Method 68

Example	Compound	¹ H NMR (300 MHz)	m/z	Starting Material
29	4-[(2-Fluoro-4-methylphenyl)amino]-6-(1-isopropyl-1,2,3,6-tetrahydropyridin-4-yl)-7-methoxycinnoline-3-carboxamide	12.37 (s, 1 H), 10.34 (s, 1 H), 8.77 (s, 1 H), 8.19 (s, 1 H), 7.64 (s, 1 H), 7.30 (m, 3 H), 7.11 (m, 1 H), 5.74 (s, 1 H), 4.01 (s, 3 H), 3.71 (m, 2 H), 3.47 (m, 2 H), 2.99 (m, 1 H), 2.71 (m, 1 H), 2.40 (s, 3 H), 2.31 (m, 1 H), 1.28 (d, 6 H) isolated as HCl salt	450	4-[(2-fluoro-4-methylphenyl)amino]-6-(1-isopropyl-1,2,3,6-tetrahydropyridin-4-yl)-7-methoxycinnoline-3-carbonitrile Method 86
30	4-[(2-Fluoro-4-methylphenyl)amino]-7-methoxy-6-[4-(2-methoxyethyl)piperazin-1-yl]cinnoline-3-carboxamide	11.29 (s, 1 H), 8.76 (s, 1 H), 7.91 (s, 1 H), 7.57 (s, 1 H), 7.19 (m, 2 H), 7.04 (m, 1 H), 6.60 (s, 1 H), 3.99 (s, 3 H), 3.41 (m, 2 H), 3.22 (s, 3 H), 2.71 (m, 4 H), 2.39 (m, 6 H), 2.32 (s, 3 H)	469	4-[(2-fluoro-4-methylphenyl)amino]-7-methoxy-6-[4-(2-methoxyethyl)piperazin-1-yl]cinnoline-3-carbonitrile Method 69
31	6-(5,6-Dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carboxamide	11.34 (s, 1 H), 8.79 (s, 1 H), 8.46 (s, 1 H), 7.95 (s, 1 H), 7.66 (s, 1 H), 7.23 (m, 2 H), 7.17 (m, 1 H), 6.75 (s, 1 H), 4.06 (m, 5 H), 3.97 (s, 2 H), 3.17 (s, 2 H), 2.41 (s, 3 H)	449	6-(5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile Method 70

Example	Compound	¹ H NMR (300 MHz)	m/z	Starting Material
32	4-[(2-Fluoro-4-methylphenyl)amino]-6-(3-hydroxy-2,5,6,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrazin-7(3H)-yl)-7-methoxycinnoline-3-carboxamide	11.18 (s, 1 H), 8.76 (s, 1 H), 7.91 (s, 1 H), 7.59 (s, 1 H), 7.20 (s, 1 H), 7.11 (m, 1 H), 7.04 (m, 2 H), 7.00 (m, 1 H), 6.86 (s, 1 H), 6.63 (s, 1 H), 3.99 (s, 3 H), 3.62 (s, 2 H), 3.07 (m, 2 H), 2.87 (m, 2 H), 2.34 (s, 3 H) Byproduct from synthesis of Ex 31	467	6-(5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile Method 70
33	4-[(2-Fluoro-4-methylphenyl)amino]-6-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-7-methoxycinnoline-3-carboxamide		451	4-[(2-fluoro-4-methylphenyl)amino]-6-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-7-methoxycinnoline-3-carbonitrile Method 71
34	4-[(2-Fluoro-4-methylphenyl)amino]-6-[1-(2-hydroxyethyl)-1,2,3,6-tetrahydropyridin-4-yl]-7-methoxycinnoline-3-carboxamide	MeOD 7.49 (s, 1 H), 7.41 (s, 2 H), 7.28 (m, 2 H), 5.73 (s, 1 H), 4.12 (s, 3 H), 4.04 (m, 1 H), 3.95 (t, 2 H), 3.84 (m, 1 H), 3.70 (m, 1 H), 3.37 (m, 3 H), 2.75 (m, 1 H), 2.54 (m, 1 H), 2.51 (s, 3 H)	452	6-[1-(2-{[<i>tert</i> -butyl(dimethyl)silyl]oxy}ethyl)-1,2,3,6-tetrahydropyridin-4-yl]-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile Method 87

Example	Compound	¹ H NMR (300 MHz)	m/z	Starting Material
35	4-[(2-Fluoro-4-methylphenyl)amino]-7-methoxy-6-morpholin-4-ylcinnoline-3-carboxamide	11.33 (s, 1 H), 8.77 (s, 1 H), 7.92 (s, 1 H), 7.59 (s, 1 H), 7.18 (m, 2 H), 7.04 (m, 1 H), 6.62 (s, 1 H), 4.00 (s, 3 H), 3.60 (m, 4 H), 2.68 (m, 4 H), 2.31 (s, 3 H)	412	4-[(2-fluoro-4-methylphenyl)amino]-7-methoxy-6-morpholin-4-ylcinnoline-3-carbonitrile Method 72
36	6-[(3R,5S)-3,5-Dimethylpiperazin-1-yl]-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carboxamide	11.33 (s, 1 H), 8.76 (s, 1 H), 7.90 (s, 1 H), 7.55 (s, 1 H), 7.21 (m, 2 H), 7.06 (m, 1 H), 6.61 (s, 1 H), 4.07 (br s, 1 H), 4.00 (s, 3 H), 3.00 (d, 2 H), 2.71 (m, 2 H), 2.32 (s, 3 H), 1.75 (m, 2 H), 0.85 (d, 6 H)	439	6-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile Method 73
37	6-[(2R,6S)-2,6-Dimethylmorpholin-4-yl]-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carboxamide	11.36 (s, 1 H), 8.77 (s, 1 H), 7.91 (s, 1 H), 7.58 (s, 1 H), 7.23 (m, 2 H), 7.08 (m, 1 H), 6.63 (s, 1 H), 4.00 (s, 3 H), 3.59 (m, 2 H), 3.04 (d, 2 H), 2.32 (s, 3 H), 1.90 (m, 2 H), 0.99 (d, 6 H)	440	6-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile Method 74

Example	Compound	¹ H NMR (300 MHz)	m/z	Starting Material
38	4-[(2-Fluoro-4-methylphenyl)amino]-6-[4-(2-hydroxyethyl)piperazin-1-yl]-7-methoxycinnoline-3-carboxamide	11.30 (s, 1 H), 8.77 (s, 1 H), 7.92 (s, 1 H), 7.58 (s, 1 H), 7.19 (m, 2 H), 7.06 (m, 1 H), 6.62 (s, 1 H), 4.40 (t, 1 H), 4.01 (s, 3 H), 3.50 (m, 2 H), 2.73 (m, 4 H), 2.42 (m, 6 H), 2.33 (s, 3 H)	455	6-[4-(2-{[<i>tert</i> -butyl(dimethyl)silyl]oxy}ethyl)piperazin-1-yl]-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile Method 75
39	6-[4-(Dimethylamino)piperidin-1-yl]-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carboxamide	11.28 (s, 1 H), 8.76 (s, 1 H), 7.91 (s, 1 H), 7.57 (s, 1 H), 7.18 (m, 2 H), 7.05 (m, 1 H), 6.63 (s, 1 H), 4.01 (s, 3 H), 3.22 (m, 2 H), 2.34 (s, 3 H), 2.28 (m, 2 H), 2.15 (s, 6 H), 2.10 (m, 1 H), 1.63 (m, 2 H), 1.38 (m, 2 H)	453	6-[4-(dimethylamino)piperidin-1-yl]-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile Method 76
40	4-[(2-Fluoro-4-methylphenyl)amino]-7-methoxy-6-(4-methyl-1,4-diazepan-1-yl)cinnoline-3-carboxamide	MeOD 7.33 (s, 1 H), 6.94 (m, 3 H), 6.43 (s, 1 H), 3.93 (s, 3 H), 3.12 (m, 2 H), 2.85 (m, 2 H), 2.58 (m, 2 H), 2.49 (m, 2 H), 2.26 (s, 3 H), 2.23 (s, 3 H), 1.75 (m, 2 H)	439	4-[(2-fluoro-4-methylphenyl)amino]-7-methoxy-6-(4-methyl-1,4-diazepan-1-yl)cinnoline-3-carbonitrile Method 77

Example	Compound	¹ H NMR (300 MHz)	m/z	Starting Material
41	6-[(3S)-3-(Dimethylamino)pyrrolidin-1-yl]-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carboxamide	11.12 (s, 1 H), 8.71 (s, 1 H), 7.85 (s, 1 H), 7.48 (s, 1 H), 7.13 (m, 2 H), 7.02 (m, 1 H), 6.17 (s, 1 H), 3.96 (s, 3 H), 2.97 (m, 1 H), 2.79 (m, 1 H), 2.62 (m, 1 H), 2.28 (s, 3 H), 2.13 (s, 6 H), 1.98 (m, 1 H), 1.60 (m, 1 H). Two protons masked by solvent	439	6-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile Method 78
42	4-[(2-Fluoro-4-methylphenyl)amino]-7-methoxy-6-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]cinnoline-3-carboxamide	11.30 (s, 1 H), 8.75 (s, 1 H), 7.90 (s, 1 H), 7.57 (s, 1 H), 7.19 (m, 2 H), 7.06 (m, 1 H), 6.61 (s, 1 H) 3.99 (s, 3 H), 3.18 (q, 2 H), 2.70 (m, 4 H), 2.62 (m, 4 H), 2.31 (s, 3 H)	493	4-[(2-fluoro-4-methylphenyl)amino]-7-methoxy-6-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]cinnoline-3-carbonitrile Method 79
43	7-Ethoxy-4-[(2-fluoro-4-methylphenyl)amino]-6-[4-(2-hydroxyethyl)piperazin-1-yl]cinnoline-3-carboxamide	CDCl ₃ 11.00 (s, 1 H), 8.38 (br s, 1 H), 7.55 (s, 1 H), 7.07 (m, 1 H), 6.93 (m, 2 H), 6.75 (m, 1 H), 5.59 (br s, 1 H), 4.26 (q, 2 H), 3.66 (m, 2 H), 2.88 (m, 4 H), 2.62 (m, 6 H), 2.35 (s, 3 H), 1.53 (t, 3 H)	469	6-[4-(2-[[<i>tert</i> -butyl(dimethyl)silyl]oxy]ethyl)piperazin-1-yl]-7-ethoxy-4-[(2-fluoro-4-methylphenyl)amino]cinnoline-3-carbonitrile Method 80

Example	Compound	¹ H NMR (300 MHz)	m/z	Starting Material
44	4-[(2,4-Difluorophenyl)amino]-6-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-7-methoxycinnoline-3-carboxamide	11.38 (s, 1 H), 8.81 (s, 1 H), 7.97 (s, 1 H), 7.62 (s, 1 H), 7.43 (m, 1 H), 7.21 (m, 2 H), 6.52 (s, 1 H), 4.00 (s, 3 H), 3.06 (d, 2 H), 2.76 (m, 2 H), 1.86 (m, 2 H), 0.86 (d, 6 H)	443	4-[(2,4-difluorophenyl)amino]-6-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-7-methoxycinnoline-3-carbonitrile Method 81
45	4-[(3-Chloro-2-fluorophenyl)amino]-6-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-7-methoxycinnoline-3-carboxamide	11.34 (s, 1 H), 8.79 (s, 1 H), 7.94 (s, 1 H), 7.59 (s, 1 H), 7.45 (m, 2 H), 7.17 (m, 1 H), 6.55 (s, 1 H), 4.01 (s, 3 H), 3.04 (d, 2 H), 2.77 (m, 2 H), 1.80 (m, 2 H), 0.88 (d, 6 H)	459	4-[(3-chloro-2-fluorophenyl)amino]-6-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-7-methoxycinnoline-3-carbonitrile Method 82
46	4-[(2-Fluoro-4-methylphenyl)amino]-7-methoxy-6-piperazin-1-ylcinnoline-3-carboxamide		411	4-[(2-fluoro-4-methylphenyl)amino]-7-methoxy-6-piperazin-1-ylcinnoline-3-carbonitrile Method 83

Example 47

4-[(2-Fluoro-4-methylphenyl)amino]-6-(1-isopropylpiperidin-4-yl)-7-methoxycinnoline-3-carboxamide hydrochloride

- 5 A solution of 4-(2-fluoro-4-methylphenylamino)-6-(1-isopropyl-1,2,3,6-tetrahydropyridin-4-yl)-7-methoxycinnoline-3-carboxamide (Example 29, 0.250 g, 0.56 mmol) in MeOH (20 ml) with a few drops of c.HCl, was run through an H-Cube apparatus at 1 mL/min using a 20 wt% Pd(OH)₂/Carbon cartridge at 10 bar. When the reduction was

judged complete by LCMS, the solution was concentrated under reduced pressure to give 0.234 g (86 %) product. ¹H NMR: 12.51 (s, 1 H), 10.51 (s, 1 H), 8.76 (s, 1 H), 8.21 (s, 1 H), 7.65 (s, 1 H), 7.36 (m, 3 H), 7.18 (m, 1 H), 4.03 (s, 3 H), 3.38 (m, 1 H), 3.26 (m, 2 H), 3.05 (m, 3 H), 2.41 (s, 3 H), 1.72 (m, 2 H), 1.61 (m, 2 H), 1.26 (d, 6 H); *m/z* 452.

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Example 48

The following example was prepared according to the procedure of Example 47 using the appropriate starting material, with additional purification by reverse phase HPLC.

Example	Compound	¹ H NMR (300 MHz)	<i>m/z</i>	Starting Material
48	4-[(2-Fluoro-4-methylphenyl)amino]-6-[1-(2-hydroxyethyl)piperidin-4-yl]-7-methoxycinnoline-3-carboxamide	MeOD 7.48 (s, 1 H), 7.28 (s, 1 H), 7.16 (m, 1 H), 7.05 (m, 2 H), 4.02 (s, 3 H), 3.67 (t, 2 H), 2.96 (m, 2 H), 2.85 (m, 1 H), 2.54 (t, 2 H), 2.38 (s, 3 H), 2.17 (m, 2 H), 1.60 (m, 2 H), 1.18 (m, 2 H)	454	4-[(2-fluoro-4-methylphenyl)amino]-6-[1-(2-hydroxyethyl)-1,2,3,6-tetrahydropyridin-4-yl]-7-methoxycinnoline-3-carboxamide Example 34

10 **Example 49**

4-[(2-Fluoro-4-methylphenyl)amino]-6-{4-[(2R)-2-hydroxypropanoyl]piperazin-1-yl}-7-methoxycinnoline-3-carboxamide

To a solution of 4-(2-fluoro-4-methylphenylamino)-7-methoxy-6-(piperazin-1-yl)cinnoline-3-carboxamide (Example 46, 0.395 g, 0.96 mmol) in CH₂Cl₂ (20 mL) and MeOH (5 mL) was added benzotriazol-1-yloxytripyrrolidino-phosphonium hexafluorophosphate (0.551 g, 1.06 mmol), (R)-2-hydroxypropanoic acid (0.079 mL, 1.06 mmol), and *N*-ethyl-diisopropylamine (0.181 mL, 1.06 mmol). After 1 hour, an additional portion of benzotriazol-1-yloxytripyrrolidino-phosphonium hexafluorophosphate (1.10 g, 2.12 mmol) was added. After 2 hours, water (100 mL) was added, and the mixture extracted with CH₂Cl₂. The organic extract was concentrated under reduced pressure, and the residue purified with silica chromatography (Hex/EtOAc, then with CH₂Cl₂/MeOH). The crude product was triturated with CH₃CN and filtered to give 173 mg (37 %) yellow solid. ¹H NMR: 11.33 (s, 1

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H), 8.77 (s, 1 H), 7.91 (s, 1 H), 7.60 (s, 1 H), 7.17 (m, 2 H), 7.06 (m, 1 H), 6.62 (s, 1 H), 4.98 (d, 1 H), 4.39 (m, 1 H), 4.01 (s, 3 H), 3.54 (m, 4 H), 2.72 (m, 4 H), 2.32 (s, 3 H), 1.16 (d, 3 H); m/z 484.

5 Example 50

4-[(2-Fluoro-4-methylphenyl)amino]-7-methoxy-6-[1-(methylsulfonyl)piperidin-4-yl]cinnoline-3-carboxamide

To a solution of 4-(2-fluoro-4-methylphenylamino)-7-methoxy-6-(piperidin-4-yl)cinnoline-3-carboxamide (Example 51, 0.1 g, 0.24 mmol) in CH_2Cl_2 (2.5 ml) and DMF (2.5 ml) was added *N*-ethyldiisopropylamine (0.127 ml, 0.73 mmol) and methanesulphonyl chloride (0.021 ml, 0.27 mmol). The reaction mixture was stirred at for 1 hour, diluted with CH_2Cl_2 and washed with water. The organic layer was concentrated under reduced pressure and the residue purified by reverse phase chromatography using 0.1% formic acid in water and methanol (50-70%) to give 28 mg (24 %) off-white solid. ^1H NMR: 11.56 (s, 1 H), 8.78 (s, 1 H), 7.94 (s, 1 H), 7.61 (s, 1 H), 7.29 (m, 1 H), 7.21 (m, 1 H), 7.11 (m, 2 H), 4.01 (s, 3 H), 3.51 (m, 2 H), 2.91 (m, 1 H), 2.84 (s, 3 H), 2.74 (m, 2 H), 2.35 (s, 3 H), 1.63 (m, 2 H), 0.97 (m, 2 H); m/z 488.

Example 51

20 4-[(2-Fluoro-4-methylphenyl)amino]-7-methoxy-6-piperidin-4-ylcinnoline-3-carboxamide

A solution of 4-(2-fluoro-4-methylphenylamino)-7-methoxy-6-(1,2,3,6-tetrahydropyridin-4-yl)cinnoline-3-carboxamide (Example 52, 0.9 g, 2.21 mmol) in MeOH (44.2 ml) with a few drops of conc. HCl was passed through an H Cube apparatus using a 20 wt% $\text{Pd}(\text{OH})_2$ /Carbon cartridge, at 10 bar. The solvent was removed under reduced pressure and the residue was purified with silica chromatography CH_2Cl_2 /10% MeOH(1% NH_4OH) to give 692 mg (77 %) of a light yellow solid. ^1H NMR: MeOD 7.61 (s, 1 H), 7.37 (m, 1 H), 7.23 (m, 1 H), 7.12 (m, 2 H), 4.09 (s, 3 H), 3.38 (m, 2 H), 3.22 (m, 1 H), 3.12 (m, 2 H), 2.43 (s, 3 H), 1.90 (m, 2 H), 1.36 (m, 2 H); m/z 410.

30 Example 52

4-[(2-Fluoro-4-methylphenyl)amino]-7-methoxy-6-(1,2,3,6-tetrahydropyridin-4-yl)cinnoline-3-carboxamide

A solution of *tert*-butyl 4-(3-carbamoyl-4-(2-fluoro-4-methylphenylamino)-7-methoxycinnolin-6-yl)-5,6-dihydropyridine-1(2H)-carboxylate (Example 53, 1.5 g, 2.96 mmol) in CH₂Cl₂ (11.84 mL) and trifluoroacetic acid (11.84 mL, 153.68 mmol) was stirred for 16 hours, concentrated under reduced pressure, and the residue purified with silica chromatography CH₂Cl₂/5% MeOH(1% NH₄OH) to give 960 mg (80 %) product. *m/z* 408.

Example 53

tert-Butyl 4-{3-(aminocarbonyl)-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnolin-6-yl}-3,6-dihydropyridine-1(2H)-carboxylate

10 A mixture of 6-bromo-4-(2-fluoro-4-methylphenylamino)-7-methoxycinnoline-3-carboxamide hydrochloride (Example 54, 1.40 g, 3.169 mmol), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (1.47 g, 4.75 mmol), tripotassium phosphate (2.018 g, 9.51 mmol), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (0.260 g, 0.63 mmol) and tris(dibenzylideneacetone)dipalladium(0) (0.29 g, 0.32 mmol) in *n*-butanol (4.53 ml) and water (1.81 ml) was stirred under N₂ (g) at 100 °C overnight. The reaction mixture was cooled, concentrated under reduced pressure and the residue purified with silica chromatography (CH₂Cl₂/MeOH) to give 1.54 g (96 %) of a light brown solid. ¹H NMR: 11.54 (s, 1 H), 8.79 (s, 1 H), 7.94 (s, 1 H), 7.62 (s, 1 H), 7.25 (m, 2 H), 7.08 (m, 2 H), 5.56 (s, 1 H), 3.97 (s, 3 H), 3.82 (m, 2 H), 3.37 (m, 2 H), 2.35 (s, 3 H), 2.14 (m, 20 2 H), 1.41 (s, 6 H), 1.06 (s, 9 H); *m/z* 508.

Example 54

6-Bromo-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carboxamide hydrochloride

25 To a suspension of 6-bromo-4-chloro-7-methoxycinnoline-3-carboxamide (Method 21, 8.89 g, 28.09 mmol) in ethanol (70 ml) was added 2-fluoro-4-methylaniline (3.49 ml, 30.89 mmol) and acetic acid (0.016 ml, 0.28 mmol). The reaction mixture was stirred at 80 °C for 1 hour, cooled, and filtered. The solid material was washed with ethanol and dried to give 9.16 g (74 %) of a brown solid, assumed to be the HCl salt. ¹H NMR: 12.15 (s, 1 H), 30 8.79 (s, 1 H), 8.13 (s, 1 H), 7.73 (s, 1 H), 7.66 (s, 1 H), 7.33 (m, 2 H), 7.12 (m, 1 H), 4.07 (s, 3 H), 2.38 (s, 3 H); *m/z* 406.

Preparation of Starting Materials

Method 1

1-{4,5-Dimethoxy-2-[(*E*)-pyrrolidin-1-yl diazenyl]phenyl}ethanone

To a 100 mL round bottom flask charged with a magnetic stir bar and 1-(2-amino-4,5-dimethoxyphenyl)ethanone (1.23 g, 6.29 mmol) was added water (4 mL). The mixture was cooled to 0° C with an ice bath and concentrated aqueous HCl (1.95 mL) was added to the reaction mixture. With efficient stirring, a solution of sodium nitrite (0.434 g, 6.9 mmol) in water (3 mL) was added to the reaction mixture via Pasteur pipette. The reaction was allowed to stir for 5 minutes at this temperature followed by the slow addition of a solution of pyrrolidine (0.447 g, 6.30 mmol) in 50 mL of 0.4 N aqueous potassium hydroxide. The reaction was allowed to stir at this temperature for 0.5 h before being poured into a separatory funnel and extracted with DCM (2 × 100 mL). The combined organic extract was dried with MgSO₄, filtered, and concentrated *in vacuo* to yield the crude product which was purified on 80 g of silica using hexanes/EtOAc (1:1) as eluent to give 1.49 g (85 %) of the title compound as a brown solid. ¹H NMR: 7.12 (s, 1 H), 7.01 (s, 1 H), 3.92 (m, 2 H), 3.80 (s, 3 H), 3.75 (s, 3 H), 3.58 (m, 2 H), 2.60 (s, 3 H), 2.00 (M, 4 H); *m/z*: 278.

Method 2

The following intermediate was prepared according to the procedure in Method 1 using the appropriate starting material.

Method	Compound	¹ H NMR (300 MHz)	<i>m/z</i>	Starting Material
2	1-{5-Bromo-4-ethoxy-2-[(<i>E</i>)-pyrrolidin-1-yl diazenyl]phenyl}ethanone	7.79 (s, 1 H), 7.11 (s, 1 H), 4.20 (q, 2 H), 4.05 (m, 2 H), 3.69 (m, 2 H), 2.62 (s, 3 H), 2.07 (m, 4 H), 1.45 (t, 3 H)	341	1-(2-amino-5-bromo-4-ethoxyphenyl)ethanone (Method 46)

Method 3

Ethyl 3-{4,5-dimethoxy-2-[(*E*)-pyrrolidin-1-yl diazenyl]phenyl}-3-oxopropanoate sodium salt

To a 250 mL three-necked flask charged with a magnetic stir bar and anhydrous THF (55 mL) was added sodium hydride (1.73 g, 43.3 mmol) and freshly distilled diethyl carbonate (1.28 g, 10.83 mmol). The reaction mixture was brought to reflux and a solution of

1-{4,5-dimethoxy-2-[(*E*)-pyrrolidin-1-yl]diazanyl]phenyl}ethanone (3.0 g, 10.83 mmol) (Method 1) in anhydrous THF (25 mL) was added dropwise via an addition funnel. The mixture was refluxed for an additional 8 h before being allowed to cool to rt. The light yellow precipitate was isolated via vacuum filtration using a Buchner funnel, washed with diethyl ether (~ 2 × 100 mL), collected, and dried *in vacuo* to yield 4.03 g (99 %) of the title compound as its sodium salt which was used without further purification. ¹H NMR: 7.10 (s, 1 H), 6.71 (s, 1 H), 4.75 (s, 1 H), 3.85 (m, 2 H), 3.71 (s, 3 H), 3.70 (s, 3 H), 3.62 (m, 2 H), 3.44 (m, 2 H), 1.96 (M, 4 H), 1.05 (m, 3 H); *m/z*: 350.

10 Method 4

The following intermediate was prepared according to the procedure in Method 3 using the appropriate starting materials.

Method	Compound	¹ H NMR (300 MHz)	<i>m/z</i>	Starting Material
4	Ethyl 3-{5-bromo-4-ethoxy-2-[(<i>E</i>)-pyrrolidin-1-yl]diazanyl]phenyl}-3-oxopropanoate	7.66 (s, 1 H), 6.75 (s, 1 H), 4.80 (s, 1 H), 4.05-3.30 (m, 8 H), 1.32 (t, 2 H), 1.02 (m, 8 H)	413	1-{5-bromo-4-ethoxy-2-[(<i>E</i>)-pyrrolidin-1-yl]diazanyl]phenyl}ethanone (Method 2)

Method 5

15 Ethyl 6,7-dimethoxy-4-oxo-1,4-dihydrocinnoline-3-carboxylate

To a 100 mL round bottom flask charged with a magnetic stir bar was added TFA (30 mL). The flask was cooled to 0 °C in an ice bath and ethyl 3-{4,5-dimethoxy-2-[(*E*)-pyrrolidin-1-yl]diazanyl]phenyl}-3-oxopropanoate sodium salt (4.03 g, 10.83 mmol) (Method 3) was added to the reaction mixture in portions over 10 minutes. The mixture was stirred at this temperature for an additional 2 h before being poured over 0 °C ice-water (~ 300 mL). The desired product precipitated from the mixture and was collected via vacuum filtration using a Buchner funnel. The solid was rinsed with water (1 × 100 mL) and diethyl ether (1 × 100 mL) to yield 1.55 g (51 %) of the title compound as an off white solid that was used without further purification. ¹H NMR: 13.70 (s, NH, 1 H), 7.39 (s, 1 H), 7.00 (s, 1 H), 4.30 (q, 2 H), 3.95 (s, 3 H), 3.89 (s, 3 H), 1.30 (t, 3 H); *m/z* 279.

Method 6

The following intermediate was prepared according to the procedure in Method 5 using the appropriate starting material.

Method	Compound	¹ H NMR (300 MHz)	m/z	Starting Material
6	Ethyl 6-bromo-7-ethoxy-4-oxo-1,4-dihydrocinnoline-3-carboxylate	13.76 (s, 1 H), 8.20 (s, 1 H), 7.08 (s, 1 H), 4.30 (m, 4 H), 1.48 (t, 3 H), 1.27 (t, 3 H)	342	ethyl 3-{5-bromo-4-ethoxy-2-[(<i>E</i>)-pyrrolidin-1-yl]diazanyl]phenyl}-3-oxopropanoate (Method 4)

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Method 7

Ethyl 4-chloro-6,7-dimethoxycinnoline-3-carboxylate

To a 50 mL round bottom flask charged with a magnetic stir bar and ethyl 6,7-dimethoxy-4-oxo-1,4-dihydrocinnoline-3-carboxylate (1.00 g, 3.6 mmol) (Method 5) was added phosphorous oxychloride (15 mL). The reaction flask was fitted with a reflux condenser and heated to reflux for 2 h before being allowed to cool to rt. The crude reaction mixture was concentrated *in vacuo*, and the residue was treated with aqueous NaHCO₃ (~ 25 mL). The crude product precipitated from solution and was collected via vacuum filtration using a Buchner funnel. The solid was washed water (1 × 100 mL) and diethyl ether (1 × 100 mL) to yield 0.941 g (88 %) of the title compound as a light brown solid that was used without further purification. ¹H NMR: 7.98 (s, 1 H), 7.50 (s, 1 H), 4.55 (q, 2 H), 4.13 (s, 6 H), 1.45 (t, 3 H); *m/z* 298.

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Method 8

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The following intermediate was prepared according to the procedure in Method 7 using the appropriate starting material.

Method	Compound	m/z	Starting Material
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Method	Compound	m/z	Starting Material
8	Ethyl 6-bromo-4-chloro-7-ethoxycinnoline-3-carboxylate	361	ethyl 6-bromo-7-ethoxy-4-oxo-1,4-dihydrocinnoline-3-carboxylate (Method 6)

Method 9**2-Bromo-5-nitrophenol**

To a 500 mL round bottom flask charged with 2-bromo-5-nitroanisole (11.0 g, 47 mmol) was added 100 mL of anhydrous DCM. Aluminum chloride (25 g, 150 mmol) was then added to the reaction mixture. The resulting suspension was heated overnight under nitrogen at 50 °C. The reaction was allowed to cool to rt, poured over ice, and acidified to pH 4 with the addition of aqueous 10 % HCl. The resulting mixture was filtered through a bed of Celite and the filtrate was transferred to a separatory funnel. The aqueous phase was extracted with methylene chloride (~ 2 x 200 mL). The combined organic phase was dried over Na₂SO₄ and conc *in vacuo* giving the crude title compound which was purified by silica gel chromatography (330 g) using EtOAc/hexanes (1:1) as eluent to afford the title compound (8.0 g, 78 %) *m/z*: 217.

Method 10**1-Bromo-2-(2-methoxyethoxy)-4-nitrobenzene**

To a solution of 2-bromo-5-nitrophenol (7.24 g, 33.2 mmol) (Method 9) in anhydrous DMF was added 2-methoxy-1-bromoethane (6.92 g, 49.8 mmol) and a catalytic amount of potassium iodide (~ 100 mg). The reaction was heated at 70 °C for 4 h before being allowed to cool to rt. The reaction was then poured into a separatory funnel and partitioned between EtOAc (~ 250 mL) and water (~ 250 mL). The organic phase was dried over Na₂SO₄ and conc *in vacuo* giving the crude title compound which was taken up in a minimum volume of warm EtOAc. The resulting solution was cooled in an ice bath and hexanes were slowly added to induce crystallization. The resulting precipitate was isolated via vacuum filtration through a fritted funnel and air dried to give pure title compound (8.3 g, 91%). ¹H NMR: (300 MHz) 7.87-7.92 (m, 2 H), 7.76 (dd, 1 H), 4.35 (t, 2 H), 3.73 (t, 2 H), 3.35 (s, 3 H).

Method 11

4-Bromo-3-(2-methoxyethoxy)aniline

An open 250 mL round bottom flask was charged with 1-bromo-2-(2-methoxyethoxy)-4-nitrobenzene (Method 10) (5 g, 18.11 mmol), 5 wt % FeCl₃ on SiO₂ (17.6 g, 5.43 mmol), activated carbon (10 g), and 100 mL MeOH. This resulting mixture was heated with stirring to 80 °C. Hydrazine monohydrate (10.6 mL, 217 mmol) was then carefully added to the reaction mixture. After complete addition of the hydrazine monohydrate, the reaction mixture was stirred at 80 °C for an additional 40 min. The reaction was then allowed to cool to rt and filtered through a bed of Celite. The filter cake was washed with MeOH (~ 150 mL) and EtOAc (~ 150 mL). The resulting filtrate was conc *in vacuo* to give the title compound which was used without further purification (3.16 g, 71 %) *m/z*: 247.

Method 12

2-[(4-Bromo-3-methoxyphenyl)diazenyl]-2-cyanoacetamide

Sodium nitrite (8.54 g, 123.7 mmol) dissolved in water (100 ml) was added to an ice-cold suspension of 4-bromo-3-methoxyaniline (25 g, 123.7 mmol) in concentrated HCl (46 ml, 1514 mmol) and water (100 ml). After stirring for 10 minutes, 2-cyanoacetamide (10.40 g, 123.7 mmol) and sodium acetate trihydrate (84 g, 617 mmol) in water (1.8 L) was added and the reaction was allowed to stir overnight. The resulting solid was collected by filtration, washed with water, dried, giving an orange solid which was refluxed in 1.4 L of ethanol for 30 min. The mixture was cooled to room temperature, the solid was collected by filtration, washed with ethanol (100 ml x 3), and dried to yield the title compound as a yellow solid (34.4 g, 94 %). ¹H NMR: 11.70 (s, 1 H), 7.90 (s, 1 H), 7.50 (m, 2 H), 7.35 (s, 1 H), 7.20 (d, 1 H), 3.90 (s, 3 H); *m/z*: 296.

Methods 13-14

The following intermediates were prepared according to the procedure in Method 12 using the appropriate starting material.

Method	Compound	m/z	Starting Material
13	2-[(E)-(4-Bromo-3-ethoxyphenyl)diazenyl]-2-cyanoacetamide	312	4-bromo-3-ethoxyaniline

Method	Compound	m/z	Starting Material
14	2-[(E)-[4-Bromo-3-(2-methoxyethoxy)phenyl]diazenyl]-2-cyanoacetamide	342	4-bromo-3-(2-methoxyethoxy)aniline Method 11

Method 15

4-Amino-6-bromo-7-methoxycinnoline-3-carboxamide:

To a mixture of 2-[(4-bromo-3-methoxyphenyl)diazenyl]-2-cyanoacetamide (Method 12) (34.4 g, 115.8 mmol) in toluene (250 ml) under N₂ was added TiCl₄ (51.1 ml, 463 mmol). The reaction mixture was stirred at reflux for 4 hours before being allowed to cool to room temperature. The reaction mixture was carefully poured over an ice cold solution of 3N HCl (~ 600 ml), the mixture was then allowed to warm to rt, and was then stirred at 90 °C for 10 minutes. A precipitate formed which was collected via vacuum filtration, washed with water (~ 200 mL), ethanol (~ 200 mL), ether (~ 200 mL), and dried *in vacuo* to yield the title compound as a brown solid which was used without further purification (30.0 g, 87 %). ¹H NMR: 10.30 (s, br, 1 H), 9.95 (s, br, 1 H), 9.15 (s, 1 H), 8.55 (s, 1 H), 8.09 (s, 1 H), 7.68 (s, 1 H), 4.15 (s, 3 H); m/z 298.

Methods 16-17

The following intermediates were prepared according to the procedure in Method 15 using the appropriate starting material.

Method	Compound	m/z	Starting Material
16	4-Amino-6-bromo-7-ethoxycinnoline-3-carboxamide	312	2-[(E)-(4-bromo-3-ethoxyphenyl)diazenyl]-2-cyanoacetamide Method 13
17	4-Amino-6-bromo-7-(2-methoxyethoxy)cinnoline-3-carboxamide	342	2-[(E)-[4-bromo-3-(2-methoxyethoxy)phenyl]diazenyl]-2-cyanoacetamide Method 14

Method 18**6-Bromo-4-hydroxy-7-methoxycinnoline-3-carboxylic acid**

A 1 L flask was charged with 4-amino-6-bromo-7-methoxycinnoline-3-carboxamide (Method 15) (30 g, 101 mmol) and ethanol (650 ml). A suspension of potassium hydroxide (100 g, 1782 mmol) in water (350 ml) was added to the reaction and the mixture was stirred at reflux for 9 days. The reaction was then cooled and filtered through a pad of Celite which was washed with water (~ 250 mL). The resulting filtrate was conc. *in vacuo* to remove the ethanol and the resulting aqueous solution was acidified with conc. HCl to pH ~3. A precipitate formed which was collected by vacuum filtration. The resulting solid was suspended in 1.4 L of ethanol, heated to 75 °C for 15 minutes, and cooled to room temperature which provided the crude precipitate which was collected by vacuum filtration. The filter cake was washed with ethanol (~ 200 mL) and diethyl ether (~ 200 mL) to yield the title compound as a brown solid which was used without further purification (26.0 g, 86 %). ¹H NMR: 14.60 (m, br, 2 H), 8.35 (s, 1 H), 7.23 (s, 1 H), 4.08 (s, 3 H); *m/z*: 310.

Methods 19-20

The following intermediates were prepared according to the procedure in Method 18 using the appropriate starting material.

Method	Compound	<i>m/z</i>	Starting Material
19	6-Bromo-7-ethoxy-4-hydroxycinnoline-3-carboxylic acid	314	4-amino-6-bromo-7-ethoxycinnoline-3-carboxamide Method 16
20	6-Bromo-4-hydroxy-7-(2-methoxyethoxy)cinnoline-3-carboxylic acid	342 (M-H) ⁻	4-amino-6-bromo-7-(2-methoxyethoxy)cinnoline-3-carboxamide Method 17

Method 21**6-Bromo-4-chloro-7-methoxycinnoline-3-carboxamide**

To a 1 L round bottom flask charged with 6-bromo-4-hydroxy-7-methoxycinnoline-3-carboxylic acid (Method 18) (14 g, 46.8 mmol) was added SOCl_2 (342 ml) and DMF (1 ml). The resulting mixture was heated to reflux for 4 hours before being cooled to rt. The reaction mixture was conc. *in vacuo* to yield a residue which was suspended in acetone (~ 400ml). The suspension was cooled to 0 °C in an ice bath and conc. aqueous ammonia (50 ml, 1284 mmol) was added drop wise via an addition funnel and the resulting mixture was allowed to stir at 0 °C for an additional 15 minutes. A precipitate formed which was collected via vacuum filtration. The filter cake was washed with water (3 x 100 mL), acetone (3 x 50 mL), collected, and dried *in vacuo* to yield the title compound as an off white solid (14.00 g, 94 %) which was used without further purification. ^1H NMR: 8.55 (s, 1 H), 8.40 (s, 1 H), 8.05 (m, 2 H), 4.10 (s, 3 H); m/z : 317.

Methods 22-23

The following intermediates were prepared according to the procedure in Method 21 using the appropriate starting material.

Method	Compound	m/z	Starting Material
22	6-Bromo-4-chloro-7-ethoxycinnoline-3-carboxamide	331	6-bromo-7-ethoxy-4-hydroxycinnoline-3-carboxylic acid Method 19
23	6-Bromo-4-chloro-7-(2-methoxyethoxy)cinnoline-3-carboxamide	361	6-bromo-4-hydroxy-7-(2-methoxyethoxy)cinnoline-3-carboxylic acid Method 20

Method 24

6-Bromo-4-chloro-7-methoxycinnoline-3-carbonitrile

To a suspension of 6-bromo-4-chloro-7-methoxycinnoline-3-carboxamide (Method 21) (12 g, 37.9 mmol) in DCM (400 ml) was added POCl_3 (200 ml). Triethylamine (15 ml) was then added carefully to the mixture which was stirred at reflux for 7 h. The reaction was then allowed to cool to rt and conc. *in vacuo*. The crude residue was then carefully treated with sat'd aqueous NaHCO_3 at 0 °C. A precipitate formed which was collected via vacuum

filtration. The filter cake washed with water (~ 100 mL), collected, and dried *in vacuo* to provide the title compound as a grey solid (9.80 g, 87 %) which was used without further purification. ¹H NMR: 8.71 (s, 1 H), 8.29 (s, 1 H), 4.30 (s, 3 H); *m/z*: 299.

5 Methods 25-26

The following intermediates were prepared according to the procedure in Method 24 using the appropriate starting material.

Method	Compound	<i>m/z</i>	Starting Material
25	6-Bromo-4-chloro-7-ethoxycinnoline-3-carbonitrile	313	6-bromo-4-chloro-7-ethoxycinnoline-3-carboxamide Method 22
26	6-Bromo-4-chloro-7-(2-methoxyethoxy)cinnoline-3-carbonitrile	343	6-bromo-4-chloro-7-(2-methoxyethoxy)cinnoline-3-carboxamide Method 23

Method 27

10 Ethyl 4-[(2,4-difluorophenyl)amino]-6,7-dimethoxycinnoline-3-carboxylate

To a 50 mL round bottom flask charged with a magnetic stir bar and ethyl 4-chloro-6,7-dimethoxycinnoline-3-carboxylate (0.200 g, 0.675 mmol) (Method 7) was added anhydrous ethanol (10 mL), 2,4-difluoroaniline (0.087 g, 0.675 mmol), and glacial acetic acid (~ 100 µL). The reaction mixture was then heated to 75 °C for 1 h, cooled to rt, and diluted
 15 with concentrated aqueous ammonia (~ 5 mL). The crude product precipitated from this reaction mixture and was collected via vacuum filtration using a Buchner funnel. The solid was washed water (1 × 100 mL) and diethyl ether (1 × 100 mL) to yield the crude product which was purified on 40 g silica using EtOAc as eluent providing 0.231 g (88 %) of the title compound as a yellow solid. ¹H NMR: 9.25 (s, 1 H), 7.70 (s, 1 H), 7.50 (s, 1 H), 7.40 (m, 1
 20 H), 7.30 (m, 1 H), 7.10 (m, 1 H), 4.02 (s, 3 H), 3.95 (q, 2 H), 3.85 (s, 3 H), 1.20 (t, 3 H); *m/z* 390.

Methods 28-45

The following intermediates were prepared according to the procedure in Method 27 using the appropriate starting materials.

Method	Compound	¹ H NMR (300 MHz)	m/z	Starting Material
28	Ethyl 6-bromo-7-ethoxy-4-[(2-fluoro-5-methylphenyl)amino]cinnoline-3-carboxylate	10.47 (s, 1 H), 7.72 (s, 2 H), 7.06 (d, 2 H), 6.99 (s, 1 H), 4.57 (q, 2 H), 4.30 (q, 2 H), 2.29 (s, 3 H), 1.53 (m, 6 H)	449	ethyl 6-bromo-4-chloro-7-ethoxycinnoline-3-carboxylate (Method 8) and 2-fluoro-5-methylaniline
29	Ethyl 4-[(2-fluoro-4-methylphenyl)amino]-6,7-dimethoxycinnoline-3-carboxylate	9.29 (s, 1 H), 7.70 (s, 1 H), 7.40 (s, 1 H), 7.18-7.09 (m, 2 H), 7.00 (d, 1 H), 4.00 (s, 3 H), 3.95 (q, 2 H), 3.75 (s, 3 H), 2.30 (s, 3 H), 1.20 (t, 3 H)	386	ethyl 4-chloro-6,7-dimethoxycinnoline-3-carboxylate (Method 7) and 2-fluoro-4-methylaniline
30	Ethyl 4-[(3-chloro-2-fluorophenyl)amino]-6,7-dimethoxycinnoline-3-carboxylate	9.30 (s, 1 H), 7.74 (s, 1 H), 7.59 (s, 1 H), 7.35 (t, 1 H), 7.15 (t, 1 H), 7.10 (t, 1 H), 4.05 (s, 3 H), 3.90-3.87 (m, 5 H), 1.15 (t, 3 H)	407	ethyl 4-chloro-6,7-dimethoxycinnoline-3-carboxylate (Method 7) and 2-fluoro-3-chloroaniline
31	Ethyl 4-[(2-fluoro-5-methylphenyl)amino]-6,7-dimethoxycinnoline-3-carboxylate	9.25 (s, 1 H), 7.70 (s, 1 H), 7.52 (s, 1 H), 7.20 (t, 1 H), 7.00 (m, 2 H), 4.05 (s, 3 H), 3.90 (q, 2 H), 3.80 (s, 3 H), 2.22 (s, 3 H), 1.19 (t, 3 H)	386	ethyl 4-chloro-6,7-dimethoxycinnoline-3-carboxylate (Method 7) and 2-fluoro-5-methylaniline

Method	Compound	¹ H NMR (300 MHz)	m/z	Starting Material
32	Ethyl 4-[(2,3-dichlorophenyl)amino]-6,7-dimethoxycinnoline-3-carboxylate	9.40 (s, 1 H), 7.78 (s, 1 H), 7.41 (d, 1 H), 7.26 (m, 2 H), 7.00 (d, 1 H), 4.05 (m, 5 H), 3.79 (s, 3 H), 1.20 (t, 3 H)	423	ethyl 4-chloro-6,7-dimethoxycinnoline-3-carboxylate (Method 7) and 2,3-dichloroaniline
33	Ethyl 6-bromo-4-[(2,4-difluorophenyl)amino]-7-ethoxycinnoline-3-carboxylate	9.25 (s, 1 H), 7.70 (s, 1 H), 7.50 (s, 1 H), 7.40 (m, 1 H), 7.30 (m, 1 H), 7.10 (m, 1 H), 4.02 (s, 3 H), 3.95 (q, 2 H), 3.85 (s, 3 H), 1.20 (t, 3 H)	453	ethyl 6-bromo-4-chloro-7-ethoxycinnoline-3-carboxylate (Method 8) and 2,4-difluoroaniline
34	Ethyl 6-bromo-4-[(2,3-dichlorophenyl)amino]-7-ethoxycinnoline-3-carboxylate		486	ethyl 6-bromo-4-chloro-7-ethoxycinnoline-3-carboxylate (Method 8) and 2,3-dichloroaniline
35	Ethyl 6-bromo-4-[(3-chloro-2-fluorophenyl)amino]-7-ethoxycinnoline-3-carboxylate		470	ethyl 6-bromo-4-chloro-7-ethoxycinnoline-3-carboxylate (Method 8) and 2-fluoro-3-chloroaniline

Method	Compound	¹ H NMR (300 MHz)	m/z	Starting Material
36	Ethyl 6-bromo-7-ethoxy-4-[(2-fluoro-4-methylphenyl)amino]cinnoline-3-carboxylate	9.58 (s, 1 H), 8.56 (s, 1 H), 7.77 (s, 1 H), 7.17 (d, 2 H), 7.02 (s, 1 H), 4.36 (q, 2 H), 3.88 (q, 2 H), 2.32 (s, 3 H), 1.45 (t, 3 H), 1.16 (t, 3 H)	449	ethyl 6-bromo-4-chloro-7-ethoxycinnoline-3-carboxylate (Method 8) and 2-fluoro-4-methylaniline
37	6-Bromo-4-[(3-chloro-2-fluorophenyl)amino]-7-methoxycinnoline-3-carbonitrile		408	6-bromo-4-chloro-7-methoxycinnoline-3-carbonitrile Method 24 and 3-chloro-2-fluoroaniline
38	6-Bromo-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile		388	6-bromo-4-chloro-7-methoxycinnoline-3-carbonitrile Method 24 and 2-fluoro-4-methylaniline
39	6-Bromo-4-[(2,4-difluorophenyl)amino]-7-methoxycinnoline-3-carbonitrile		392	6-bromo-4-chloro-7-methoxycinnoline-3-carbonitrile Method 24 and 2,4-difluoroaniline

Method	Compound	¹ H NMR (300 MHz)	m/z	Starting Material
40	6-Bromo-4-[(2-fluoro-5-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile	:	388	6-bromo-4-chloro-7-methoxycinnoline-3-carbonitrile Method 24 and 2-fluoro-5-methylaniline
41	6-Bromo-4-[(2,4-difluorophenyl)amino]-7-(2-methoxyethoxy)cinnoline-3-carbonitrile		436	6-bromo-4-chloro-7-(2-methoxyethoxy)cinnoline-3-carbonitrile Method 26 and 2,4-difluoroaniline
42	6-Bromo-4-[(2-fluoro-4-methylphenyl)amino]-7-(2-methoxyethoxy)cinnoline-3-carbonitrile		432	6-bromo-4-chloro-7-(2-methoxyethoxy)cinnoline-3-carbonitrile Method 26 and 2-fluoro-4-methylaniline
43	6-Bromo-4-[(2-fluoro-5-methylphenyl)amino]-7-(2-methoxyethoxy)cinnoline-3-carbonitrile		432	6-bromo-4-chloro-7-(2-methoxyethoxy)cinnoline-3-carbonitrile Method 26 and 2-fluoro-5-methylaniline

Method	Compound	¹ H NMR (300 MHz)	m/z	Starting Material
44	6-Bromo-4-[(3-chloro-2-fluorophenyl)amino]-7-(2-methoxyethoxy)cinnoline-3-carbonitrile		453	6-bromo-4-chloro-7-(2-methoxyethoxy)cinnoline-3-carbonitrile Method 26 and 3-chloro-2-fluoroaniline
45	6-Bromo-7-ethoxy-4-[(2-fluoro-4-methylphenyl)amino]cinnoline-3-carbonitrile		402	6-bromo-4-chloro-7-ethoxycinnoline-3-carbonitrile Method 25 and 2-fluoro-4-methylaniline

The intermediates described in Methods 37-45 can also be prepared in two steps from the intermediates of Methods 21-23, using the aniline addition procedure described for Example 54, followed by the conversion of the amide to the nitrile described in Method 24.

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Method 46

1-(2-Amino-5-bromo-4-ethoxyphenyl)ethanone

A 1 L three-necked flask fitted with a reflux condenser and an addition funnel was charged with a magnetic stir bar, 4-bromo-3-ethoxyaniline hydrochloride (25 g, 100 mmol), and anhydrous toluene (300 mL). The reaction mixture was cooled to 0 °C and 100 mL a 1 M solution of boron trichloride in DCM was added to the reaction dropwise via addition funnel. After the addition of the boron trichloride was complete, acetonitrile (6.56 mL, 125 mmol) was added followed by dropwise addition of 110 mL of a 1M solution of TiCl₄ in DCM. The resulting heterogenous reaction mixture was heated to reflux for 16 h before being allowed to cool to rt. The crude reaction mixture was carefully poured over 2 M HCl_(aq) (~ 250 mL) and the reaction mixture was warmed to 80 °C for 1 h. After cooling to rt the pH of the reaction mixture was adjusted to 6 by the careful addition of 2 N NaOH_(aq). The solids were filtered

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and filtrate was extracted with EtOAc (2×1000 mL). The combined organic extract was dried with MgSO_4 , filtered, and concentrated *in vacuo* to yield the crude product as a dark oil. MeOH (~ 100 mL) was added to the crude oil and the desired product precipitated and was collected via vacuum filtration using a Buchner funnel to yield 10.9 g (42 %) of the title compound as a brown solid. *m/z* 259.

Method 47

Ethyl 7-ethoxy-4-[(2-fluoro-5-methylphenyl)amino]-6-(4-methylpiperazin-1-yl)cinnoline-3-carboxylate

To a 50 mL round bottom flask charged with a magnetic stir bar and ethyl 6-bromo-7-ethoxy-4-[(2-fluoro-5-methylphenyl)amino]cinnoline-3-carboxylate (0.100 g, 0.223 mmol) (Method 28) was added 2.5 mL of anhydrous dimethylacetamide. $\text{Pd}_2(\text{dba})_3$ (50 mg, 0.55 mmol), racemic BINAP (70 mg, 0.11 mmol), cesium carbonate (150 mg, 0.45 mmol), and 1-methylpiperazine (0.334 mmol) were added to the reaction. The mixture was heated to 90°C for 4 h before being cooled to rt and filtered through a pad of diatomaceous earth. The filtrate was concentrated *in vacuo* giving the crude product which was purified on 12 g silica using EtOAc/MeOH (4:1) as eluent yielding 0.033 g (32 %) of the title compound as a yellow solid. *m/z* 468.

Methods 48-83

The following intermediates were prepared according to the procedure in Method 47 using the appropriate starting materials. Some intermediates were prepared using sodium *tert*-butoxide in place of cesium carbonate, or 2-dicyclohexylphosphino-2',4',6'-tri-iso-propyl-1,1'-biphenyl (XPHOS) in place of BINAP.

Method	Compound	<i>m/z</i>	Starting Material
48	Ethyl 4-[(2,4-difluorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)cinnoline-3-carboxylate	472	ethyl 6-bromo-4-[(2,4-difluorophenyl)amino]-7-ethoxycinnoline-3-carboxylate (Method 33)

Method	Compound	m/z	Starting Material
49	Ethyl 4-[(2,3-dichlorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)cinnoline-3-carboxylate	505	ethyl 6-bromo-4-[(2,3-dichlorophenyl)amino]-7-ethoxycinnoline-3-carboxylate (Method 34)
50	Ethyl 4-[(3-chloro-2-fluorophenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)cinnoline-3-carboxylate	489	ethyl 6-bromo-4-[(3-chloro-2-fluorophenyl)amino]-7-ethoxycinnoline-3-carboxylate (Method 35)
51	Ethyl 7-ethoxy-4-[(2-fluoro-4-methylphenyl)amino]-6-(4-methylpiperazin-1-yl)cinnoline-3-carboxylate	469	ethyl 6-bromo-7-ethoxy-4-[(2-fluoro-4-methylphenyl)amino]cinnoline-3-carboxylate (Method 36)
52	Ethyl 4-[(2,4-difluorophenyl)amino]-7-ethoxy-6-(4-propan-2-ylpiperazin-1-yl)cinnoline-3-carboxylate	501	ethyl 6-bromo-4-[(2,4-difluorophenyl)amino]-7-ethoxycinnoline-3-carboxylate (Method 33)
53	Ethyl 4-[(2,4-difluorophenyl)amino]-7-ethoxy-6-(4-ethylpiperazin-1-yl)cinnoline-3-carboxylate	486	ethyl 6-bromo-4-[(2,4-difluorophenyl)amino]-7-ethoxycinnoline-3-carboxylate (Method 33)
54	4-[(3-Chloro-2-fluorophenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)cinnoline-3-carbonitrile	428	6-bromo-4-[(3-chloro-2-fluorophenyl)amino]-7-methoxycinnoline-3-carbonitrile Method 37

Method	Compound	m/z	Starting Material
55	4-[(2-Fluoro-4-methylphenyl)amino]-6-(4-isopropylpiperazin-1-yl)-7-methoxycinnoline-3-carbonitrile	435	6-bromo-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile Method 38
56	6-(4- <i>tert</i> -Butylpiperazin-1-yl)-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile	449	6-bromo-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile Method 38
57	4-[(2,4-Difluorophenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)cinnoline-3-carbonitrile	411	6-bromo-4-[(2,4-difluorophenyl)amino]-7-methoxycinnoline-3-carbonitrile Method 39
58	4-[(2-Fluoro-5-methylphenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)cinnoline-3-carbonitrile	407	6-bromo-4-[(2-fluoro-5-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile Method 40
59	4-[(2-Fluoro-5-methylphenyl)amino]-6-(4-isopropylpiperazin-1-yl)-7-methoxycinnoline-3-carbonitrile	435	6-bromo-4-[(2-fluoro-5-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile Method 40
60	4-[(2-Fluoro-4-methylphenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)cinnoline-3-carbonitrile	407	6-bromo-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile Method 38

Method	Compound	m/z	Starting Material
61	4-[(2,4-Difluorophenyl)amino]-7-(2-methoxyethoxy)-6-(4-methylpiperazin-1-yl)cinnoline-3-carbonitrile	456	6-bromo-4-[(2,4-difluorophenyl)amino]-7-(2-methoxyethoxy)cinnoline-3-carbonitrile Method 41
62	4-[(2-Fluoro-4-methylphenyl)amino]-7-(2-methoxyethoxy)-6-(4-methylpiperazin-1-yl)cinnoline-3-carbonitrile	451	6-bromo-4-[(2-fluoro-4-methylphenyl)amino]-7-(2-methoxyethoxy)cinnoline-3-carbonitrile Method 42
63	4-[(2-Fluoro-5-methylphenyl)amino]-7-(2-methoxyethoxy)-6-(4-methylpiperazin-1-yl)cinnoline-3-carbonitrile	451	6-bromo-4-[(2-fluoro-5-methylphenyl)amino]-7-(2-methoxyethoxy)cinnoline-3-carbonitrile Method 43
64	4-[(3-Chloro-2-fluorophenyl)amino]-7-(2-methoxyethoxy)-6-(4-methylpiperazin-1-yl)cinnoline-3-carbonitrile	472	6-bromo-4-[(3-chloro-2-fluorophenyl)amino]-7-(2-methoxyethoxy)cinnoline-3-carbonitrile Method 44
65	4-[(2,4-Difluorophenyl)amino]-6-(4-isopropylpiperazin-1-yl)-7-(2-methoxyethoxy)cinnoline-3-carbonitrile	483	6-bromo-4-[(2,4-difluorophenyl)amino]-7-(2-methoxyethoxy)cinnoline-3-carbonitrile Method 41

Method	Compound	m/z	Starting Material
66	7-Ethoxy-4-[(2-fluoro-4-methylphenyl)amino]-6-(4-isopropylpiperazin-1-yl)cinnoline-3-carbonitrile	449	6-bromo-7-ethoxy-4-[(2-fluoro-4-methylphenyl)amino]cinnoline-3-carbonitrile Method 45
67	7-Ethoxy-4-[(2-fluoro-4-methylphenyl)amino]-6-(4-methyl-1,4-diazepan-1-yl)cinnoline-3-carbonitrile	435	6-bromo-7-ethoxy-4-[(2-fluoro-4-methylphenyl)amino]cinnoline-3-carbonitrile Method 45
68	6-[(3R,5S)-3,5-Dimethylpiperazin-1-yl]-7-ethoxy-4-[(2-fluoro-4-methylphenyl)amino]cinnoline-3-carbonitrile	435	6-bromo-7-ethoxy-4-[(2-fluoro-4-methylphenyl)amino]cinnoline-3-carbonitrile Method 45
69	4-[(2-Fluoro-4-methylphenyl)amino]-7-methoxy-6-[4-(2-methoxyethyl)piperazin-1-yl]cinnoline-3-carbonitrile	451	6-bromo-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile Method 38
70	6-(5,6-Dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile	431	6-bromo-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile Method 38
71	4-[(2-Fluoro-4-methylphenyl)amino]-6-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-7-methoxycinnoline-3-carbonitrile	433	6-bromo-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile Method 38

Method	Compound	m/z	Starting Material
72	4-[(2-Fluoro-4-methylphenyl)amino]-7-methoxy-6-morpholin-4-ylcinnoline-3-carbonitrile	394	6-bromo-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile Method 38
73	6-[(3R,5S)-3,5-Dimethylpiperazin-1-yl]-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile	421	6-bromo-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile Method 38
74	6-[(2R,6S)-2,6-Dimethylmorpholin-4-yl]-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile	422	6-bromo-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile Method 38
75	6-[4-(2-{[<i>tert</i> -Butyl(dimethyl)silyl]oxy}ethyl)piperazin-1-yl]-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile	551	6-bromo-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile Method 38 and 1-(2-{[<i>tert</i> -butyl(dimethyl)silyl]oxy}ethyl)piperazine Method 89
76	6-[4-(Dimethylamino)piperidin-1-yl]-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile	435	6-bromo-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile Method 38

Method	Compound	m/z	Starting Material
77	4-[(2-Fluoro-4-methylphenyl)amino]-7-methoxy-6-(4-methyl-1,4-diazepan-1-yl)cinnoline-3-carbonitrile	421	6-bromo-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile Method 38
78	6-[(3S)-3-(Dimethylamino)pyrrolidin-1-yl]-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile	421	6-bromo-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile Method 38
79	4-[(2-Fluoro-4-methylphenyl)amino]-7-methoxy-6-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]cinnoline-3-carbonitrile	475	6-bromo-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile Method 38
80	6-[4-(2-{{ <i>tert</i> -Butyl(dimethyl)silyl}oxy}ethyl)piperazin-1-yl]-7-ethoxy-4-[(2-fluoro-4-methylphenyl)amino]cinnoline-3-carbonitrile	565	6-bromo-7-ethoxy-4-[(2-fluoro-4-methylphenyl)amino]cinnoline-3-carbonitrile Method 45 and 1-(2-{{ <i>tert</i> -butyl(dimethyl)silyl}oxy}ethyl)piperazine Method 89
81	4-[(2,4-Difluorophenyl)amino]-6-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-7-methoxycinnoline-3-carbonitrile	425	6-bromo-4-[(2,4-difluorophenyl)amino]-7-methoxycinnoline-3-carbonitrile Method 39

Method	Compound	m/z	Starting Material
82	4-[(3-Chloro-2-fluorophenyl)amino]-6-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-7-methoxycinnoline-3-carbonitrile	441	6-bromo-4-[(3-chloro-2-fluorophenyl)amino]-7-methoxycinnoline-3-carbonitrile Method 37
83	4-[(2-Fluoro-4-methylphenyl)amino]-7-methoxy-6-piperazin-1-ylcinnoline-3-carbonitrile	393	6-bromo-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile Method 38

Method 84

4-[(2-Fluoro-4-methylphenyl)amino]-7-methoxy-6-pyridin-4-ylcinnoline-3-carbonitrile

To a mixture of 6-bromo-4-(2-fluoro-4-methylphenylamino)-7-methoxycinnoline-3-carbonitrile (Method 38, 0.25 g, 0.65 mmol), pyridin-4-ylboronic acid (0.159 g, 1.29 mmol) and K₂CO₃ (0.357 g, 2.58 mmol) in DMA (3.0 ml) and water (0.30 ml), was added Pd(Ph₃P)₄ (0.224 g, 0.19 mmol). The reaction was stirred under argon at 90 °C for 12 hours, cooled, diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extract was dried (MgSO₄), filtered, and the residue purified with silica chromatography (EtOAc) to give 0.175 g (64 %) product. *m/z* 386.

Method 85

The following intermediate was prepared according to the procedure of Method 84 using the appropriate starting materials.

Method	Compound	m/z	Starting Materials
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Method	Compound	m/z	Starting Materials
85	<i>tert</i> -Butyl 4-{3-cyano-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnolin-6-yl}-3,6-dihydropyridine-1(2H)-carboxylate	490	6-bromo-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile Method 38 and <i>tert</i> -butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate

Method 86

4-[(2-Fluoro-4-methylphenyl)amino]-6-(1-isopropyl-1,2,3,6-tetrahydropyridin-4-yl)-7-methoxycinnoline-3-carbonitrile

- 5 To a solution of 4-(2-fluoro-4-methylphenylamino)-7-methoxy-6-(1,2,3,6-tetrahydropyridin-4-yl)cinnoline-3-carbonitrile (Method 88, 200 mg, 0.51 mmol) in dichloroethane (5 mL), acetone (0.566 mL, 7.70 mmol), and acetic acid (0.147 mL, 2.57 mmol) was added sodium triacetoxyborohydride (544 mg, 2.57 mmol) and the reaction stirred at 55 °C for 6 hours. The reaction mixture was concentrated under reduced pressure and the
- 10 residue purified with silica chromatography (MeOH/EtOAc (1:1)) to give 120 mg (50 %) product. *m/z* 432.

Method 87

- 15 The following intermediate was prepared according to the procedure of Method 86 using the appropriate starting materials.

Method	Compound	m/z	Starting Material
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Method	Compound	m/z	Starting Material
87	6-[1-(2-{[<i>tert</i> -Butyl(dimethyl)silyl]oxy}ethyl)-1,2,3,6-tetrahydropyridin-4-yl]-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile	549	4-[(2-fluoro-4-methylphenyl)amino]-7-methoxy-6-(1,2,3,6-tetrahydropyridin-4-yl)cinnoline-3-carbonitrile Method 88 and (<i>tert</i> -butyldimethylsilyloxy)acetaldehyde

Method 88

4-[(2-Fluoro-4-methylphenyl)amino]-7-methoxy-6-(1,2,3,6-tetrahydropyridin-4-yl)cinnoline-3-carbonitrile

- 5 A solution of *tert*-butyl 4-(3-cyano-4-(2-fluoro-4-methylphenylamino)-7-methoxycinnolin-6-yl)-5,6-dihydropyridine-1(2H)-carboxylate (Method 85, 600 mg, 1.23 mmol) in CH₂Cl₂ (4.9 mL) and trifluoroacetic acid (4.9 mL, 63.6 mmol) was stirred for 2 hours. The reaction mixture was concentrated under reduced pressure, azeotroped with chloroform to remove trifluoroacetic acid, and the residue purified with reverse phase HPLC
10 (MeCN/water) to give 302 mg (63 %) product. *m/z* 390.

Method 89

1-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)piperazine

- A mixture of benzyl 4-(2-(*tert*-butyldimethylsilyloxy)ethyl)piperazine-1-carboxylate
15 (Method 90, 2.1 g, 5.55 mmol) and Pd/C (0.059 g, 0.55 mmol) in methanol (30 mL) was stirred under H₂ (g) for 24 hours. The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure to give 1.20 g, (88 %) of a yellow oil. ¹H NMR: CD₃Cl 3.74 (t, 2 H), 2.90 (m, 4 H), 2.51 (m, 6 H), 0.88 (s, 9 H), 0.04 (s, 6 H).

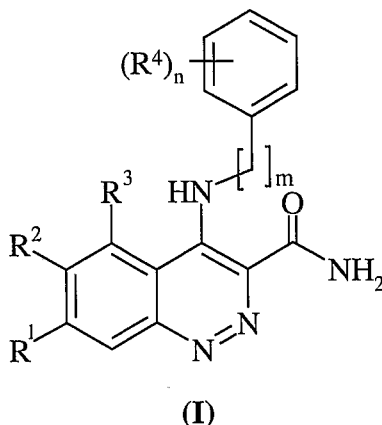
Method 90

Benzyl 4-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)piperazine-1-carboxylate

A mixture of benzyl 1-piperazinecarboxylate (1.751 mL, 9.08 mmol) and 2-(*tert*-butyldimethylsilyloxy)acetaldehyde (1.209 mL, 9.99 mmol), in MeOH (5 mL) and dichloroethane (5 mL) was stirred for 20 minutes with 4 Å molecular sieves. The mixture was added to a solution of sodium triacetoxyborohydride (4.81 g, 22.70 mmol) in tetrahydrofuran (5 mL) and stirred overnight. The reaction mixture was added to sodium bicarbonate (100 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic extracts were concentrated under reduced pressure, and the residue purified with silica chromatography (EtOAc/MeOH) to give 2.10 g, (61 %) of a clear oil. ¹H NMR: 7.34 (m, 5 H), 5.05 (s, 2 H), 3.67 (t, 2 H), 3.36 (m, 4 H), 2.40 (m, 6 H), 0.84 (s, 9 H), 0.02 (s, 6 H).

Claim

1. A compound of formula (I):



wherein:

R^1 and R^2 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, N -(C_{1-6} alkyl)amino, N,N -(C_{1-6} alkyl) $_2$ amino, N -(C_{1-6} alkyl)- N -(C_{1-6} alkoxy)amino, C_{1-6} alkanoylamino, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl) $_2$ carbamoyl, C_{1-6} alkoxycarbonyl, N -(C_{1-6} alkyl)sulphamoyl, N,N -(C_{1-6} alkyl) $_2$ sulphamoyl, C_{1-6} alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein R^1 and R^2 independently of each other may be optionally substituted on carbon by one or more R^5 ; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^6 ;

R^3 is hydrogen or halo;

m is 0 or 1;

R^4 is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, methoxy, ethoxy, acetyl, acetoxyl, methylamino, ethylamino, dimethylamino, diethylamino, N -methyl- N -ethylamino, acetylamino, N -methylcarbamoyl, N -ethylcarbamoyl, N,N -dimethylcarbamoyl, N,N -diethylcarbamoyl, N -methyl- N -ethylcarbamoyl, phenyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, N -methylsulphamoyl, N -ethylsulphamoyl, N,N -dimethylsulphamoyl, N,N -diethylsulphamoyl or N -methyl- N -ethylsulphamoyl;

or wherein if two R^4 groups are on adjacent carbons, they may optionally form a carbocyclic ring or a heterocyclic ring; wherein said carbocyclic ring or heterocyclic ring may

be optionally substituted on carbon by one or more R^7 ; and wherein if said heterocyclic ring contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^8 ;

n is 0-5; wherein the values of R^4 are the same or different;

- 5 R^5 is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, N -(C_{1-6} alkyl)amino, N,N -(C_{1-6} alkyl)₂amino, N -(C_{1-6} alkyl)- N -(C_{1-6} alkoxy)amino, C_{1-6} alkanoylamino, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl)₂carbamoyl, C_{1-6} alkylS(O)_a wherein a is 0 to 2, C_{1-6} alkoxycarbonyl,
10 C_{1-6} alkoxycarbonylamino, N -(C_{1-6} alkyl)sulphamoyl, N,N -(C_{1-6} alkyl)₂sulphamoyl, C_{1-6} alkylsulphonylamino, carbocyclyl- R^9 - or heterocyclyl- R^{10} -; wherein R^5 may be optionally substituted on carbon by one or more R^{11} ; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{12} ;

- R^6 and R^{12} are independently selected from C_{1-6} alkyl, C_{1-6} alkanoyl,
15 C_{1-6} alkylsulphonyl, C_{1-6} alkoxycarbonyl, carbamoyl, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl; wherein R^6 and R^{12} independently of each other may be optionally substituted on carbon by one or more R^{13} ;

- R^{13} is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy,
20 carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, N -(C_{1-6} alkyl)amino, N,N -(C_{1-6} alkyl)₂amino, N -(C_{1-6} alkyl)- N -(C_{1-6} alkoxy)amino, C_{1-6} alkanoylamino, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl)₂carbamoyl, C_{1-6} alkylS(O)_a wherein a is 0 to 2, C_{1-6} alkoxycarbonyl, C_{1-6} alkoxycarbonylamino, N -(C_{1-6} alkyl)sulphamoyl, N,N -(C_{1-6} alkyl)₂sulphamoyl,
25 C_{1-6} alkylsulphonylamino, carbocyclyl- R^{14} - or heterocyclyl- R^{15} -; wherein R^{13} may be optionally substituted on carbon by one or more R^{16} ; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{17} ;

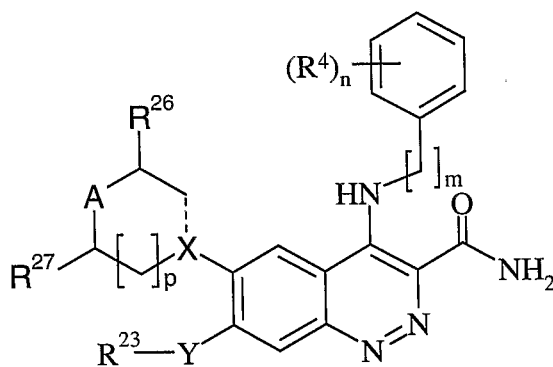
R^9 , R^{10} , R^{14} and R^{15} are independently selected from a direct bond, -O-, -N(R^{18})-, -C(O)-, -N(R^{19})C(O)-, -C(O)N(R^{20})-, -S(O)_s-, -SO₂N(R^{21})- or -N(R^{22})SO₂-; wherein R^{18} , R^{19} ,

- 30 R^{20} , R^{21} and R^{22} are independently selected from hydrogen or C_{1-6} alkyl and s is 0-2;

R^8 and R^{17} are independently selected from C_{1-6} alkyl, C_{1-6} alkanoyl, C_{1-6} alkylsulphonyl, C_{1-6} alkoxycarbonyl, carbamoyl, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

- R^7 , R^{11} and R^{16} are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, methoxy, ethoxy, acetyl, acetoxymethyl, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, phenyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;
- or a pharmaceutically acceptable salt thereof.

2. A compound of formula (IA):



formula (IA)

- or a pharmaceutically acceptable salt thereof, wherein:

--- is selected from a single and double bond;

if --- is a single bond, then X is selected from CR^{24} and N;

if --- is a double bond, then X is C;

Y is selected from O and S;

- A is selected from O, S, NR^{25} , and $CR^{28}R^{29}$;

p is 0-2;

m is 0 or 1;

- R^4 is independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, methoxy, ethoxy, acetyl, acetoxymethyl, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, phenyl,

methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

or wherein if two **R⁴** groups are on adjacent carbons, they may optionally form a carbocyclic ring or a heterocyclic ring; wherein said carbocyclic ring or heterocyclic ring may be optionally substituted on carbon by one or more **R⁷**; and wherein if said heterocyclic ring contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from **R⁸**;

n is 0-5; wherein the values of **R⁴** are the same or different;

R⁷ may be independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, methoxy, ethoxy, acetyl, acetoxymethyl, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, phenyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

R⁸ may be selected from C₁₋₆alkyl, C₁₋₆alkanoyl, C₁₋₆alkylsulphonyl, C₁₋₆alkoxycarbonyl, carbamoyl, *N*-(C₁₋₆alkyl)carbamoyl, *N,N*-(C₁₋₆alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R²³ is selected from H, and C₁₋₆alkyl wherein C₁₋₆alkyl is optionally substituted with C₁₋₆alkoxy;

R²⁴, R²⁶, R²⁷, R²⁸ are each independently selected from hydrogen and C₁₋₆alkyl;

R²⁵ may be selected from hydrogen, C₁₋₆alkyl and C₁₋₆alkanoyl, wherein C₁₋₆alkyl and C₁₋₆alkanoyl may be optionally substituted on carbon by one or more **R³⁰**;

or **R²⁵** and **R²⁷** together with the atom they are attached may optionally form a heterocyclic ring; wherein said heterocyclic ring may be optionally substituted on carbon by one or more **R³⁵**; and wherein if said heterocyclic ring contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from **R³⁶**;

R²⁹ may be selected from hydrogen and amino, wherein amino may be optionally substituted with one or more C₁₋₆alkyl;

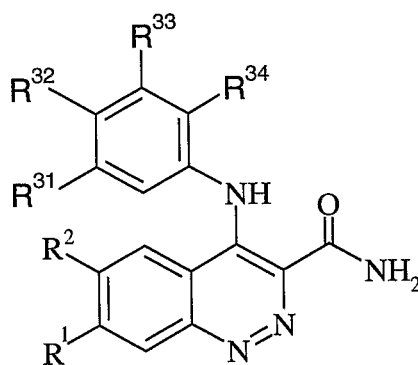
R³⁰ may be selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₆alkyl, C₂₋₆alkenyl,

C₂₋₆alkynyl, methoxy, ethoxy, acetyl, acetoxymethyl, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, phenyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl and *N*-methyl-*N*-ethylsulphamoyl;

R³⁵ may be independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, methoxy, ethoxy, acetyl, acetoxymethyl, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, phenyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl; and

R³⁶ may be selected from C₁₋₆alkyl, C₁₋₆alkanoyl, C₁₋₆alkylsulphonyl, C₁₋₆alkoxycarbonyl, carbamoyl, *N*-(C₁₋₆alkyl)carbamoyl, *N,N*-(C₁₋₆alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl.

3. A compound of formula (IB):



formula (IB)

or a pharmaceutically acceptable salt thereof, wherein:

R¹ and **R²** are independently selected from hydrogen, halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, C₁₋₆alkanoyl, C₁₋₆alkanoyloxy, *N*-(C₁₋₆alkyl)amino, *N,N*-(C₁₋₆alkyl)₂amino, *N*-(C₁₋₆alkyl)-*N*-(C₁₋₆alkoxy)amino, C₁₋₆alkanoylamino, *N*-(C₁₋₆alkyl)carbamoyl, *N,N*-(C₁₋₆alkyl)₂carbamoyl, C₁₋₆alkoxycarbonyl,

N-(C₁₋₆alkyl)sulphamoyl, *N,N*-(C₁₋₆alkyl)₂sulphamoyl, C₁₋₆alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein R¹ and R² independently of each other may be optionally substituted on carbon by one or more R⁵; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R⁶;

- 5 R⁵ is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, C₁₋₆alkanoyl, C₁₋₆alkanoyloxy, *N*-(C₁₋₆alkyl)amino, *N,N*-(C₁₋₆alkyl)₂amino, *N*-(C₁₋₆alkyl)-*N*-(C₁₋₆alkoxy)amino, C₁₋₆alkanoylamino, *N*-(C₁₋₆alkyl)carbamoyl, *N,N*-(C₁₋₆alkyl)₂carbamoyl, C₁₋₆alkylS(O)_a wherein a is 0 to 2, C₁₋₆alkoxycarbonyl, C₁₋₆alkoxycarbonylamino, *N*-(C₁₋₆alkyl)sulphamoyl, *N,N*-(C₁₋₆alkyl)₂sulphamoyl, C₁₋₆alkylsulphonylamino, carbocyclyl-R⁹- or heterocyclyl-R¹⁰-; wherein R⁵ may be optionally substituted on carbon by one or more R¹¹; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R¹²;

- 10 R⁶ and R¹² are independently selected from C₁₋₆alkyl, C₁₋₆alkanoyl, C₁₋₆alkylsulphonyl, C₁₋₆alkoxycarbonyl, carbamoyl, *N*-(C₁₋₆alkyl)carbamoyl, *N,N*-(C₁₋₆alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl; wherein R⁶ and R¹² independently of each other may be optionally substituted on carbon by one or more R¹³;

- 15 R¹³ is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, C₁₋₆alkanoyl, C₁₋₆alkanoyloxy, *N*-(C₁₋₆alkyl)amino, *N,N*-(C₁₋₆alkyl)₂amino, *N*-(C₁₋₆alkyl)-*N*-(C₁₋₆alkoxy)amino, C₁₋₆alkanoylamino, *N*-(C₁₋₆alkyl)carbamoyl, *N,N*-(C₁₋₆alkyl)₂carbamoyl, C₁₋₆alkylS(O)_a wherein a is 0 to 2, C₁₋₆alkoxycarbonyl, C₁₋₆alkoxycarbonylamino, *N*-(C₁₋₆alkyl)sulphamoyl, *N,N*-(C₁₋₆alkyl)₂sulphamoyl, C₁₋₆alkylsulphonylamino, carbocyclyl-R¹⁴- or heterocyclyl-R¹⁵-; wherein R¹³ may be optionally substituted on carbon by one or more R¹⁶; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R¹⁷;

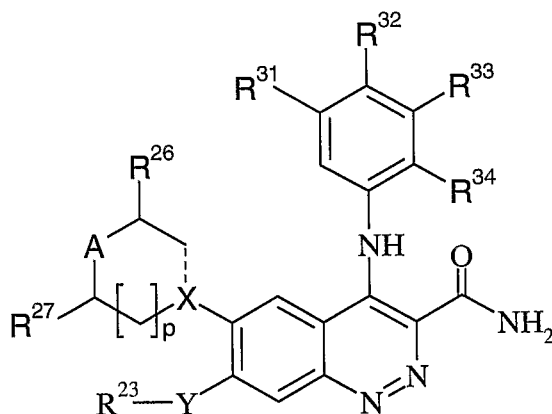
- 20 R⁹, R¹⁰, R¹⁴ and R¹⁵ are independently selected from a direct bond, -O-, -N(R¹⁸)-, -C(O)-, -N(R¹⁹)C(O)-, -C(O)N(R²⁰)-, -S(O)_s-, -SO₂N(R²¹)- or -N(R²²)SO₂-; wherein R¹⁸, R¹⁹, R²⁰, R²¹ and R²² are independently selected from hydrogen or C₁₋₆alkyl and s is 0-2;

- 25 R¹⁷ are independently selected from C₁₋₆alkyl, C₁₋₆alkanoyl, C₁₋₆alkylsulphonyl, C₁₋₆alkoxycarbonyl, carbamoyl, *N*-(C₁₋₆alkyl)carbamoyl, *N,N*-(C₁₋₆alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R^{11} and R^{16} are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, phenyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl; and

R^{31} , R^{32} , R^{33} , and R^{34} are each independently selected from hydrogen, halo, and C_{1-4} alkyl.

4. A compound of formula (IC):



formula (IC)

or a pharmaceutically acceptable salt thereof, wherein:

--- is selected from a single and double bond;

if --- is a single bond, then X is selected from CR^{24} and N;

if --- is a double bond, then X is C;

Y is selected from O and S;

A is selected from O, S, NR^{25} , and $CR^{28}R^{29}$;

p is 0-2;

R^{23} is C_{1-6} alkyl;

R^{24} , R^{26} , R^{27} , R^{28} are each independently selected from hydrogen and C_{1-6} alkyl;

R^{25} may be selected from hydrogen, C_{1-6} alkyl and C_{1-6} alkanoyl wherein C_{1-6} alkyl and C_{1-6} alkanoyl may be optionally substituted on carbon by one or more R^{30} ;

R^{29} may be selected from hydrogen and amino optionally substituted with one or more C_{1-6} alkyl;

R^{30} may be selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, methoxy, ethoxy, acetyl, acetoxymethyl, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, phenyl, methylthio, ethylthio, methylsulphanyl, ethylsulphanyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl, and *N*-methyl-*N*-ethylsulphamoyl;

R^{31} is selected from hydrogen and C_{1-4} alkyl;

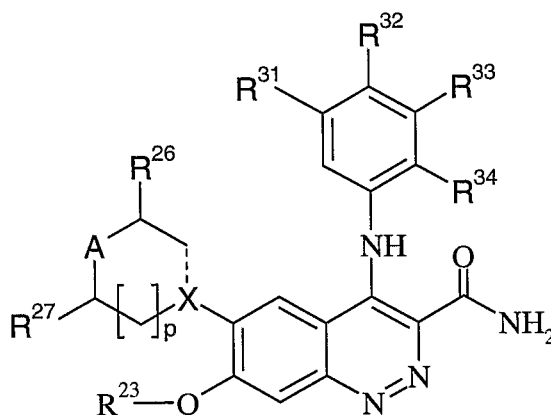
R^{32} is selected from hydrogen, halo, and C_{1-4} alkyl;

R^{33} is selected from hydrogen and halo; and

R^{34} is selected from halo.

15

5. A compound of formula (ID):



formula (ID)

or a pharmaceutically acceptable salt thereof, wherein:

- 20 --- is selected from a single and double bond;
 if --- is a single bond, then X is selected from CH and N;
 if --- is a double bond, then X is C;
 A is selected from O, NR^{25} , and CHR^{29} ;
 p is 0-2;
 25 R^{23} is selected from methyl and ethyl;

R²⁵ is selected from hydrogen, methyl, ethyl, isopropyl, tert-butyl, 1-methoxy-2-ethyl, 1-hydroxy-2-ethyl, 1,1,1-trifluoro-2-ethyl, 2-hydroxy-1-propionyl, and mesyl;

R²⁶ and **R**²⁷ are each independently selected from hydrogen and methyl;

R²⁹ may be dimethylamino;

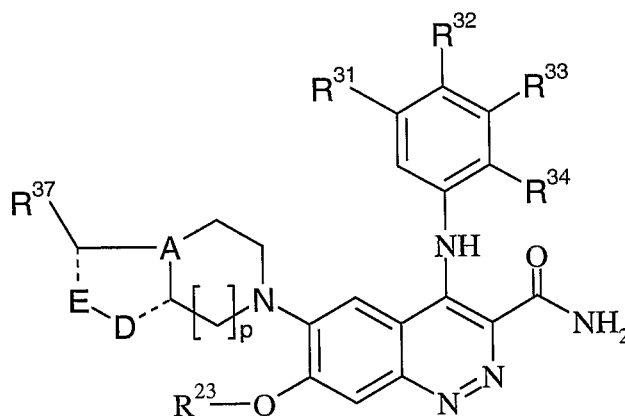
5 **R**³¹ is selected from hydrogen and methyl;

R³² is selected from hydrogen, fluoro, and methyl;

R^{33} is selected from hydrogen and chloro; and

R³⁴ is selected from fluoro and chloro.

10 6. A compound of formula (IE):

**formula (IE)**

or a pharmaceutically acceptable salt thereof, wherein:

--- is selected from a single and double bond;

15 **A** is selected from N, and CH;

D is selected from N, NH, CH, and CH₂;

E is selected from N, NH, CH, and CH₂;

p is 0-1;

R²³ is selected from C₁₋₆alkyl;

20 **R³¹** is selected from hydrogen and C₁₋₄alkyl;

R³² is selected from hydrogen, halo, and C₁₋₄alkyl;

R^{33} is selected from hydrogen and halo; and

R³⁴ is halo; and

R^{37} is selected from H and OH.

25

7. A compound of formula (I) or a pharmaceutically acceptable salt thereof selected from:

7-Ethoxy-4-[(2-fluoro-4-methyl-phenyl)amino]-6-(4-methylpiperazin-1-yl)cinnoline-3-carboxamide;

4-(2-Fluoro-4-methylphenylamino)-7-methoxy-6-(4-methylpiperazin-1-yl)cinnoline-3-carboxamide;

5 4-[(2,4-Difluorophenyl)amino]-7-methoxy-6-(4-methylpiperazin-1-yl)cinnoline-3-carboxamide;

6-[(3R,5S)-3,5-Dimethylpiperazin-1-yl]-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carboxamide;

10 4-[(2-Fluoro-4-methylphenyl)amino]-6-[4-(2-hydroxyethyl)piperazin-1-yl]-7-methoxycinnoline-3-carboxamide;

7-Ethoxy-4-[(2-fluoro-4-methylphenyl)amino]-6-[4-(2-hydroxyethyl)piperazin-1-yl]cinnoline-3-carboxamide;

4-[(3-Chloro-2-fluorophenyl)amino]-6-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-7-methoxycinnoline-3-carboxamide;

15 4-[(2-Fluoro-4-methylphenyl)amino]-6-(1-isopropylpiperidin-4-yl)-7-methoxycinnoline-3-carboxamide hydrochloride;

4-[(2-Fluoro-4-methylphenyl)amino]-6-[1-(2-hydroxyethyl)piperidin-4-yl]-7-methoxycinnoline-3-carboxamide; and

20 4-[(2-Fluoro-4-methylphenyl)amino]-6-{4-[(2R)-2-hydroxypropanoyl]piperazin-1-yl}-7-methoxycinnoline-3-carboxamide.

8. A compound of the formula (I) as in Claims 1-7, or a pharmaceutically acceptable salt thereof, for use as a medicament.

25 9. A compound of the formula (I) as in Claims 1-7, 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.

10. A compound of the formula (I) as in Claims 1-7, 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.

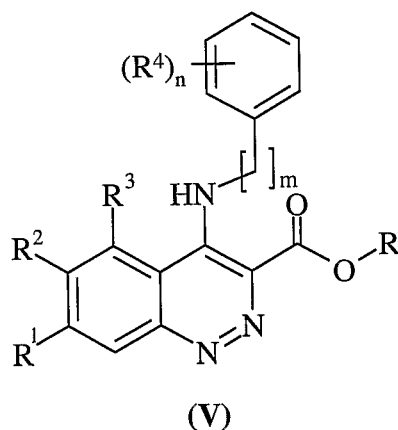
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11. A compound of formula (I) as in Claims 1-7, or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for the treatment of breast, ovarian, bladder, cervical, endometrial, prostate, lung, kidney and pancreatic tumors; haematological malignancies including myelodysplastic syndrome, acute myelogenous leukemia, chronic myelogenous leukemia, non Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma and chronic lymphocytic leukemia; and glioma, squamous cell carcinoma of the esophagus, malignant uveal melanoma and follicular lymphoma.

12. A method of treating cancer comprising providing a subject at risk for, diagnosed with, or exhibiting symptoms of cancer and administering a pharmaceutical composition comprising a compound of formula (I) as in Claims 1-7 to said subject.

13. A method of inhibiting CSF-1R kinase comprising providing a CSF-1R kinase and a compound of formula (I) as in Claims 1-7, and mixing under conditions such that CSF-1R kinase is inhibited.

14. A process of producing a compound of formula (I), or a pharmaceutically acceptable salt thereof, as in Claims 1-7 comprising reacting a compound of formula (V):



wherein R is C₁₋₆alkyl with formamide and a base, such that a compound of formula (I) is formed;

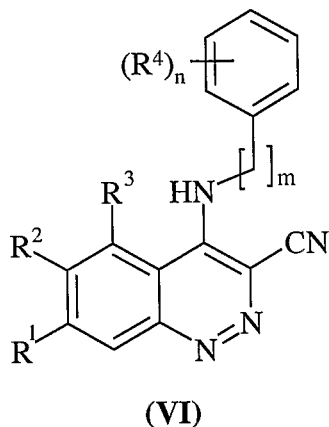
and optionally thereafter:

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

15. The process of Claim 14, wherein R is selected from methyl and ethyl.

16. A process of producing a compound of formula (I), or a pharmaceutically acceptable salt thereof, as in Claims 1-7 comprising

5 hydrolysis of a compound of formula (VI):



such that a compound of formula (I) is formed;

and optionally thereafter:

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

17. The process of Claim 16, wherein said hydrolysis is performed by reacting a compound of
 15 formula (VI) with a metal hydroxide and a tertiary alcohol.

18. The process of Claim 17, wherein said metal hydroxide is potassium hydroxide.

19. The process of Claim 17, wherein said tertiary alcohol is tert-butyl alcohol.