(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 November 2009 (12.11.2009)

PCT

(10) International Publication Number
WO 2009/136191 A1

(51) International Patent Classification:
C07D 237/28 (2006.01) *C07D 487/04* (2006.01)
C07D 401/04 (2006.01) *A61K 31/502* (2006.01)
C07D 403/04 (2006.01) *A61P 35/00* (2006.01)
C07D 417/04 (2006.01)

(21) International Application Number:
PCT/GB2009/050467

(22) International Filing Date:
6 May 2009 (06.05.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/051,188 7 May 2008 (07.05.2008) US
61/082,891 23 July 2008 (23.07.2008) US

(71) Applicant *(for all designated States except MG, US)*: **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(71) Applicant *(for MG only)*: **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London, Greater London W1K 1LN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DALY, Kevin** [US/US]; AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, Massachusetts 02451 (US). **DEL VALLE, David** [US/US]; AstraZeneca Intellectual Property, AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, Massachusetts 02451 (US). **SCOTT, David** [GB/US]; AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, Massachusetts 02451 (US). **YE, Qing** [CA/US]; AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, Massachusetts 02451 (US).

(74) Agent: **ASTRAZENECA INTELLECTUAL PROPERTY**; AstraZeneca AB, S-151 85 Södertälje (SE).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

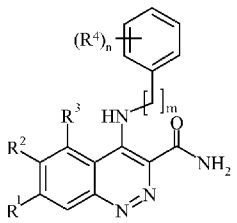
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) Title: CHEMICAL COMPOUNDS



(I)

(57) Abstract: The invention relates to chemical compounds of formula (I): or pharmaceutically acceptable salts thereof which possess CSF-IR 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.

WO 2009/136191 A1

CHEMICAL COMPOUNDS

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 (PDGFRα and PDGFRβ). 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).

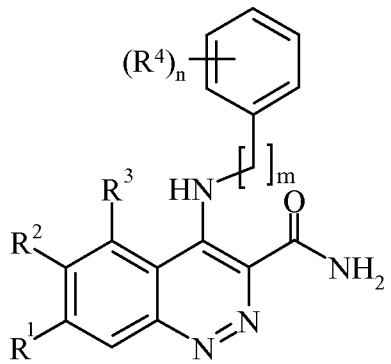
CSF-1R is normally expressed in myeloid cells of the mononuclear phagocytic lineage and their bone-marrow progenitors as well as the epithelial cells of the ducts and alveoli in the lactating, but not normal resting, breast tissue. CSF-1R activation stimulates the proliferation, survival, motility and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



(I)

wherein:

R^1 and **R^2** are independently 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)$_2$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}alkylS(O)$_a$ wherein a is 0 to 2, 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 is optionally substituted on carbon by one or more R^5; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen is 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, 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 is optionally substituted on carbon by one or more R^7; and wherein if said heterocyclic ring contains an -NH- moiety that nitrogen is 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)$_2$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}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)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl-R^9- or heterocyclyl-R^{10}-; wherein R^5 is optionally substituted on carbon by one or more R^{11}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen is 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 is 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)$_2$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}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)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl-R^{14}- or heterocyclyl-R^{15}-; wherein R^{13} is optionally substituted on carbon by one or more R^{16}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen is optionally substituted by a group selected from R^{17};

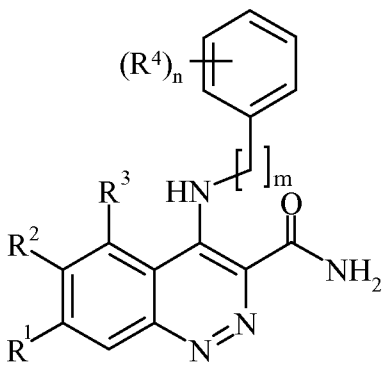
R^9, **R^{10}**, **R^{14}** and **R^{15}** are independently selected from a direct bond, -O-, -N(R^{18})-, -C(O)-, -N(R^{19})C(O)-, -C(O)N(R^{20})-, -S(O)$_s$-, -SO$_2$N(R^{21})- or -N(R^{22})SO$_2$-; wherein **R^{18}**, **R^{19}**, **R^{20}**, **R^{21}** and **R^{22}** are independently selected from 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)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, 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 a pharmaceutically acceptable salt thereof.

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



(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 is optionally substituted on carbon by one or more R^5; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen is 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, 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 is optionally substituted on carbon by one or more R^7; and wherein if said heterocyclic ring contains an -NH- moiety that nitrogen is 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)$_2$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}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)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl-R^9- or heterocyclyl-R^{10}-; wherein R^5 is optionally

substituted on carbon by one or more R^{11}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen is 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 is 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)$_2$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}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)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl-R^{14}- or heterocyclyl-R^{15}-; wherein R^{13} is optionally substituted on carbon by one or more R^{16}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen is optionally substituted by a group selected from R^{17};

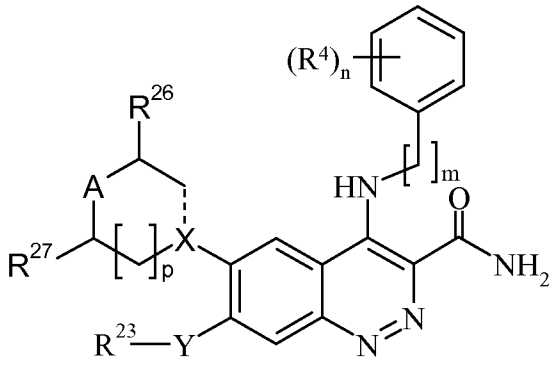
R^9, **R^{10}**, **R^{14}** and **R^{15}** are independently selected from a direct bond, -O-, -N(R^{18})-, -C(O)-, -N(R^{19})C(O)-, -C(O)N(R^{20})-, -S(O)$_s$-, -SO$_2$N(R^{21})- or -N(R^{22})SO$_2$-; wherein **R^{18}**, **R^{19}**, **R^{20}**, **R^{21}** and **R^{22}** are independently selected from 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)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, 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 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 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;

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

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

$\mathbf{R^7}$ is 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;

R^8 is 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} is selected from hydrogen, C_{1-6}alkyl and C_{1-6}alkanoyl , wherein C_{1-6}alkyl and C_{1-6}alkanoyl is 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 is optionally substituted on carbon by one or more R^{35}; and wherein if said heterocyclic ring contains an -NH- moiety that nitrogen is optionally substituted by a group selected from R^{36};

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

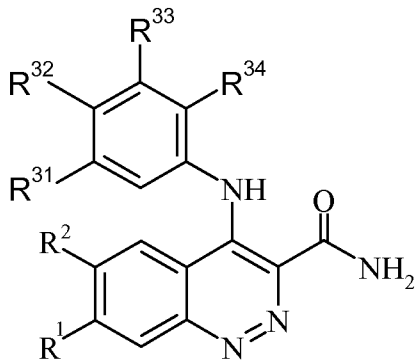
R^{30} is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *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; and

R^{35} is 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;

R^{36} is 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)$_2$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 is optionally substituted on carbon by one or more R^5; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen is 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)$_2$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}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)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl-R^9- or heterocyclyl-R^{10}-; wherein R^5 is optionally

substituted on carbon by one or more R^{11}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen is 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 is 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)$_2$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}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)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl-R^{14}- or heterocyclyl-R^{15}-; wherein R^{13} is optionally substituted on carbon by one or more R^{16}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen is optionally substituted by a group selected from R^{17};

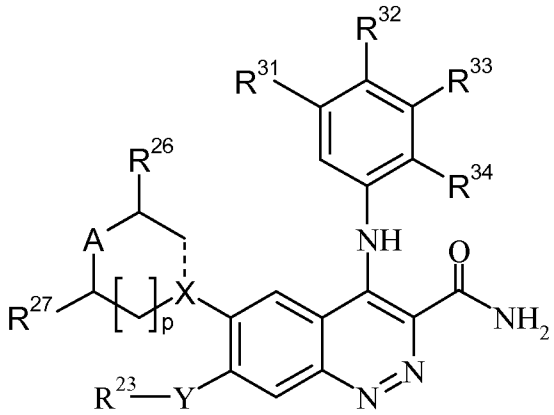
R^9, **R^{10}**, **R^{14}** and **R^{15}** are independently selected from a direct bond, -O-, -N(R^{18})-, -C(O)-, -N(R^{19})C(O)-, -C(O)N(R^{20})-, -S(O)$_s$-, -SO$_2$N(R^{21})- or -N(R^{22})SO$_2$-; wherein **R^{18}**, **R^{19}**, **R^{20}**, **R^{21}** and **R^{22}** are independently selected from 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, 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.

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 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;

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

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

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

$\mathbf{R^{29}}$ is selected from hydrogen and amino optionally substituted with one or more C_{1-6}alkyl;

$\mathbf{R^{30}}$ is 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;

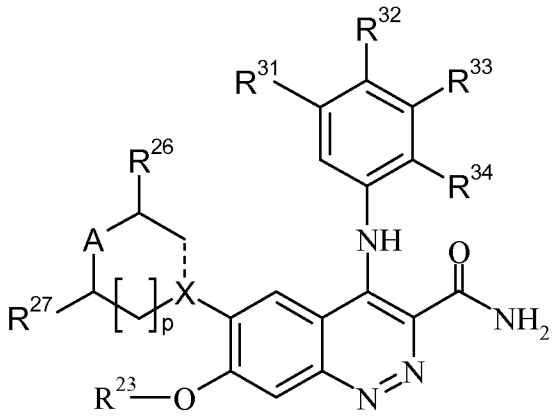
$\mathbf{R^{31}}$ is selected from hydrogen and C_{1-4}alkyl;

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

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

$\mathbf{R^{34}}$ 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;

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

$\mathbf{R^{25}}$ 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;

$\mathbf{R^{26}}$ and $\mathbf{R^{27}}$ are each independently selected from hydrogen and methyl;

$\mathbf{R^{29}}$ is dimethylamino;

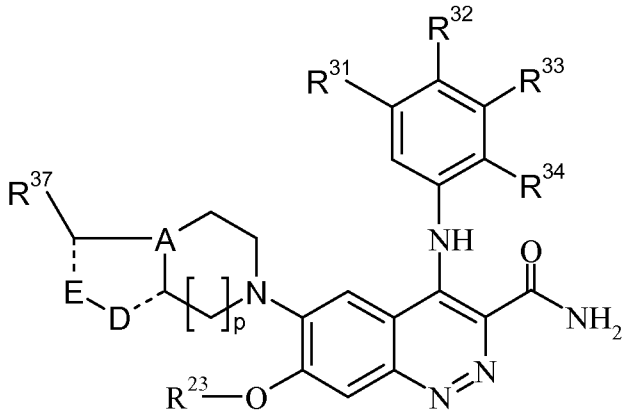
$\mathbf{R^{31}}$ is selected from hydrogen and methyl;

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

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

$\mathbf{R^{34}}$ is selected from fluoro and chloro.

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



formula (IE)

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 CH_2;

E is selected from N, NH, CH, and CH_2;

p is 0-1;

$\mathbf{R^{23}}$ is selected from $C_{1\text{-}6}$alkyl;

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

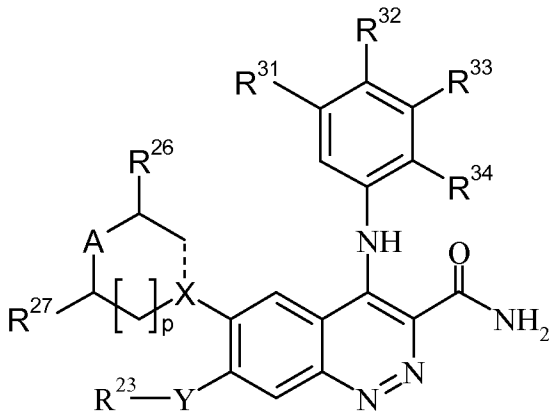
$\mathbf{R^{32}}$ is selected from hydrogen, halo, and $C_{1\text{-}4}$alkyl;

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

$\mathbf{R^{34}}$ is halo; and

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

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 CR^{24} and N;

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

Y is selected from O and S;

A is selected from SO_2, NR^{25}, and $CR^{28}R^{29}$;

p is selected from 0, 1, and 2;

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

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

$\mathbf{R^{25}}$ is C_{1-6}alkylsuflonyl;

$\mathbf{R^{29}}$ is C_{1-6}alkoxy optionally substituted with one or more R^{30};

$\mathbf{R^{30}}$ is 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;

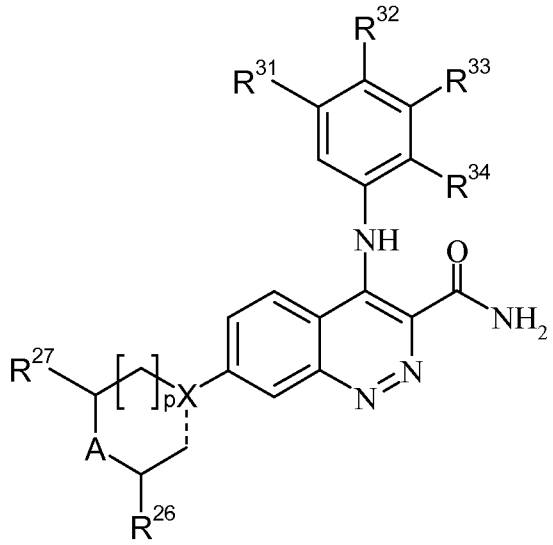
$\mathbf{R^{31}}$ is selected from hydrogen and C_{1-4}alkyl;

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

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

$\mathbf{R^{34}}$ is selected from halo.

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



formula (IF)

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;

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

p is 0-2;

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

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

R^{29} is selected from hydrogen, amino, and C_{1-6}alkoxy optionally substituted on carbon with one or more R^{30};

R^{30} is 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 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, "C_{1-6}alkyl" includes C_{1-4}alkyl, C_{1-3}alkyl, propyl, isopropyl and *t*-butyl. A similar convention applies to other radicals, for example "phenylC_{1-6}alkyl" includes phenylC_{1-4}alkyl, 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 -CH_2- group can optionally be replaced by a -C(O)- and a ring sulphur atom is 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 -CH_2- group can optionally be replaced by a -C(O)-and a ring sulphur atom is 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 -CH_2- 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 R^4 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 $-CH_2-$ 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 $-CH_2-$ group can optionally be replaced by a -C(O)- and a ring sulphur atom is optionally oxidised to form the S-oxides. Suitable examples of a "heterocyclic ring" fused to the phenyl ring in formula **(I)** include indolinyl (heterocyclic ring is a partially saturated 5 membered ring containing one nitrogen atom) and quinoxalinyl (heterocyclic ring is a totally unsaturated 6 membered ring containing two nitrogen atoms).

An example of "C_{1-6}alkanoyloxy" is acetoxy. Examples of "C_{1-6}alkoxycarbonyl" include methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl. Examples of "C_{1-6}alkoxy" include methoxy, ethoxy and propoxy. Examples of "C_{1-6}alkanoylamino" include formamido, acetamido and propionylamino. Examples of "C_{1-6}alkyl$S(O)_a$ wherein a is 0 to 2" include methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl. Examples of "C_{1-6}alkanoyl" include propionyl and acetyl. Examples of "*N*-(C_{1-6}alkyl)amino" include methylamino and ethylamino. Examples of "*N,N*-(C_{1-6}alkyl)$_2$amino" include di-*N*-methylamino, di-(*N*-ethyl)amino and *N*-ethyl-*N*-methylamino. Examples of "C_{2-6}alkenyl" are vinyl, allyl and 1-propenyl. Examples of "C_{2-6}alkynyl" are ethynyl, 1-propynyl and 2-propynyl. Examples of "*N*-(C_{1-6}alkyl)sulphamoyl" are *N*-(methyl)sulphamoyl and *N*-(ethyl)sulphamoyl. Examples of "*N*-(C_{1-6}alkyl)$_2$sulphamoyl" are *N,N*-(dimethyl)sulphamoyl and *N*-(methyl)-*N*-(ethyl)sulphamoyl. Examples of "*N*-(C_{1-6}alkyl)carbamoyl" are *N*-(C_{1-4}alkyl)carbamoyl, methylaminocarbonyl and ethylaminocarbonyl. Examples of "*N,N*-(C_{1-6}alkyl)$_2$carbamoyl" are *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, dimethylaminocarbonyl and methylethylaminocarbonyl. Examples of "C_{1-6}alkylsulphonyl" are mesyl, ethylsulphonyl and

isopropylsulphonyl. Examples of "C_{1-6}alkylsulphonylamino" are mesylamino, ethylsulphonylamino and isopropylsulphonylamino. Examples of "C_{1-6}alkoxycarbonylamino" are methoxycarbonylamino and *t*-butoxycarbonylamino. Examples of "C_{1-6}alkoxycarbonylamino" 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 is 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 is optionally substituted on carbon by one or more R^5; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen is 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 is 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 is optionally substituted on carbon by one or more R^5; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen is 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 piperazinyl; wherein said piperazinyl is optionally substituted on nitrogen 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 methoxy, ethoxy or piperazin-1-yl; wherein R^1 and R^2 independently of each other is optionally substituted on carbon by one or more R^5; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen is optionally substituted by a group selected from R^6; wherein

R^5 is methoxy; and

R^6 is methyl, ethyl, isopropyl or *t*-butyl.

R^1 and R^2 are independently selected from methoxy, ethoxy or piperazinyl; wherein said piperazinyl is optionally substituted on nitrogen by a group selected from R^6; wherein R^6 is selected from methyl, ethyl or isopropyl.

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^1 and R^2 are independently selected from methoxy, ethoxy, 1-methylpiperazin-4-yl, 1-ethylpiperazin-4-yl or 1-isopropylpiperazin-4-yl.

R^1 and R^2 are both methoxy or R^1 is ethoxy and R^2 is selected from 1-methylpiperazin-4-yl, 1-ethylpiperazin-4-yl or 1-isopropylpiperazin-4-yl.

R^1 and R^2 are both methoxy.

R^1 is ethoxy and R^2 is selected from 1-methylpiperazin-4-yl, 1-ethylpiperazin-4-yl or 1-isopropylpiperazin-4-yl.

R^1 is 2-methoxyethoxy, ethoxy or methoxy.

R^2 is 4-ethylpiperazin-1-yl, 4-isopropylpiperazin-1-yl, 4-methylpiperazin-1-yl, 4-*tert*-butylpiperazin-1-yl or methoxy.

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

R^3 is hydrogen.

m is 0.

m is 1.

R^4 is selected from halo or methyl.

R^4 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.

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

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;

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:

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 is 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;

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:

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;

R^4 is selected from fluoro, chloro 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:

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

R^3 is hydrogen;

m is 0;

R^4 is selected from fluoro, chloro or methyl; and

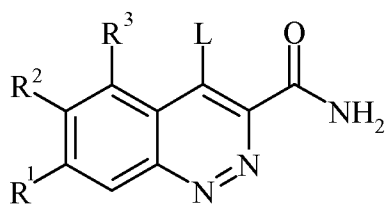
n is 2; wherein the values of R^4 are the same or different;

or a pharmaceutically acceptable salt thereof.

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

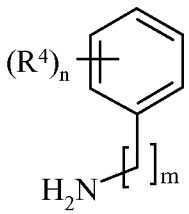
Another aspect of the present invention provides a process for preparing a compound of formula **(I)** or a pharmaceutically acceptable salt thereof which process (wherein variable groups are, unless otherwise specified, as defined in formula **(I)**) comprises of:

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



(II)

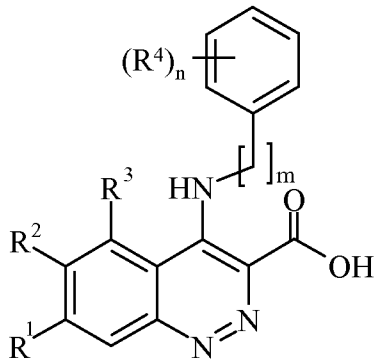
wherein L is a displaceable atom or group; with a compound of formula **(III)**:



(III)

or

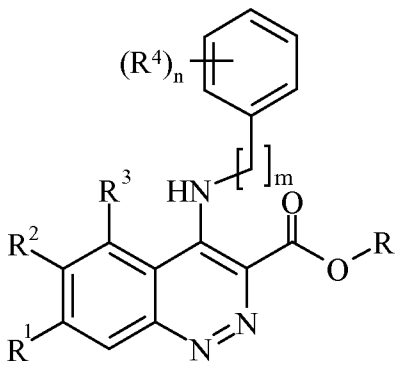
Process b) reacting a compound of formula **(IV)**:



(IV)

or an activated derivative thereof; with ammonia;

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

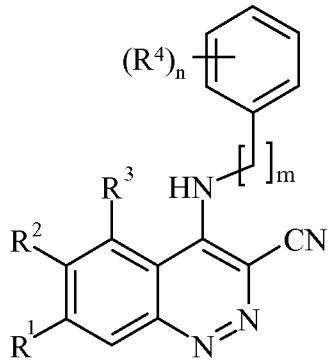


(V)

wherein R is C_{1-6}alkyl, in particular methyl and ethyl; with formamide and a base;

or

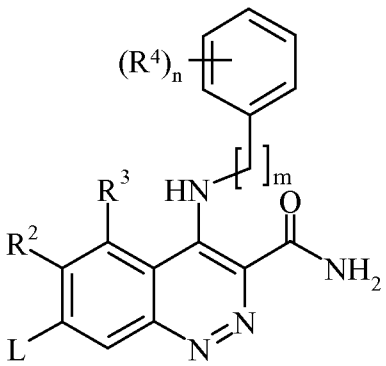
Process d) hydrolysis of a compound of formula **(VI)**:



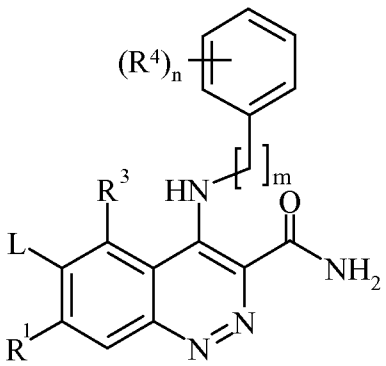
(VI)

or

Process e) for compounds of formula **(I)** when one of R^1 and R^2 is a carbon linked group; by reaction of a compound of formula **(VIIa)** or **(VIIb)**:



(VIIa)



(VIIb)

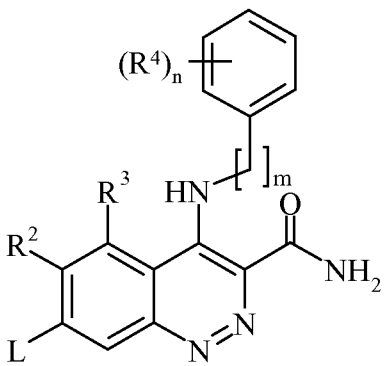
wherein L is a displaceable group; with a compound of formula **(VIIIa)** or **(VIIIb)**:

R^1-B(R^a)$_2$ R^2-B(R^a)$_2$

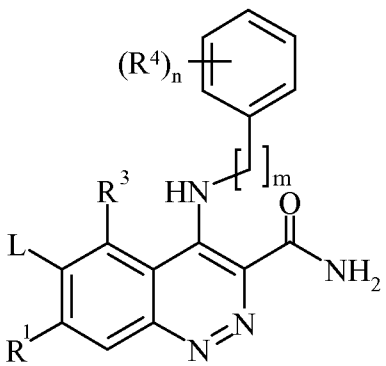
(VIIIa) **(VIIIb)**

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

Process f) for compounds of formula **(I)** when one of R^1 and R^2 is a nitrogen linked group; by reaction of a compound of formula **(IXa)** or **(IXb)**:



(IXa)



(IXb)

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

R^1-H	R^2-H
(Xa)	**(Xb)**

and thereafter if necessary:

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 triakylborane is 9-borabicyclo[3.3.1]nonyl.

Specific reaction conditions for the above reactions are as follows.

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).

Compounds of formula **(III)** are commercially available compounds or they are literature compounds or they may be 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 dicyclohexyl-carbodiimide, optionally in the presence of a catalyst such as dimethylaminopyridine or 4-pyrrolidinopyridine, optionally in the presence of a base for example triethylamine, pyridine, or 2,6-di-*alkyl*-pyridines such as 2,6-lutidine or 2,6-di-*tert*-butylpyridine. Suitable solvents include dimethylacetamide, dichloromethane, benzene, tetrahydrofuran and

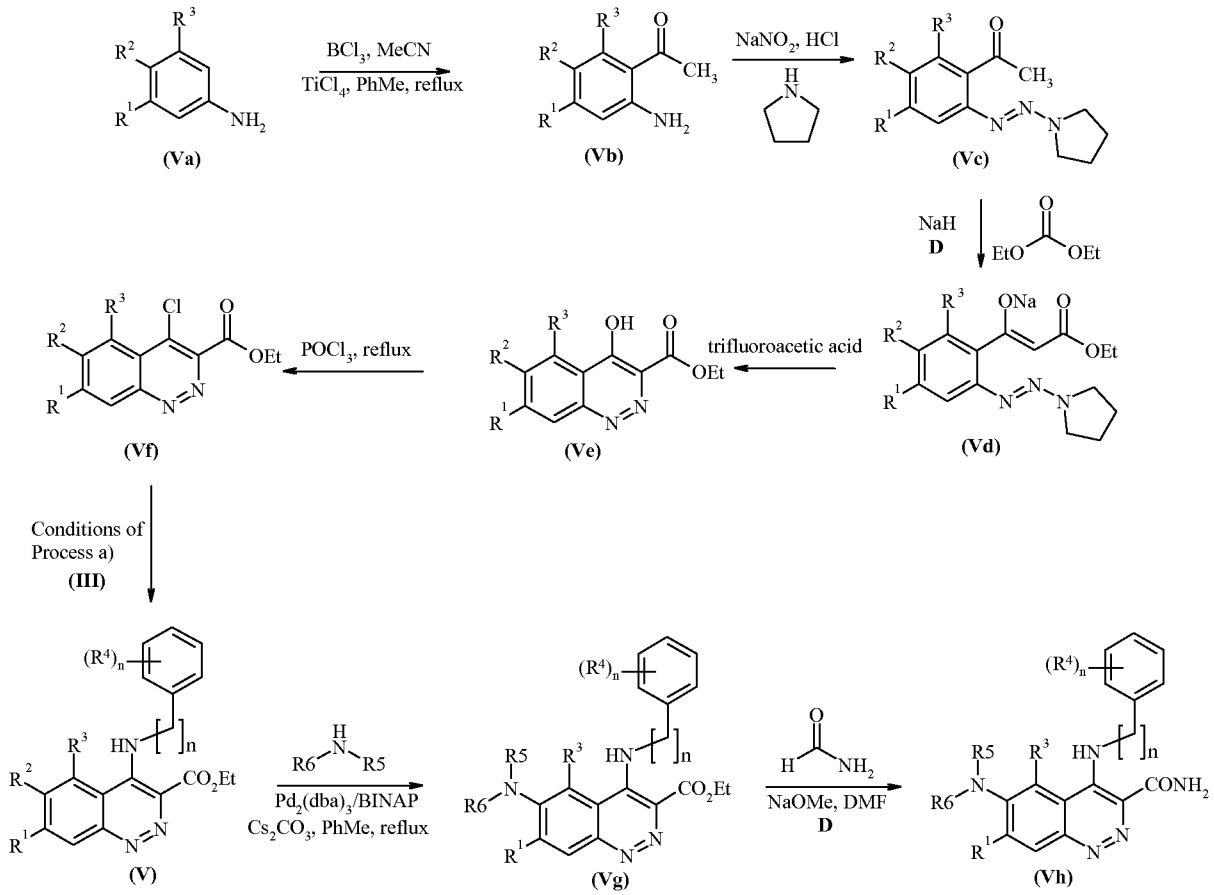
dimethylformamide. The coupling reaction may conveniently be performed at a temperature in the range of -40 to 40 °C.

Suitable activated acid derivatives include acid halides, for example acid chlorides, and active esters, for example pentafluorophenyl esters. The reaction of these types of compounds with amines is well known in the art, for example they is 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 $Pd(PPh_3)_4$ 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*.

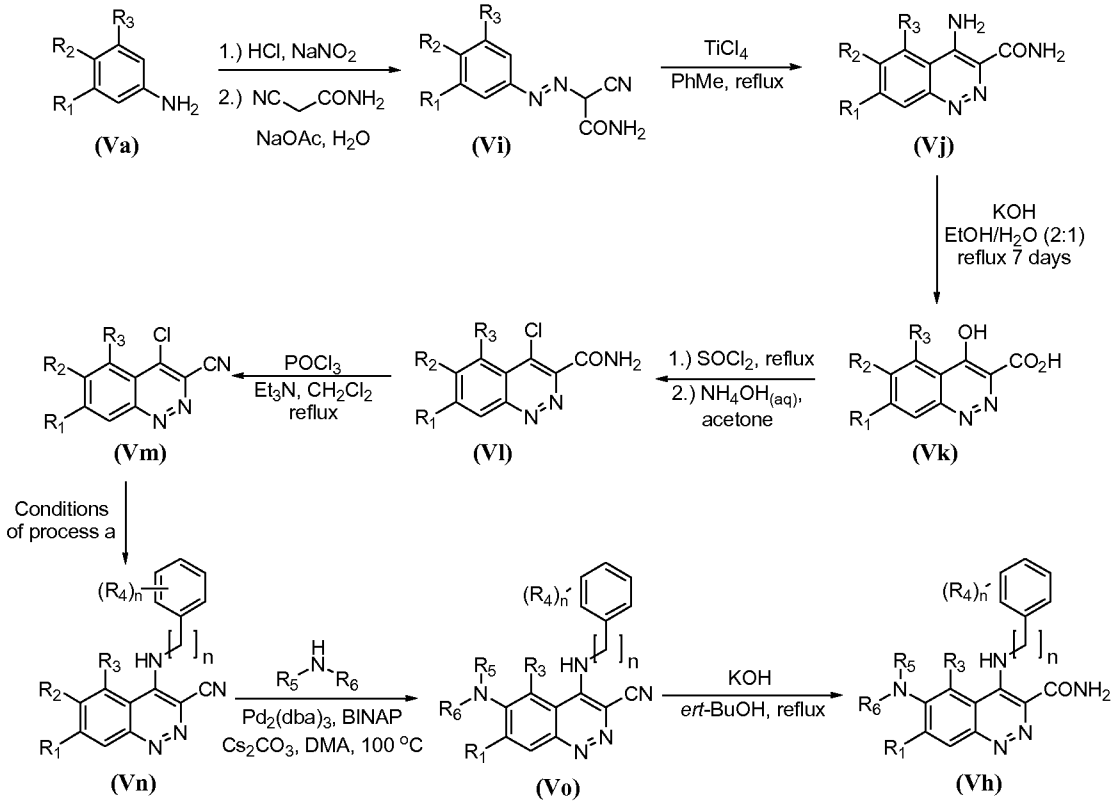
Compounds of formula **(VIIIa)** and **(VIIIb)** are commercially available compounds or they are literature compounds or they are readily prepared by processes known to the person skilled in the art.

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 $Pd_2(dba)_3$, 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*.

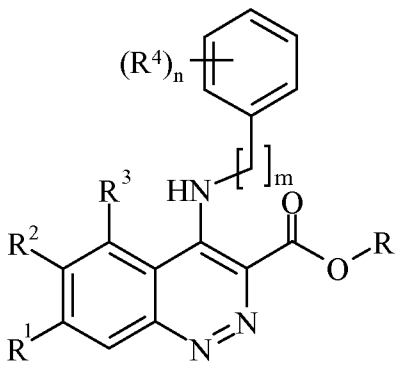
Compounds of formula **(Xa)** and **(Xb)** are commercially available compounds or they are literature compounds or they are readily prepared by processes known to the person skilled in the art.

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*:



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)**:



(V)

wherein R is $C_{1\text{-}6}$alkyl with formamide and a base, such that a compound of formula **(I)** is formed;

and optionally thereafter:

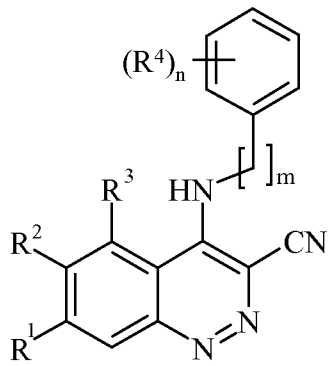
i) converting a compound of the formula **(I)** into another compound of the formula **(I)**;

ii) removing any protecting groups; or

iii) forming a pharmaceutically acceptable salt.

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.

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

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

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

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

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

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

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 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 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.

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 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 IC_{50}s 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 $MgCl_2$ 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 IC_{50}s 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 μM. For example the following results 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	

Example No		**Assay 1 IC_{50}**	**Assay 2 IC_{50}**
24		< 3 nM	
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			

Example No		Assay 1 IC_{50}	Assay 2 IC_{50}
47			6 nM
48			< 3 nM
49			20 nM
50			33 nM
51			
52			
53			
54			
55			3 nM
56			11 nM
57			8 nM
58			3 nM
59			48 nM
60			39 nM

Example No		Assay 1 IC_{50}	Assay 2 IC_{50}
61			23 nM
62			26 nM
63			12 nM
64			
65			6 nM
66			4 nM
67			5 nM
68			6 nM
69			23 nM
70			24 nM
71			39 nM
72			52 nM
73			52 nM

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 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 herein before in the manufacture of a medicament for use in the treatment of breast, ovarian, bladder, cervical, endometrial, prostate, lung, kidney and pancreatic tumors; haematological malignancies including myelodysplastic syndrome, acute myelogenous leukemia, chronic myelogenous leukemia, non Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma and 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 before in the manufacture of a medicament for use in the treatment of tumor-associated osteolysis, osteoporosis including ovariectomy-induced bone loss, orthopedic implant failure, autoimmune disorders including systemic lupus erythematosus, arthritis including rheumatoid arthritis, osteoarthritis, renal inflammation and glomerulonephritis; inflammatory bowel disease; transplant rejection including renal and bone marrow allografts and skin xenograft,

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

According to a further feature of this aspect of the invention there is provided a method for producing a CSF-1R kinase inhibitory effect in a warm-blooded animal, such as 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 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 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 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 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.

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 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 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 iodoxyfene), oestrogen receptor down regulators (for example fulvestrant), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and

buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5α-reductase such as finasteride;

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

(iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies (for example the anti-erbb2 antibody trastuzumab [Herceptin™] and the anti-erbb1 antibody cetuximab [C225]) , farnesyl transferase inhibitors, MEK inhibitors, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-*N*-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, (for example the anti-vascular endothelial cell growth factor antibody bevacizumab [Avastin™], compounds such as those disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354) and compounds that work by other mechanisms (for example linomide, inhibitors of integrin αvβ3 function and angiostatin);

(vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO00/40529, WO 00/41669, WO01/92224, WO02/04434 and WO02/08213;

(vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy;

(ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies;

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

(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.

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.

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

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; 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;

(iv) final products had satisfactory proton nuclear magnetic resonance (NMR) spectra and/or mass spectral data;

(v) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 400 MHz using perdeuterio dimethyl sulphoxide (DMSO-d_6) 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 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

and

(xii) the following abbreviations have been used:

DMA	*N,N*-dimethylacetamide
DMF	*N,N*-dimethylformamide;
EtOAc	ethyl acetate;
MeOH	methanol;
THF	tetrahydrofuran;
TFA	trifluoroacetic acid;
DMSO	dimethylsulphoxide; and

DCM dichloromethane.

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) (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 0.174 g (96 %) of the title compound as a white solid. ^{1}H 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)

Ex.	Compound	^{1}H NMR (300 MHz)	m/z	Starting Material
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 9m, 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)
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)

Ex.	Compound	^{1}H NMR (300 MHz)	m/z	Starting Material
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-fluoro-phenyl)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)
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)

Ex.	Compound	^{1}H NMR (300 MHz)	m/z	Starting Material
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.

Example 13

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 $MgSO_4$, 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. ^{1}H 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)	m/z	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
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

Example	Compound	^{1}H NMR (300 MHz)	m/z	Starting Material
16	6-(4-*tert*-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-*tert*-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
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

Example	Compound	^{1}H NMR (300 MHz)	m/z	Starting Material
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
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

Example	Compound	^{1}H NMR (300 MHz)	m/z	Starting Material
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
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

Example	Compound	^{1}H NMR (300 MHz)	m/z	Starting Material
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
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

Example	Compound	^{1}H NMR (300 MHz)	m/z	Starting Material
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
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

Example	Compound	^{1}H NMR (300 MHz)	m/z	Starting Material
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
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

Example	Compound	^{1}H NMR (300 MHz)	m/z	Starting Material
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-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)-1,2,3,6-tetrahydropyridin-4-yl]-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile Method 87
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

Example	Compound	^{1}H NMR (300 MHz)	m/z	Starting Material
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
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-{[*tert*-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

Example	Compound	^{1}H NMR (300 MHz)	m/z	Starting Material
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
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

Example	Compound	^{1}H NMR (300 MHz)	m/z	Starting Material
43	7-Ethoxy-4-[(2-fluoro-4-methylphenyl)amino]-6-[4-(2-hydroxyethyl)piperazin-1-yl]cinnoline-3-carboxamide	CDCl3 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-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)piperazin-1-yl]-7-ethoxy-4-[(2-fluoro-4-methylphenyl)amino]cinnoline-3-carbonitrile Method 80
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

Example	Compound	^{1}H NMR (300 MHz)	m/z	Starting Material
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

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. ^{1}H 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.

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)	m/z	Starting Material

Example	Compound	^{1}H NMR (300 MHz)	m/z	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**

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 CH_2Cl_2 (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*-ethyldiisopropylamine (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 CH_2Cl_2. The organic extract was concentrated under reduced pressure, and the residue purified with silica chromatography (Hex/EtOAc, then with CH_2Cl_2/MeOH). The crude product was triturated with CH_3CN and filtered to give 173 mg (37 %) yellow solid. ^{1}H NMR: 11.33 (s, 1 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.

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. ^{1}H 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

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% $Pd(OH)_2$/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. ^{1}H 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.

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 CH_2Cl_2 (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 CH_2Cl_2/5% MeOH(1% NH_4OH) 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(2*H*)-carboxylate

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 N_2 (g) at 100 °C overnight. The reaction mixture was cooled, concentrated under reduced pressure and the residue purified with silica chromatography (CH_2Cl_2/MeOH) to give 1.54 g (96 %) of a light brown solid. ^{1}H 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, 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

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. ^{1}H NMR: 12.15 (s, 1 H), 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-yldiazenyl]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 $MgSO_4$, 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. ^{1}H 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)	m/z	Starting Material
2	1-{5-Bromo-4-ethoxy-2-[(*E*)-pyrrolidin-1-yldiazenyl]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-yldiazenyl]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-yldiazenyl]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. ^{1}H 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.

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)	m/z	Starting Material
4	Ethyl 3-{5-bromo-4-ethoxy-2-[(*E*)-pyrrolidin-1-yldiazenyl]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-[(*E*)-pyrrolidin-1-yldiazenyl]phenyl} ethanone (Method 2)

Method 5

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-yldiazenyl]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. ^{1}H 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

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-[(*E*)-pyrrolidin-1-yldiazenyl]phenyl}-3-oxopropanoate (Method 4)

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 $NaHCO_3$ (~ 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. ^{1}H 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.

Method 8

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

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 Na_2SO_4 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 Na_2SO_4 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%). ^{1}H 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, 18.11mmol), 5 wt % $FeCl_3$ on SiO_2 (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 %). ^{1}H 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
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 N_2 was added $TiCl_4$ (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 %). ^{1}H 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 %). ^{1}H 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	m/z	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. ^{1}H 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. ^{1}H NMR: 8.71 (s, 1 H), 8.29 (s, 1 H), 4.30 (s, 3 H); *m/z*: 299.

Methods 25-26

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

Method	Compound	m/z	Starting Material

Method	Compound	m/z	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

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 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. ^{1}H NMR: 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); *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

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-ethoxy-cinnoline-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-fluoro-phenyl)amino]-7-ethoxy-cinnoline-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-methyl-phenyl)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.

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 $TiCl_4$ 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

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. $Pd_2(dba)_3$ (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 though 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	m/z	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-ethoxy-cinnoline-3-carboxylate (Method 34)
50	Ethyl 4-[(3-chloro-2-fluoro-phenyl)amino]-7-ethoxy-6-(4-methylpiperazin-1-yl)cinnoline-3-carboxylate	489	ethyl 6-bromo-4-[(3-chloro-2-fluoro-phenyl)amino]-7-ethoxy-cinnoline-3-carboxylate (Method 35)
51	Ethyl 7-ethoxy-4-[(2-fluoro-4-methyl-phenyl)amino]-6-(4-methylpiperazin-1-yl)cinnoline-3-carboxylate	469	ethyl 6-bromo-7-ethoxy-4-[(2-fluoro-4-methyl-phenyl)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-*tert*-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-{[*tert*-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-{[*tert*-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-{[*tert*-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-{[*tert*-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 K_2CO_3 (0.357 g, 2.58 mmol) in DMA (3.0 ml) and water (0.30 ml), was added $Pd(Ph_3P)_4$ (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 ($MgSO_4$), 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

Method	Compound	m/z	Starting Materials
85	*tert*-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 *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate

Method 86

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

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 residue purified with silica chromatography (MeOH/EtOAc (1:1)) to give 120 mg (50 %) product. *m/z* 432.

Method 87

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

Method	Compound	m/z	Starting Material

Method	Compound	m/z	Starting Material
87	6-[1-(2-{[*tert*-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 (*tert*-butyldimethylsilyloxy)acetaldehyde

Method 88

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

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 CH_2Cl_2 (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 (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 (Method 90, 2.1 g, 5.55 mmol) and Pd/C (0.059 g, 0.55 mmol) in methanol (30 mL) was stirred under H_2 (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. ^{1}H NMR: CD_3Cl 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 CH_2Cl_2 (3 x 50 mL). The combined organic extracts were concentrated under reduced pressure, and the residue purifed with silica chromatography (EtOAc/MeOH) to give 2.10 g, (61 %) of a clear oil. ^{1}H 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).

Example 55

4-[(2-Fluoro-4-methylphenyl)amino]-7-(4-methylpiperazin-1-yl)cinnoline-3-carboxamide

To a suspension of 4-(2-fluoro-4-methylphenylamino)-7-(4-methylpiperazin-1-yl)cinnoline-3-carbonitrile (Method 96, 180 mg, 0.48 mmol) in ^{t}BuOH (4.80 ml) was added powdered potassium hydroxide (2.154g, 38.4 mmol) and the reaction mixture stirred at 100 °C for 1 hour. The reaction mixture was cooled and concentrated under reduced pressure. Water was added and the mixture extracted with DCM/10%MeOH. The organic layer was dried with (Na_2SO_4), filtered, concentrated and the residue purified with silica chromatography (DCM to DCM / 10% MeOH / 1% NH_4OH)) to give 141 mg (74 %) of a yellow solid. ^{1}H NMR: 11.41 (s, 1 H), 8.73 (s, 1 H), 7.87 (s, 1 H), 7.41 (s, 1 H), 7.32 (d, 1 H), 7.27 (d, 1 H), 7.18 (m, 2 H), 7.01 (d, 1 H), 3.39 (m, 4 H), 2.44 (m, 4 H), 2.33 (s, 3 H), 2.22 (s, 3 H); *m/z* 395.

Examples 56-63

The following examples were prepared according to the procedure in Example 55 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

Ex.	Compound	^{1}H NMR (300 MHz)	m/z	Starting Material
56	4-[(2-Fluoro-4-methylphenyl)amino]-7-[4-(methylsulfonyl)piperazin-1-yl]cinnoline-3-carboxamide	11.45 (s, 1 H), 8.75 (s, 1 H), 7.88 (s, 1 H), 7.49 (s, 1 H), 7.37 (d, 1 H), 7.30 (d, 1 H), 7.19 (m, 2 H), 7.04 (d, 1 H), 3.55 (m, 4 H), 3.25 (m, 4 H), 2.93 (s, 3 H), 2.34 (s, 3 H)	459	4-[(2-fluoro-4-methylphenyl)amino]-7-[4-(methylsulfonyl)piperazin-1-yl]cinnoline-3-carbonitrile (Method 97)
57	4-[(2-Fluoro-4-methylphenyl)amino]-7-[4-(2-hydroxyethyl)piperazin-1-yl]cinnoline-3-carboxamide	11.41 (s, 1 H), 8.72 (s, 1 H), 7.87 (s, 1 H), 7.40 (s, 1 H), 7.37 (d, 1 H), 7.27 (d, 1 H), 7.17 (m, 2 H), 7.02 (d, 1 H), 4.46 (t, 1 H), 3.54 (m, 2 H), 3.39 (m, 4 H), 2.55 (m, 4 H), 2.42 (t, 2 H), 2.33 (s, 3 H)	425	4-[(2-fluoro-4-methylphenyl)amino]-7-[4-(2-hydroxyethyl)piperazin-1-yl]cinnoline-3-carbonitrile (Method 105)
58	4-[(2-Fluoro-4-methylphenyl)amino]-6-[4-(2-hydroxyethyl)-1,4-diazepan-1-yl]-7-methoxycinnoline-3-carboxamide	11.16 (s, 1 H), 8.75 (s, 1 H), 7.89 (s, 1 H), 7.53 (s, 1 H), 7.17 (d, 1 H), 7.10 (dd, 1 H), 7.01 (d, 1 H), 6.48 (s, 1 H), 4.33 (t, 1 H), 3.99 (s, 3 H), 3.43 (m, 2 H), 3.14 (m, 2 H), 3.05 (m, 2 H), 2.59 (m, 2 H), 2.54 (m, 4 H), 2.32 (s, 3 H), 1.63 (m, 2 H)	469	4-[(2-fluoro-4-methylphenyl)amino]-6-[4-(2-hydroxyethyl)-1,4-diazepan-1-yl]-7-methoxycinnoline-3-carbonitrile (Method 99)

Ex.	Compound	^{1}H NMR (300 MHz)	m/z	Starting Material
59	4-[(2-Fluoro-4-methylphenyl)amino]-7-methoxy-6-(4-methoxypiperidin-1-yl)cinnoline-3-carboxamide	11.26 (s, 1 H), 8.75 (s, 1 H), 7.89 (s, 1 H), 7.56 (s, 1 H), 7.16 (m, 2 H), 7.04 (m, 1 H), 6.62 (s, 1 H), 3.99 (s, 3 H), 3.21 (s, 3 H), 3.15 (m, 1 H), 2.96 (m, 2 H), 2.51 (m, 2 H), 2.32 (s, 3 H), 1.76 (m, 2 H), 1.38 (m, 2 H)	440	4-[(2-fluoro-4-methylphenyl)amino]-7-methoxy-6-(4-methoxypiperidin-1-yl)cinnoline-3-carbonitrile (Method 100)
60	4-[(2-Fluoro-4-methylphenyl)amino]-7-methoxy-6-[4-(2-methoxyethoxy)piperidin-1-yl]cinnoline-3-carboxamide	11.27 (s, 1 H), 8.76 (s, 1 H), 7.91 (s, 1 H), 7.56 (s, 1 H), 7.16 (m, 2 H), 7.03 (m, 1 H), 6.61 (s, 1 H), 3.99 (s, 3 H), 3.50 (m, 2 H), 3.41 (m, 2 H), 3.32 (m, 1 H), 3.24 (s, 3 H), 2.98 (m, 2 H), 2.48 (m, 2 H), 2.32 (s, 3 H), 1.75 (m, 2 H), 1.39 (m, 2 H)	484	4-[(2-fluoro-4-methylphenyl)amino]-7-methoxy-6-[4-(2-methoxyethoxy)piperidin-1-yl]cinnoline-3-carbonitrile (Method 101)
61	4-[(2-Fluoro-4-methylphenyl)amino]-7-methoxy-6-[4-(methylsulfonyl)piperazin-1-yl]cinnoline-3-carboxamide	11.33 (s, 1 H), 8.78 (s, 1 H), 7.93 (s, 1 H), 7.62 (s, 1 H), 7.20 (m, 2 H), 7.08 (m, 1 H), 6.66 (s, 1 H), 4.01 (s, 3 H), 3.13 (m, 4 H), 2.90 (s, 3 H), 2.80 (m, 4 H), 2.33 (s, 3 H)	489	4-[(2-fluoro-4-methylphenyl)amino]-7-methoxy-6-[4-(methylsulfonyl)piperazin-1-yl]cinnoline-3-carbonitrile (Method 102)

Ex.	Compound	^{1}H NMR (300 MHz)	m/z	Starting Material
62	6-(1,1-Dioxidothio morpholin-4-yl)-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carboxamide	11.32 (s, 1 H), 8.78 (s, 1 H), 7.93 (s, 1 H), 7.62 (s, 1 H), 7.18 (m, 2 H), 7.08 (m, 1 H), 6.71 (s, 1 H), 4.02 (s, 3 H), 3.24 (m, 4 H), 3.06 (m, 4 H), 2.33 (s, 3 H)	460	6-(1,1-dioxidothiomorpholin-4-yl)-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile (Method 103)
63	4-[(2-Fluoro-4-methylphenyl)amino]-6-[(3R,5S)-4-(2-hydroxyethyl)-3,5-dimethylpiperazin-1-yl]-7-methoxycinnoline-3-carboxamide	CDCl3 11.02 (s, 1 H), 8.37 (s, 1 H), 7.51 (s, 1 H), 7.05 (m, 1 H), 6.89 (m, 2 H), 6.73 (s, 1 H), 5.75 (s, 1 H), 3.99 (s, 3 H), 3.54 (m, 2 H), 3.03 (m, 2 H), 2.72 (m, 4 H), 2.30 (s, 3 H), 2.06 (m, 2 H) 0.98 (d, 6 H)	483	6-[(3*R*,5*S*)-4-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-3,5-dimethylpiperazin-1-yl]-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile (Method 104)

Example 64

7-Bromo-4-[(2-fluoro-4-methylphenyl)amino]cinnoline-3-carboxamide

To a suspension of 7-bromo-4-chlorocinnoline-3-carboxamide (Method 94, 1.3 g, 4.54 mmol) in ethanol (11.3 mL) was added 2-fluoro-4-methylaniline (0.77 ml, 6.81 mmol) and acetic acid (0.026 mL, 0.45 mmol), and the reaction mixture stirred at 80 °C for 2 hours. After cooling, the reaction mixture was filtered, and the residue washed with ethanol and then dried to give 1.39 g (82 %) of a brown solid. ^{1}H NMR: 11.71 (s, 1 H), 8.90 (s, 1 H), 8.54 (s, 1 H), 8.11 (s, 1 H), 7.67 (d, 1 H), 7.41 (d, 1 H), 7.23 (m, 2 H), 7.04 (m, 1 H), 2.34 (s, 3 H); *m/z* 374.

Example 65

4-[(2-Fluoro-4-methylphenyl)amino]-7-methoxy-6-{4-[2-(methylsulfonyl)ethyl]piperazin-1-yl}cinnoline-3-carboxamide

To a solution of 4-(2-fluoro-4-methylphenylamino)-7-methoxy-6-(piperazin-1-yl)cinnoline-3-carboxamide (Example 46, 0.1 g, 0.24 mmol) in DCM (10 mL) at -78°C was added 1-bromo-2-(methylsulfonyl)ethane (0.046 g, 0.24 mmol). The reaction was stirred at room temperature for 20 hours, *N,N*-diisopropylethylamine (0.042 mL, 0.24 mmol) was added and the reaction stirred for another 48 hours. Water (30 mL) was added, and the mixture extracted with DCM. The organic extracts were concentrated and the residue purified with silica chromatography (MeOH/DCM 0-5%). The material obtained from chromatography was triturated in acetonitrile, and filtered to give 33 mg (27 %) of a solid. ^{1}H NMR: 11.31 (s, 1 H), 8.79 (s, 1 H), 7.94 (s, 1 H), 7.61 (s, 1 H), 7.19 (m, 2 H), 7.05 (m, 1 H), 6.63 (s, 1 H), 4.01 (s, 3 H), 3.29 (m, 2 H), 3.01 (s, 3 H), 2.71 (m, 6 H), 2.44 (m, 4 H), 2.34 (s, 3 H); *m/z* 517.

Example 66

4-[(2-Fluoro-4-methylphenyl)amino]-6-{4-[2-hydroxy-1-(hydroxymethyl)ethyl]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, 0.3 g, 0.73 mmol) in methanol (15 mL) was added 1,3-dihydroxypropan-2-one dimer (0.263 g, 1.46 mmol), acetic acid (1.55 mL, 27.0 mmol) and sodium cyanoborohydride (0.092 g, 1.46 mmol). After stirring for 48 hours, the reaction mixture was concentrated and purified by silica chromatography (7% MeOH in DCM (1% NH_4OH)) to give 56mg (16 %) of a yellow solid. ^{1}H NMR: CD_3OD 7.49 (s, 1 H), 7.17 (m, 1 H), 7.07 (m, 2 H), 6.74 (s, 1 H), 4.05 (s, 3 H), 3.68 (m, 4 H), 2.82 (m, 8 H), 2.67 (m, 1 H), 2.38 (s, 3 H); *m/z* 485.

Example 67

6-{4-[(2*S*)-2,3-Dihydroxypropyl]piperazin-1-yl}-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carboxamide

To a suspension of 4-(2-fluoro-4-methylphenylamino)-7-methoxy-6-(piperazin-1-yl)cinnoline-3-carboxamide (Example 46, 0.12 g, 0.29 mmol) in ethanol (4 mL) was added (*R*)-oxiran-2-ylmethanol (0.024 g, 0.32 mmol). After stirring at 70 °C for 4 hours, the solvent was removed under reduced pressure and the residue purified by silica chromatography (10 % MeOH in DCM (1 % NH_4OH)) to give 54 mg (38 %) solid. ^{1}H NMR: 11.30 (s, 1 H), 8.78 (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), 4.52 (m, 1 H),

4.41 (m, 1 H), 4.01 (s, 3 H), 3.59 (m, 1 H), 3.31 (m, 2 H), 2.73 (m, 4 H), 2.42 (m, 4 H), 2.37 (m, 1 H), 2.33 (s, 3 H), 2.27 (m, 1 H); *m/z* 485.

The following example was made by a procedure similar to that used in Example 67 form Example 46, (*S*)-oxiran-2-ylmethanol:

Example 68

6-{4-[(2*R*)-2,3-Dihydroxypropyl]piperazin-1-yl}-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carboxamide

^{1}H NMR: 11.28 (s, 1 H), 8.76 (s, 1 H), 7.90 (s, 1 H), 7.56 (s, 1 H), 7.17 (m, 2 H), 7.05 (m, 1 H), 6.60 (s, 1 H), 4.50 (t, 1 H), 4.39 (d, 1 H), 3.99 (s, 3 H), 3.58 (m, 1 H), 3.29 (m, 2 H), 2.71 (m, 4 H), 2.40 (m, 4 H), 2.35 (m, 1 H), 2.32 (s, 3 H), 2.21 (m, 1 H); *m/z* 485.

Example 69

4-[(2-Fluoro-4-methylphenyl)amino]-6-[4-(2-hydroxy-2-methylpropanoyl)piperazin-1-yl]-7-methoxycinnoline-3-carboxamide

A solution of 4-(2-fluoro-4-methylphenylamino)-7-methoxy-6-(piperazin-1-yl)cinnoline-3-carboxamide (Example 46, 0.23 g, 0.56 mmol), *N, N*-diisopropylethylamine (0.146 mL, 0.84 mmol) and 2-chloro-1,1-dimethyl-2-oxoethyl acetate (0.092 g, 0.56 mmol) in DMF (3 mL) was stirred for 30 minutes. The solvent was removed under reduced pressure, DCM (10 ml) was added, and the mixture washed with saturated $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4), filtered and concentrated to give 0.29 g of 2-(4-{3-carbamoyl-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnolin-6-yl}piperazin-1-yl)-1,1-dimethyl-2-oxoethyl acetate as a gum, used without further purification. *m/z* 540.

To a solution of 2-(4-{3-carbamoyl-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnolin-6-yl}piperazin-1-yl)-1,1-dimethyl-2-oxoethyl acetate (0.29 g, 0.54 mmol) in methanol (4 mL) was added lithium hydroxide (0.026 g, 1.08 mmol). After stirring for 1.5 hours, the solvent was removed under reduced pressure and the residue purified by silica chromatography (6 % MeOH in DCM (1 % NH_4OH)) to give 107 mg (40 %) solid. ^{1}H NMR: 11.38 (s, 1 H), 8.77 (s, 1 H), 7.93 (s, 1 H), 7.59 (s, 1 H), 7.21 (m, 2 H), 7.06 (m, 1 H), 6.62 (s, 1 H), 5.44 (s, 1 H), 4.01 (s, 3 H), 3.94 (m, 2 H), 3.47 (m, 2 H), 2.68 (m, 4 H), 2.32 (s, 3 H), 1.29 (s, 6 H); *m/z* 497.

The following example was made by a procedure similar to that used in Example 69, starting from Example 51 and (1*S*)-2-chloro-1-methyl-2-oxoethyl acetate:

Example 70

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

^{1}H NMR: CD_3OD 7.46 (m, 1 H), 7.32 (m, 2 H), 7.25 (m, 2 H), 4.56 (m, 2 H), 4.11 (s, 3 H), 4.07 (m, 1 H), 3.21 (m, 1 H), 3.13 (m, 1 H), 2.68 (m, 1 H), 2.48 (s, 3 H), 1.76 (m, 1 H), 1.63 (m, 1 H), 1.33 (m, 3 H), 0.96 (m, 1 H), 0.87 (m, 1 H); *m/z* 482.

Example 71

6-[1-(2,2-Difluoroethyl)piperidin-4-yl]-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carboxamide

To a suspension of 4-(2-fluoro-4-methylphenylamino)-7-methoxy-6-(piperidin-4-yl)cinnoline-3-carboxamide (Example 51, 0.12 g, 0.29 mmol) in DCM (2 mL) was added *N*, *N*-diisopropylethylamine (0.152 ml, 0.88 mmol) and a solution of 2,2-difluoroethyl trifluoromethanesulfonate (0.075 g, 0.35 mmol) in DCM (1 mL). The reaction mixture was stirred at 40 °C for 1 hour, cooled and concentrated under reduced pressure. The residue was purified with silica chromatography (DCM to DCM / 10% MeOH (1% NH_4OH)), and further purified by reverse phase HPLC (0.1% NH_4OH in acetonitrile / water) to give 0.021 g (15 %) of an off-white solid. ^{1}H NMR: 11.50 (s, 1 H), 8.79 (s, 1 H), 7.94 (s, 1 H), 7.60 (s, 1 H), 7.28 (m, 1 H), 7.18 (m, 1 H), 7.14 (s, 1 H), 7.09 (m, 1 H), 6.11 (m, 1 H), 4.00 (s, 3 H), 2.85 (m, 2 H), 2.72 (m, 1 H), 2.70 (m, 2 H), 2.35 (s, 3 H), 2.20 (m, 2 H), 1.48 (m, 2 H), 1.10 (m, 2 H); *m/z* 474.

Example 72

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

To a solution of 6-((3*R*, 5*S*)-3,5-dimethylpiperazin-1-yl)-4-(2-fluoro-4-methylphenylamino)-7-methoxycinnoline-3-carboxamide (Example 36, 171 mg, 0.39 mmol) in DMF (5.5 mL) was added acetic anhydride (0.037 mL, 0.39 mmol) and triethylamine (0.163 mL, 1.17 mmol). The reaction mixture was stirred for 72 hours, and filtered to remove some precipitate. The filtrate was concentrated and the residue purified by silica

chromatography (DCM to DCM / 5% MeOH) to give 98 mg (52 %) of an orange solid. ^{1}H NMR: 11.24 (s, 1 H), 8.77 (s, 1 H), 7.92 (s, 1 H), 7.60 (s, 1 H), 7.16 (m, 2 H), 7.05 (d, 1 H), 6.59 (s, 1 H), 4.02 (s, 3 H), 2.98 (m, 4 H), 2.34 (m, 2 H), 2.32 (s, 3 H), 2.01 (s, 3 H), 1.25 (m, 6 H); *m/z* 481.

Example 73

4-[(2-Fluoro-4-methylphenyl)amino]-7-methoxy-6-(morpholin-4-ylmethyl)cinnoline-3-carboxamide

To a mixture of potassium 4-trifluoroboratomethyl-morpholine (Method 106, 80 mg, 0.39 mmol), Cs_2CO_3 (362 mg, 1.11 mmol) and 6-bromo-4-(2-fluoro-4-methylphenylamino)-7-methoxycinnoline-3-carboxamide hydrochloride (Example 54, 150 mg, 0.34 mmol) in dioxane (6 mL) and water (1 mL) was added $Pd(OAc)_2$ (2.5 mg, 0.01 mmol) and 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (10.59 mg, 0.02 mmol). The reaction mixture was stirred under N_2 at 80 °C for 48 hours. The mixture was added to water (50 mL) and extracted with DCM (3 x 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered, concentrated and the residue purified with silica chromatography (0-20 % MeOH in DCM) to give 33 mg (21 %) of a yellow solid. ^{1}H NMR: 11.40 (s, 1 H), 8.84 (s, 1 H), 7.98 (s, 1 H), 7.66 (s, 1 H), 7.61 (s, 1 H), 7.15 (m, 2 H), 6.97 (m, 1 H), 4.01 (s, 3 H), 3.42 (m, 4 H), 2.32 (s, 3 H), 2.21 (m, 4 H), 2 protons masked by solvent; *m/z* 426.

Preparation of Starting Materials

Method 91

2-[(3-Bromophenyl)diazenyl]-2-cyanoacetamide

To a suspension of 3-bromoaniline (6.33 mL, 58.1 mmol) and c. HCl (14.5 mL, 174 mmol) at 0 °C was added a solution of sodium nitrite (3.75 mL, 58.1 mmol) in water (13 mL). After 15 minutes, a solution of cyanoacetamide (4.89 g, 58.1 mmol) and sodium acetate (19.1g, 232 mmol) in water (85 mL) and ethanol (60 mL) was added dropwise to the reaction mixture. The reaction mixtue was allowed to warm to rt and stirred for 16 hours. The precipitate was filtered, washed with water, ethanol and diethyl ether, then dried in a vacuum oven to give 4.52 g (29 %) of a yellow solid. *m/z* 269.

Method 92

4-Amino-7-bromocinnoline-3-carboxamide

Aluminum chloride (3.60 ml, 65.9 mmol) was added to a suspension of 2-[(3-bromophenyl)diazenyl]-2-cyanoacetamide (Method 91, 4.4 g, 16.47 mmol) in toluene (41.2 mL) and the reaction mixture stirred at 110 °C for 16 hours. The reaction mixture was cooled, 40 mL of aq. HCl (2 M) was added dropwise, and the reaction mixture stirred at 100 °C for 2 hours. The reaction mixture was cooled, filtered and the residue washed with ethanol and water, then dried in a vacuum oven to give 2.71 g (62 %) of a brown solid. *m/z* 269.

Method 93

7-Bromo-4-hydroxycinnoline-3-carboxylic acid

To a suspension of 4-amino-7-bromocinnoline-3-carboxamide (Method 92, 2.4 g, 8.99 mmol) in dioxane (22.5 mL) was added a solution of potassium hydroxide (9.07 g, 161.7 mmol) in water (36 mL). The reaction mixture was stirred at 110 °C for 16 hours, cooled and acetic acid added. The mixture was filtered and the residue washed with water, then dried in a vacuum oven to give 2.10 g (87 %) of a light brown solid. *m/z* 271.

Method 94

7-Bromo-4-chlorocinnoline-3-carboxamide

7-Bromo-4-hydroxycinnoline-3-carboxylic acid (Method 93, 1.90 g, 7.06 mmol) in thionyl chloride (46.4 mL, 635 mmol) was stirred at 80 °C for 16 hours. The reaction mixture was cooled and concentrated under reduced pressure. The residue was suspended in acetone (20 mL), cooled to 0 °C and ammonium hydroxide (2.75 mL, 70.62 mmol) added dropwise. After stirring at 0 °C for 30 minutes, the mixture was warmed to rt, filtered, and the residue washed with water, then dried in a vacuum oven to give 1.31 g (65 %) of a brown solid. ^{1}H NMR: 8.91 (s, 1 H), 8.45 (s, 1 H), 8.29 (d, 1 H), 8.24 (d, 1 H), 8.15 (s, 1 H); *m/z* 288.

Method 95

7-Bromo-4-[(2-fluoro-4-methylphenyl)amino]cinnoline-3-carbonitrile

Phosphorus oxychloride (0.97 mL, 10.39 mmol) was added to a suspension of 7-bromo-4-(2-fluoro-4-methylphenylamino)cinnoline-3-carboxamide (Example 64, 1.3 g, 3.46 mmol) in DCM (35 mL) and the reaction mixture stirred at 45 °C for 1 hour. Triethylamine (4.8 mL, 34.6 mmol) was added dropwise to the reaction mixture. After stirring for 2 hours, the reaction mixture was cooled, diluted with DCM and washed with sat. $NaHCO_3$. The organic layer was dried, concentrated under reduced pressure, and the residue purified with

silica chromatography (DCM) to give 0.752 g (61 %) of a brown solid. ^{1}H NMR: 10.14 (s, 1 H), 8.62 (s, 1 H), 8.53 (d, 1 H), 8.13 (d, 1 H), 7.42 (m, 1 H), 7.26 (m, 1 H), 7.14 (d, 1 H), 2.39 (s, 3 H); *m/z* 359.

Methods 96-104

The following intermediates were prepared by similar procedures to those used for methods 47-83, from the appropriate starting materials.

Method	Compound	m/z	Starting Material
96	4-[(2-Fluoro-4-methylphenyl)amino]-7-(4-methylpiperazin-1-yl)cinnoline-3-carbonitrile	377	7-bromo-4-[(2-fluoro-4-methylphenyl)amino]cinnoline-3-carbonitrile (Method 95)
97	4-[(2-Fluoro-4-methylphenyl)amino]-7-[4-(methylsulfonyl)piperazin-1-yl]cinnoline-3-carbonitrile	441	7-bromo-4-[(2-fluoro-4-methylphenyl)amino]cinnoline-3-carbonitrile (Method 95)
98	4-[(2-Fluoro-4-methylphenyl)amino]-7-piperazin-1-ylcinnoline-3-carbonitrile	363	7-bromo-4-[(2-fluoro-4-methylphenyl)amino]cinnoline-3-carbonitrile (Method 95)
99	4-[(2-Fluoro-4-methylphenyl)amino]-6-[4-(2-hydroxyethyl)-1,4-diazepan-1-yl]-7-methoxycinnoline-3-carbonitrile		6-bromo-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile (Method 38) and 1-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)-1,4-diazepane (Method 107)
100	4-[(2-Fluoro-4-methylphenyl)amino]-7-methoxy-6-(4-methoxypiperidin-1-yl)cinnoline-3-carbonitrile	422	6-bromo-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile (Method 38)

Method	Compound	m/z	Starting Material
101	4-[(2-Fluoro-4-methylphenyl)amino]-7-methoxy-6-[4-(2-methoxyethoxy)piperidin-1-yl]cinnoline-3-carbonitrile	466	6-bromo-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile (Method 38)
102	4-[(2-Fluoro-4-methylphenyl)amino]-7-methoxy-6-[4-(methylsulfonyl)piperazin-1-yl]cinnoline-3-carbonitrile	472	6-bromo-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile (Method 38)
103	6-(1,1-Dioxidothiomorpholin-4-yl)-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile	442	6-bromo-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile (Method 38)
104	6-[(3*R*,5*S*)-4-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-3,5-dimethylpiperazin-1-yl]-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile	579	6-bromo-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carbonitrile (Method 38) and (2R,6S)-1-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)-2,6-dimethylpiperazine (Method 110)

Method 105

4-[(2-Fluoro-4-methylphenyl)amino]-7-[4-(2-hydroxyethyl)piperazin-1-yl]cinnoline-3-carbonitrile

A mixture of 4-(2-fluoro-4-methylphenylamino)-7-(piperazin-1-yl)cinnoline-3-carbonitrile (Method 98, 0.53 g, 1.46 mmol), acetic acid (0.067 ml, 1.17 mmol), (*tert*-butyldimethylsilyloxy)acetaldehyde (0.334 ml, 1.75 mmol) and sodium cyanoborohydride (0.184 g, 2.92 mmol) in methanol (14.6 mL) was stirred for 16 hours. HCl (1.0 M in acetic acid, 7.3 ml, 7.3 mmol) was added, and after stirring for 4 hours, the reaction mixture was concentrated and the residue purified by silica chromatography (DCM to DCM/MeOH/NH_4OH (10/1/0.1)) to give 370 mg (62 %) of a yellow solid. *m/z* 407.

Method 106

Potassium 4-trifluoroboratomethyl-morpholine

2-(Bromomethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.9 g, 8.60 mmol) in acetone (10.00 mL) was cooled to 0°C and potassium hydrogenfluoride (1.679 g, 21.50 mmol) added, followed by the dropwise addition of water (10 mL). The reaction mixture was warmed to room temperature, stirred for 30 minutes, and the solvent removed under reduced pressure. The residue was dissolved in acetone, diethyl ether was added, and the precipitate filtered to give 1.60 g (93 %) of potassium bromomethyltrifluoroborate as a white solid.

Potassium bromomethyltrifluoroborate (650 mg, 3.24 mmol) and morpholine (2 ml, 22.96 mmol) were heated at 80 °C for 30 minutes. The mixture was cooled to room temperature, concentrated, and the residue dissolved in acetone (5 mL). Potassium bicarbonate (324 mg, 3.24 mmol) was added and the resulting mixture stirred for 20 minutes. The mixture was filtered, concentrated and the residue dissolved in acetone. Diethyl ether was added, and the precipitate filtered to give 140 mg (21 %) of a yellow gum. ^{1}H NMR: $(CD_3)_2CO$ 3.93 (m, 4 H), 3.31 (m, 4 H), 2.14 (br. s, 2 H).

Method 107

1-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-1,4-diazepane

4 Å Molecular sieves were added to a mixture of benzyl 1-homopiperazinecarboxylate (1.06 mL, 5.12 mmol), 2-(*tert*-butyldimethylsilyloxy)acetaldehyde (0.744 mL, 6.15 mmol), methanol (5 mL), and DCM (5 mL). After stirring for 20 minutes, the mixture was added to a solution of sodium triacetoxyborohydride (2.71 g, 12.80 mmol) in tetrahydrofuran (10 mL) and stirred for 1 hour. The reaction mixture was added to a saturated $NaHCO_3$ solution (100 mL) and extracted with DCM. The organic extracts were combined, concentrated onto silica under reduced pressure and purified with silica chromatography (0-20% MeOH in EtOAc) to give 1.02 g (51 %) benzyl 4-(2-(*tert*-butyldimethylsilyloxy)ethyl)-1,4-diazepane-1-carboxylate as a clear oil. *m/z* 393.

A mixture of benzyl 4-(2-(*tert*-butyldimethylsilyloxy)ethyl)-1,4-diazepane-1-carboxylate (1.02 g, 2.60 mmol) and palladium on carbon (0.083 g, 0.78 mmol) in methanol (10 mL) was stirred for 20 hours under hydrogen gas. The reaction mixture was filtered and concentrated under reduced pressure to give 0.66g (98 %) of a colorless oil. ^{1}H NMR: 3.63 (t, 2 H), 2.74 (t, 2 H), 2.67 (m, 4 H), 2.57 (m, 4 H), 1.61 (m, 2 H), 0.86 (s, 9 H), 0.03 (s, 6 H); *m/z* 259.

Method 108

(3*R*,5*S*)-Benzyl 3,5-dimethylpiperazine-1-carboxylate

To a solution of (2*R*,6*S*)-2,6-dimethylpiperazine (8.0 g, 70.1 mmol) in DCM (70 mL) was added triethylamine (9.78 mL, 70.1 mmol). The reaction mixture was cooled to 0 °C and benzyl chlorocarbonate (9.86 mL, 70.1 mmol) was added. After stirring at 0 °C for 1 hour, the reaction was warmed to rt. The reaction mixture was washed with brine, dried (Na_2SO_4), concentrated and the residue purified with silica chromatography (Hex:EtOAc 1:1 to EtOAc to EtOAc:MeOH 10:1) to give 13.48g (77 %) of a colorless oil.

Method 109

(3*R*,5*S*)-Benzyl 4-(2-(*tert*-butyldimethylsilyloxy)ethyl)-3,5-dimethylpiperazine-1-carboxylate

To a solution of (3*R*,5*S*)-benzyl 3,5-dimethylpiperazine-1-carboxylate (Method 108, 5.0 g, 20.1 mmol) in DMA (25 mL) was added tetrabutylammonium iodide (7.44 g, 20.1 mmol), potassium carbonate (5.57 g, 40.3 mmol) and (2-bromoethoxy)(*tert*-butyl)dimethylsilane (8.67 g, 36.2 mmol). The reaction mixture was stirred at 120 °C for 20 hours, then concentrated. DCM (50mL) was added, and the organic layer was washed with H_2O, dried (Na_2SO_4), concentrated and purified with silica chromatography to give 7.2g (88 %) of a brown oil.

Method 110

(2*R*,6*S*)-1-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-2,6-dimethylpiperazine

A mixture of (3*R*,5*S*)-benzyl 4-(2-(*tert*-butyldimethylsilyloxy)ethyl)-3,5-dimethylpiperazine-1-carboxylate (Method 109, 7.6 g, 18.7 mmol) in methanol (30 mL) and palladium on carbon (100mg) was stirred for 16 hours under hydrogen gas. The reaction mixture was filtered through Celite, concentrated under reduced pressure, and the residue purified with silica chromatography (EtOAc then EtOAc/MeOH/Et_3N 10/1/0.1 then DCM/MeOH/Et_3N 10/1/0.1) to give 4.0 g (79 %) colorless oil. ^1H NMR: $CDCl_3$ 3.59 (t, 2 H), 2.77 (m, 2 H), 2.74 (t, 2 H), 2.49 (m, 2 H), 2.41 (m, 2 H), 1.00 (d, 6 H), 0.84 (s, 9 H), 0.00 (s, 6 H).

CLAIMS

1. A compound selected from the group:

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

4-[(2-fluoro-4-methylphenyl)amino]-7-methoxy-6-(4-methoxypiperidin-1-yl)cinnoline-3-carboxamide;

4-[(2-fluoro-4-methylphenyl)amino]-7-methoxy-6-[4-(2-methoxyethoxy)piperidin-1-yl]cinnoline-3-carboxamide;

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

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

6-{4-[(2R)-2,3-dihydroxypropyl]piperazin-1-yl}-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carboxamide;

4-[(2-fluoro-4-methylphenyl)amino]-6-[4-(2-hydroxyethyl)-1,4-diazepan-1-yl]-7-methoxycinnoline-3-carboxamide;

6-{4-[(2S)-2,3-dihydroxypropyl]piperazin-1-yl}-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carboxamide;

4-[(2-fluoro-4-methylphenyl)amino]-6-[4-(2-hydroxy-2-methylpropanoyl)piperazin-1-yl]-7-methoxycinnoline-3-carboxamide;

6-(1,1-dioxidothiomorpholin-4-yl)-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carboxamide;

4-[(2-fluoro-4-methylphenyl)amino]-6-{4-[2-hydroxy-1-(hydroxymethyl)ethyl]piperazin-1-yl}-7-methoxycinnoline-3-carboxamide;

7-bromo-4-[(2-fluoro-4-methylphenyl)amino]cinnoline-3-carboxamide;

4-[(2-fluoro-4-methylphenyl)amino]-6-{1-[(2S)-2-hydroxypropanoyl]piperidin-4-yl}-7-methoxycinnoline-3-carboxamide;

4-[(2-fluoro-4-methylphenyl)amino]-7-methoxy-6-(morpholin-4-ylmethyl)cinnoline-3-carboxamide;

6-[1-(2,2-difluoroethyl)piperidin-4-yl]-4-[(2-fluoro-4-methylphenyl)amino]-7-methoxycinnoline-3-carboxamide;

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

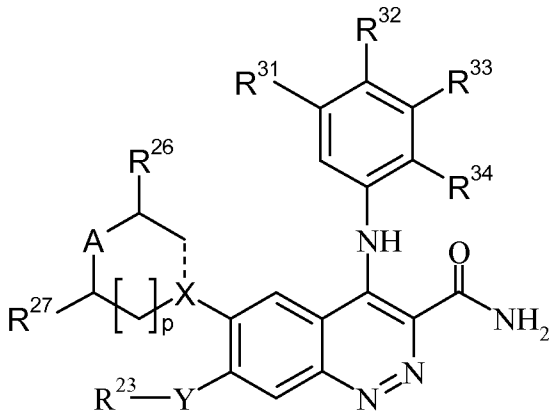
4-[(2-fluoro-4-methylphenyl)amino]-7-[4-(methylsulfonyl)piperazin-1-yl]cinnoline-3-carboxamide;

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

4-[(2-Fluoro-4-methylphenyl)amino]-7-methoxy-6-{4-[2-(methylsulfonyl)ethyl] piperazin-1-yl}cinnoline-3-carboxamide;

or pharmaceutically acceptable salts thereof.

2. 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 SO_2, NR^{25}, and $CR^{28}R^{29}$;

p is selected from 0, 1, and 2;

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

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

$\mathbf{R^{25}}$ is C_{1-6}alkylsuflonyl;

$\mathbf{R^{29}}$ is C_{1-6}alkoxy optionally substituted with one or more R^{30};

$\mathbf{R^{30}}$ is 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;

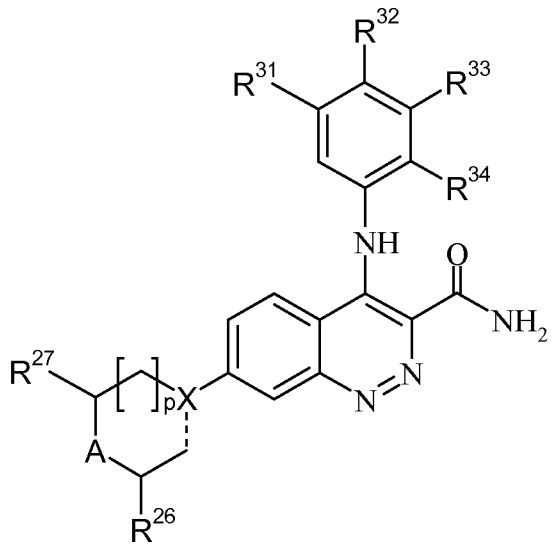
R^{31} is selected from hydrogen and C_{1-4}alkyl;

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.

3. A compound of formula **(IF)**:



formula (IF)

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;

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

p is 0-2;

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

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

R^{29} is selected from hydrogen, amino, and C_{1-6}alkoxy optionally substituted on carbon with one or more R^{30};

$\mathbf{R^{30}}$ is 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;

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

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

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

$\mathbf{R^{34}}$ is selected from halo.

4. A pharmaceutical composition comprising a compound as provided in Claims 1-3 or pharmaceutically acceptable salt thereof and pharmaceutically-acceptable diluent or carrier.

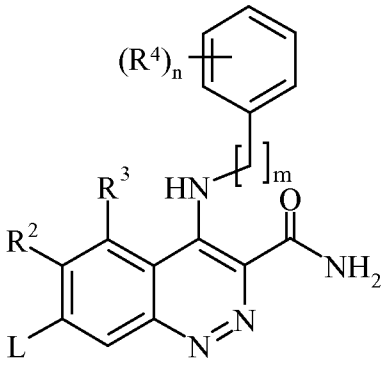
5. A method of treating cancer comprising providing a subject at risk for, diagnosed with, or exhibiting symptoms of cancer and administering a pharmaceutical composition comprising a compound as provided in Claims 1-3 to said subject.

6. A method of inhibiting CSF-1R kinase comprising providing a CSF-1R kinase and a compound as provide in Claims 1-3 or pharmaceutically acceptable salt thereof, and mixing under conditions such that CSF-1R kinase is inhibited.

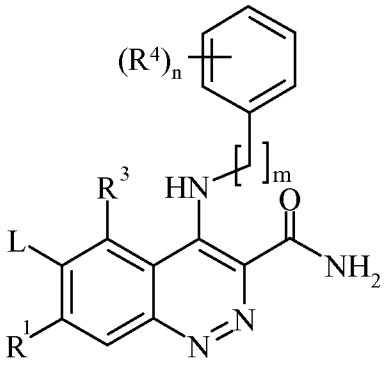
7. A compound as provided in Claims 1-3, or a pharmaceutically acceptable salt thereof, for use as a medicament.

8. The use of a compound as provided in Claims 1-3, 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

9. A process of making a compound as provided in Claims 1-3 comprising reaction of a compound of formula **(IXa)** or **(IXb)**:



(IXa)



(IXb)

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

R^1-H	R^2-H
(Xa)	**(Xb)**

and thereafter if necessary:

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.

10. The process of Claim 9, wherein L is selected from chloro, bromo, tosyl and trifluoromethylsulphonyloxy.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2009/050467

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D237/28 C07D401/04 C07D403/04 C07D417/04 C07D487/04
A61K31/502 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007/119046 A (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; COOK DONALD [US]; DAKIN) 25 October 2007 (2007-10-25) claims 1,16	1-10
P,X	WO 2008/056148 A (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; DAKIN LESLIE [US]; DALY) 15 May 2008 (2008-05-15) claim 4	2
P,A	WO 2008/090353 A (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; DAKIN LESLIE [US]; OGOE) 31 July 2008 (2008-07-31) claims 1,11	1-10

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 August 2009	10/09/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Fax: (+31–70) 340–3016	Bakboord, Joan

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2009/050467

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007119046 A	25-10-2007	AR 060508 A1	25-06-2008
		AU 2007238372 A1	25-10-2007
		CA 2649146 A1	25-10-2007
		EP 2010496 A1	07-01-2009
		KR 20080112380 A	24-12-2008
		US 2009054411 A1	26-02-2009
		UY 30282 A1	30-11-2007
WO 2008056148 A	15-05-2008	AR 063643 A1	04-02-2009
		AU 2007319059 A1	15-05-2008
		EP 2084134 A1	05-08-2009
WO 2008090353 A	31-07-2008	AR 065042 A1	13-05-2009
		AU 2008208751 A1	31-07-2008
		CL 1912008 A1	22-08-2008
		US 2009012084 A1	08-01-2009
		UY 30880 A1	02-09-2008