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Industria y Comercio
SUPERINTENDENCIA

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FORMULARIO ÚNICO DE SOLICITUD DE PATENTE 0001

PCT

ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☐ Capítulo I. ☒ Capítulo II.

2 SOLICITANTE (71)	**Nombre: ASTRAZENECA AB** **Dirección: S-151 85 Sodertalje, Suecia** **Nacionalidad o Domicilio: Suecia** **Lugar de Constitución: Suecia** **Teléfono: Fax:** **E-mail**	**IDENTIFICACION** **C.C. ☐ NIT ☐** **C.E. ☐ Otro ☐** **Cual____** **Número ____**
3 REPRESENTANTE O APODERADO	**Nombre: RAMIRO CASTRO DUQUE** **Dirección: Cra. 7 No. 16-56 Piso 9** **Teléfono: 380-2200 Fax: 380-2700** **E-mail:**	**IDENTIFICACION** **C.C. ☒ NIT ☐** **C.E. ☐ Otro ☐** **Cual____** **Número 170.322 TP 1003**
4 INVENTOR (ES) (72)	**Nombre: Andrew Peter Thomas, Nicholas John Newcombe, David William Heaton** **Dirección: Alderley Park, Macclesfield, Cheshire SK10 4TG, Reino Unido; Alderley Park, Macclesfield, Cheshire SK10 4TG, Reino Unido; Alderley Park, Macclesfield, Cheshire SK10 4TG, Reino Unido (Respectivamente)** **Nacionalidad o Domicilio: Reino Unido (Respectivamente)**	

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Publicación Internacional No. WO 02/04429 A1 Fecha 17-01-2002

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	GB	11-07-2000	0016877.3

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Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

2

10 ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud. $400.000 .- 0002
- [x] Comprobante de pago por reivindicación de prioridad. $112.000
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Fotocopia Autenticada Anexa
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [ ] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Copia del examen preliminar efectuado por la IPEA.
- [ ] Traducción del examen preliminar efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12x12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] Otros

11 FIGURA CARACTERÍSTICA:

12 Solicito la concesión de la patente.

NOMBRE: RAMIRO CASTRO DUQUE

FIRMA:

C.C. 170.322 de Bogotá T.P. 1003 del C.S.J.

Instrucciones para la presentación de los anexos, ver reverso de esta página.

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***** C O N S I G N A C I O N *****

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BRIGARD C CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	7316966	26/11/2002	6,984,000.00

***** C O N C E P T O *****

CANT.	REGISTRO	CONCEPTO	TOTAL CONCEPTO
1	50000 01 01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	378,000.00
		TOTAL : $	378,000.00

SON: TRESCIENTOS SETENTA Y OCHO MIL PESOS

RESPONSABLE : _____

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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

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FECHA : ENERO 2 DE 2003

CONSIGNACION

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DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAG	Vr. PAGO
ARIZABE & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	7416901	02/01/2003	3,720,000.00

C O N C E P T O

CANT.	PENTIETICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	82 INVOCACION DE UNA PRIORIDAD EN NU	112,000.00
		TOTAL : $	112,000.00

SON: CIENTO DOCE MIL PESOS

RESPONSABLE : _____

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FECHA : ENERO 2 DE 2003

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***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	V/r. PAGO
ORTEGA Y CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-03110-6	7416931	02/01/2003	5,720,000.00

***** C O N C E P T O *****

CANT.	PERITAJES	CONCEPTO		TOTAL CONCEPTO
1	50005-01-02 OTROS SERVICIOS DE PROPIEDAD I	99	OTROS SERVICIOS ADMINISTRATIVOS	22,000.00
			TOTAL : $	22,000.00

SON: VEINTIDOS MIL PESOS

RESPONSABLE : _____

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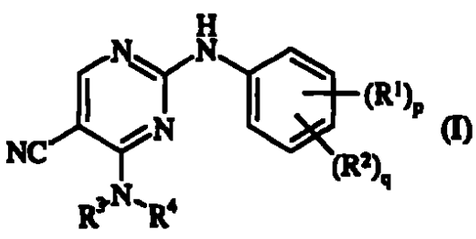
(54) Title: PYRIMIDINE DERIVATIVES



(I)

(57) Abstract: Compounds of formula (I), wherein R^1, p, R^2, q, R^3 and R^4 are defined within, and a pharmaceutically acceptable salts and *in vivo* hydrolysable esters are described. Also described are processes for their preparation and their use as medicaments, particularly medicaments for producing a cell cycle inhibitory (anti-cell-proliferation) effect in a warm-blooded animal, such as man.

PYRAMIDINE DERIVATIVES

The invention relates to pyrimidine derivatives, or pharmaceutically acceptable salts or *in vivo* hydrolysable esters thereof, which possess cell-cycle inhibitory activity and are accordingly useful for their anti-cell-proliferation (such as anti-cancer) activity and are therefore useful in methods of treatment of the human or animal body. The invention also relates to processes for the manufacture of said pyrimidine derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments of use in the production of an anti-cell-proliferation effect in a warm-blooded animal such as man.

A family of intracellular proteins called cyclins play a central role in the cell cycle. The synthesis and degradation of cyclins is tightly controlled such that their level of expression fluctuates during the cell cycle. Cyclins bind to cyclin-dependent serine/threonine kinases (CDKs) and this association is essential for CDK (such as CDK1, CDK2, CDK4 and/or CDK6) activity within the cell. Although the precise details of how each of these factors combine to regulate CDK activity is poorly understood, the balance between the two dictates whether or not the cell will progress through the cell cycle.

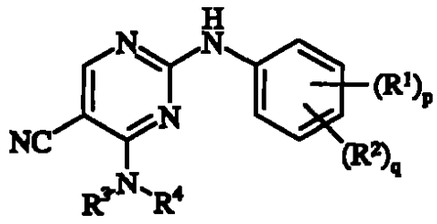
The recent convergence of oncogene and tumour suppressor gene research has identified regulation of entry into the cell cycle as a key control point of mitogenesis in tumours. Moreover, CDKs appear to be downstream of a number of oncogene signalling pathways. Disregulation of CDK activity by upregulation of cyclins and/or deletion of endogenous inhibitors appears to be an important axis between mitogenic signalling pathways and proliferation of tumour cells.

Accordingly it has been recognised that an inhibitor of cell cycle kinases, particularly inhibitors of CDK2, CDK4 and/or CDK6 (which operate at the S-phase, G1-S and G1-S phase respectively) should be of value as a selective inhibitor of cell proliferation, such as growth of mammalian cancer cells.

The present invention is based on the discovery that certain pyrimidine compounds surprisingly inhibit the effects of cell cycle kinases showing selectivity for CDK2, CDK4 and CDK6, and thus possess anti-cell-proliferation properties. Such properties are expected to be of value in the treatment of disease states associated with aberrant cell cycles and cell proliferation such as cancers (solid tumours and leukemias), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma,

acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

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



(I)

wherein:

R^1 is halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl;

p is 0-4; wherein the values of R^1 may be the same or different;

R^2 is sulphamoyl or a group B-E-;

q is 0-2; wherein the values of R^2 maybe the same or different; and wherein p + q = 1-5;

R^3 is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{3-8}cycloalkyl; wherein R^3 may be optionally substituted on carbon by one or more M;

R^4 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl or heterocyclyl; wherein R^4 may be optionally substituted by one or more M; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from Z;

or R^3 and R^4 together with the nitrogen to which they are attached form a heterocyclic ring optionally substituted on carbon by one or more M; wherein if said heterocyclic ring contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from Q;

B is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-6}alkyl, phenyl, a heterocyclic group, phenylC_{1-6}alkyl or (heterocyclic group)C_{1-6}alkyl; wherein B may be optionally substituted on carbon by one or more D; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from G;

E is -C(O)-, -N(R^a)C(O)-, -C(O)N(R^a)-, -S(O)$_r$-, -SO_2N(R^a)- or -N(R^a)SO_2-; wherein R^a is hydrogen or C_{1-6}alkyl optionally substituted by one or more D and r is 1-2;

D is independently selected from halo, nitro, cyano, hydroxy, trifluoromethyl, 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, 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 and *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl; wherein D may be optionally substituted on carbon by one or more V;

M is 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, 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_{3-8}cycloalkyl, phenyl or a heterocyclic group; wherein M may be optionally substituted on carbon by one or more P; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from T;

P, X and V are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, 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, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl; and

G, Q, T and Z are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl wherein G, Q and T may be independently optionally substituted on carbon by one or more X;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. For example, "C_{1-6}alkyl" includes C_{1-4}alkyl, C_{1-3}alkyl, propyl, isopropyl and *t*-butyl. However, references to individual alkyl groups such as 'propyl' are specific for the straight chained version only and references to individual branched chain alkyl groups

such as 'isopropyl' are specific for the branched chain version only. 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 "heterocyclic group" 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)-, a ring nitrogen atom may optionally bear a C_{1-6}alkyl group and form a quaternary compound or a ring nitrogen and/or sulphur atom may be optionally oxidised to form the *N*-oxide and or the S-oxides. Examples and suitable values of the term "heterocyclic group" are morpholino, piperidyl, pyridyl, pyranyl, pyrrolyl, 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. Preferably a "heterocyclic group" is a saturated, partially saturated or unsaturated, mono or bicyclic 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 may be optionally oxidised to form the S-oxides. In another aspect, preferably a "heterocyclic group" 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 may be optionally oxidised to form the S-oxides. More preferably a "heterocyclic group" is tetrahydrofuryl, pyridyl, pyrrolidinonyl, morpholino, imidazolyl, piperidinyl or pyrrolidinyl. Particularly a "heterocyclic group" is tetrahydrofuryl or morpholino. In another aspect of the invention, particularly a "heterocyclic group" is morpholino, tetrahydrofuryl, piperidinyl, pyridyl, imidazolyl, piperazinyl, pyrrolidinyl, triazolyl, dioxanyl and dioxolanyl.

Where "R^3 and R^4 together with the nitrogen to which they are attached form a heterocyclic ring" said "heterocyclic ring" is a saturated, partially saturated or fully

unsaturated, mono or bicyclic ring containing 4-12 atoms, one atom of which is the nitrogen atom to which R^3 and R^4 are attached to, and the other atoms are either all carbon atoms or they are carbon atoms and 1-3 heteroatoms chosen from nitrogen, sulphur or oxygen, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-, a ring nitrogen atom may optionally bear a C_{1-6}alkyl group and form a quaternary compound or a ring nitrogen and/or a ring sulphur atom may be optionally oxidised to form an *N*- and /or an S-oxide. It will be appreciated that where R^3 and R^4 together with the nitrogen atom to which they are attached form a "heterocyclic ring" this nitrogen atom is not quaternised, i.e. a neutral compound is formed. Examples and suitable values of the term "heterocyclic group" are azetidinyl, morpholino, piperidyl, piperazinyl, pyrrolidinyl, thiomorpholino, pyrrolinyl, homopiperazinyl, pyrrolyl, pyrazolyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyrazolidinyl and triazolyl. Preferably "heterocyclic group" is morpholino. In another aspect of the invention, preferably "heterocyclic group" is morpholino, piperidino, pyrrolidin-1-yl or piperazin-1-yl.

A "heterocyclyl" is a saturated 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 may be optionally oxidised to form (the) S-oxide(s). Examples of the term "heterocyclyl" are morpholinyl, piperidyl, piperazinyl, thiazolidinyl, pyrrolidinyl, thiomorpholinyl, 1,1-dioxothiomorpholinyl, homopiperazinyl, tetrahydropyranyl, 2-pyrrolidone and 4-thiazolidone. In one aspect of the invention a "heterocyclyl" is a saturated 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 may be optionally oxidised to form (the) S-oxide(s). In another aspect of the invention a "heterocyclyl" is tetrahydrofuryl.

An example of "C_{1-6}alkanoyloxy" is acetoxy. Examples of "C_{1-6}alkoxycarbonyl" include C_{1-4}alkoxycarbonyl, 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 C_{1-4}alkylsulphonyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl. Examples of "C_{1-6}alkyl$S(O)_r$ wherein r is 1 to 2" include methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl. Examples of "C_{1-6}alkanoyl" include C_{1-4}alkanoyl, propionyl and acetyl. Examples of

"*N*-C_{1-6}alkylamino" 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_{3-8}cycloalkyl" are cyclopropyl, cyclobutyl, cyclopropyl and cyclohexyl. Examples of "(heterocyclic group)C_{1-6}alkyl" include pyridylmethyl, 3-morpholinopropyl and 2-pyrimid-2-ylethyl. Examples of "C_{3-8}cycloalkylC_{1-6}alkyl" are cyclopropylethyl, cyclobutylmethyl, 2-cyclopropylpropyl and cyclohexylethyl.

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.

The compounds of the formula (I) may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the formula (I). Examples of pro-drugs include *in vivo* hydrolysable esters of a compound of the formula (I).

An *in vivo* hydrolysable ester of a compound of the formula (I) containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters,

C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

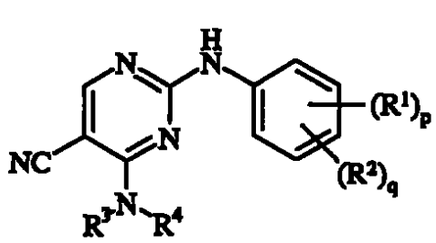
An *in vivo* hydrolysable ester of a compound of the formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazin-1-yl linked from a ring nitrogen atom via a methylene group to the 3- or 4- position of the benzoyl ring.

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 CDK inhibitory activity.

The invention relates to any and all tautomeric forms of the compounds of the formula (I) that possess CDK 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 CDK inhibitory activity.

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



(I)

wherein:

R^1 is halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl;

p is 0-4; wherein the values of R^1 may be the same or different;

R^2 is sulphamoyl or a group B-E-;

q is 0-2; wherein the values of R^2 maybe the same or different; and wherein p + q = 1-5;

R^3 is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{3-8}cycloalkyl; wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{3-8}cycloalkyl may be optionally substituted by one or more M; and

R^4 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{3-8}cycloalkyl; wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{3-8}cycloalkyl may be optionally substituted by one or more M;

or R^3 and R^4 together with the nitrogen to which they are attached form a heterocyclic ring optionally substituted on carbon by one or more M; wherein if said heterocyclic ring contains an -NH- moiety that nitrogen may be optionally substitnted by a group selected from Q;

B is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-6}alkyl, phenyl, a heterocyclic group, phenylC_{1-6}alkyl or (heterocyclic group)C_{1-6}alkyl; wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-6}alkyl, phenyl, heterocyclic group, phenylC_{1-6}alkyl or (heterocyclic group)C_{1-6}alkyl are optionally substituted on carbon by one or more D; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from G;

E is -C(O)-, -N(R^a)C(O)-, -C(O)N(R^a)-, -S(O)$_r$-, -SO_2N(R^a)- or -N(R^a)SO_2-; wherein R^a is hydrogen or C_{1-6}alkyl optionally substituted by one or more D and r is 1-2;

D is independently selected from halo, nitro, cyano, hydroxy, trifluoromethyl, 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, 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 and *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl; wherein D may be optionally substituted on carbon by a group selected from V;

M is 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, 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_{3-8}cycloalkyl, phenyl or a heterocyclic group; wherein M may be optionally substituted on carbon by a group selected from P; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from T; and

P and V are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, 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, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

G, Q and T are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl; and

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

Preferred values of R^1, R^2, R^3, R^4, p and q are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

Preferably R^1 is halo or C_{1-2}alkyl.

More preferably R^1 is fluoro, chloro or methyl.

Particularly R^1 is fluoro or chloro.

Preferably p is 0-2; wherein the values of R^1 may be the same or different.

More preferably p is 0 or 1.

In one aspect of the invention preferably p is 0.

In another aspect of the invention preferably p is 1.

In a further aspect of the invention preferably p is 2; wherein the values of R^1 may be the same or different.

Preferably when p is 1; R^1 is meta to the amino group in the aniline of formula (I).

Preferably R^2 is sulphamoyl or a group B-E-; wherein

B is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-6}alkyl, phenylC_{1-6}alkyl or (heterocyclic group)C_{1-6}alkyl; wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-6}alkyl, phenylC_{1-6}alkyl or (heterocyclic group)C_{1-6}alkyl are optionally substituted on carbon by one or more D; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from G;

E is $-N(R^a)SO_2-$; wherein R^a is hydrogen;

D is independently selected from halo, hydroxy, C_{1-6}alkoxy or *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino; and

G is C_{1-4}alkyl.

More preferably R^2 is sulphamoyl or a group B-E-; wherein

B is selected from C_{1-6}alkyl or (heterocyclic group)C_{1-6}alkyl; wherein said C_{1-6}alkyl or (heterocyclic group)C_{1-6}alkyl are optionally substituted on carbon by one or more D;

E is $-N(R^a)SO_2-$; wherein R^a is hydrogen;

D is independently selected from hydroxy or *N*-(C_{1-6}alkyl)amino.

Particularly R^2 is selected from sulphamoyl, *N*-(3-hydroxy-2,2-dimethylpropyl)sulphamoyl, *N*-(3-(*N*-isopropylamino)propyl)sulphamoyl or *N*-(tetrahydrofur-2-ylmethyl)sulphamoyl.

In another aspect of the invention, preferably R^2 is sulphamoyl or a group B-E-;

B is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or (heterocyclic group)C_{1-6}alkyl; wherein B may be optionally substituted on carbon by one or more D; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from G;

E is $-S(O)_r-$ or $-N(R^a)SO_2-$; wherein R^a is hydrogen or C_{1-6}alkyl and r is 2;

D is independently selected from halo, cyano, hydroxy, amino, C_{1-6}alkyl, C_{1-6}alkoxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino and C_{1-6}alkyl$S(O)_a$ wherein a is 0 to 2; wherein D may be optionally substituted on carbon by a group selected from V;

V is selected from hydroxy and dimethylamino; and

G is selected from C_{1-4}alkyl.

In another aspect of the invention, more preferably R^2 is sulphamoyl or a group B-E-;

B is selected from methyl, ethyl, propyl, butyl, 2,2-dimethylpropyl, pentyl, allyl, 2-propynyl, pyrrolidin-2-ylmethyl, pyrid-3-ylmethyl, 1,4-dioxan-2-ylmethyl, pyrid-2-ylmethyl,

2-morpholinoethyl, 2-1,3,4-triaziol-2-ylethyl, 2-piperidinoethyl, 2-pyrid-2-ylethyl, 2-pyrid-4-ylethyl, 2-pyrrolidin-1-ylethyl, 2-imidazol-4-ylethyl, 3-imidazol-1-ylpropyl, 3-morpholinopropyl, 3-piperidinopropyl or tetrahydrofur-2-ylmethyl; wherein B may be optionally substituted on carbon by one or more D; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from G;

E is $-S(O)_r-$ or $-N(R^a)SO_2-$; wherein R^a is hydrogen or C_{1-6}alkyl and r is 2;

D is independently selected from fluoro, cyano, hydroxy, amino, methyl, methoxy, ethoxy, isopropylamino, dimethylamino, diethylamino, acetamido, ethylthio and mesyl; wherein D may be optionally substituted on carbon by a group selected from V;

V is selected from hydroxy and dimethylamino; and

G is selected from ethyl.

In another aspect of the invention, particularly R^2 is sulphamoyl, mesyl, ethylsulphonyl, 2-ethoxyethylsulphonyl, propylsulphonyl, 3-isopropylaminopropylsulphonyl, 4-isopropylaminobutylsulphonyl, *N*-(tetrahydrofur-2-ylmethyl)sulphamoyl, *N*-(pyrid-3-ylmethyl)sulphamoyl, *N*-(pyrid-2-ylmethyl)sulphamoyl, *N*-(1,4-dioxan-2-ylmethyl)sulphamoyl, *N*-(methyl)sulphamoyl, *N*-(2-methoxyethyl)sulphamoyl, *N*-(2-ethylthioethyl)sulphamoyl, *N*-(2-morpholinoethyl)sulphamoyl, *N*-(2-piperidinoethyl)sulphamoyl, *N*-(2-pyrid-2-ylethyl)sulphamoyl, *N*-(2-pyrrolidin-1-ylethyl)sulphamoyl, *N*-(2-imidazol-4-ylethyl)sulphamoyl, *N*-(2-isopropylaminoethyl)sulphamoyl, *N*-(2-mesylethyl)sulphamoyl, *N*-[2-(2-hydroxyethoxy)ethyl]sulphamoyl, *N*-[2-(1-ethylpyrrolidin-2-yl)ethyl]sulphamoyl, *N*-(2-pyrid-2-ylethyl)sulphamoyl, *N*-(2-diethylaminoethyl)sulphamoyl, *N*-(2-pyrid-4-ylethyl)sulphamoyl, *N*-(2-acetamidoethyl)sulphamoyl, *N*-(2-dimethylaminoethyl)sulphamoyl, *N*-2-[(5-methyl-1,3,4-triazol-2-yl)ethyl]sulphamoyl, *N*-(2-hydroxyethyl)sulphamoyl, *N*-(2-cyanoethyl)sulphamoyl, *N*-(2-diethylaminoethyl)-*N*-(methyl)sulphamoyl, *N*-(2-methoxyethyl)-*N*-(methyl)sulphamoyl, *N*-(2,2,2-trifluoroethyl)sulphamoyl, *N*-(3-hydroxy-2,2-dimethylpropyl)sulphamoyl, *N*-(3-isopropylaminopropyl)sulphamoyl, *N*-(3-methoxypropyl)sulphamoyl, *N*-(3-imidazol-1-ylpropyl)sulphamoyl, *N*-(2-hydroxy-3-aminopropyl)sulphamoyl, *N*-(3-hydroxypropyl)sulphamoyl, *N*-(3-ethoxypropyl)sulphamoyl, *N*-[3-(2-dimethylaminoethyl)propyl]sulphamoyl, *N*-(3-morpholinopropyl)sulphamoyl, *N*-(2-hydroxypropyl)sulphamoyl,

N-(2-hydroxy-3-piperidinopropyl)sulphamoyl, *N*-(3-piperidinopropyl)-*N*-(methyl)sulphamoyl, *N*-(2-hydroxybutyl)sulphamoyl, *N*-(pentyl)sulphamoyl, *N*-(5-hydroxypentyl)sulphamoyl, *N*-(allyl)sulphamoyl or *N*-(2-propynyl)sulphamoyl.

Preferably E is $-NHSO_2-$.

In another aspect of the invention, preferably E is $-NHSO_2-$, $-N(Me)SO_2-$ or $-SO_2-$.

Preferably q is 0 or 1.

In one aspect of the invention preferably q is 0.

In another aspect of the invention preferably q is 1.

In a further aspect of the invention preferably q is 2; wherein the values of R^2 may be the same or different.

Preferably p + q = 1 or 2.

More preferably p + q = 1.

Preferably when q is 1; R^2 is meta or para to the amino group in the aniline of formula (I).

More preferably when q is 1; R^2 is para to the amino group in the aniline of formula (I).

Preferably R^3 is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl; wherein said C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl may be optionally substituted by one or more M; and

R^4 is C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl; wherein said C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl may be optionally substituted by one or more M;

or R^3 and R^4 together with the nitrogen to which they are attached form a heterocyclic ring optionally substituted on carbon by one or more M; wherein if said heterocyclic ring contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from Q.

More preferably R^3 is hydrogen or C_{1-6}alkyl; wherein said C_{1-6}alkyl may be optionally substituted by one or more M; and

R^4 is C_{1-6}alkyl or C_{2-6}alkenyl; wherein said C_{1-6}alkyl or C_{2-6}alkenyl may be optionally substituted by one or more M;

or R^3 and R^4 together with the nitrogen to which they are attached form a heterocyclic ring; wherein

M is independently selected from halo, cyano, C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl or a heterocyclic group.

Particularly R^3 is hydrogen or C_{1-4}alkyl; and

R^4 is C_{1-4}alkyl or C_{2-4}alkenyl; wherein said C_{1-4}alkyl or C_{2-4}alkenyl may be optionally substituted by one or more M;

or R^3 and R^4 together with the nitrogen to which they are attached form morpholino; wherein

M is independently selected from fluoro, cyano, methoxy, ethoxy, ethoxycarbonyl or morpholino.

More particularly R^3 and R^4 together with the nitrogen to which they are attached form morpholino, *i*-butylamino, ethylamino, 2-fluoroethylamino, 3-ethoxypropylamino, butylamino, (*N*-methyl)allylamino, (*N*-methyl)ethoxycarbonylmethylamino, (*N*-methyl)-2-cyanoethylamino, *N,N*-diethylamino, (*N*-methyl)-2-methoxyethylamino, 2,2,2-trifluroethylamino, *N,N*-di-(2-cyanoethyl)amino or 3-morpholinopropylamino.

In another aspect of the invention, preferably R^3 is hydrogen or C_{1-6}alkyl; wherein R^3 may be optionally substituted by one or more M; and

R^4 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{3-8}cycloalkyl; wherein R^4 may be optionally substituted by one or more M;

or R^3 and R^4 together with the nitrogen to which they are attached form a heterocyclic ring optionally substituted on carbon by one or more M; wherein if said heterocyclic ring contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from Q;

M is independently selected from halo, cyano, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkoxycarbonyl, C_{3-8}cycloalkyl or a heterocyclic group; wherein M may be optionally substituted on carbon by a group selected from P;

P and X are independently selected from hydroxy and methoxy; and

Q is selected from C_{1-4}alkyl, C_{1-4}alkylsulphonyl or C_{1-4}alkoxycarbonyl; wherein G may be optionally substituted on carbon by one or more X.

In another aspect of the invention, more preferably R^3 is hydrogen, methyl or ethyl; wherein R^3 may be optionally substituted by one or more M; and

R^4 is methyl, ethyl, butyl, isobutyl, propyl, allyl, 2-propynyl, cyclopropyl or cyclohexyl; wherein R^4 may be optionally substituted by one or more M;

or R^3 and R^4 together with the nitrogen to which they are attached form morpholino, piperidino, pyrrolidin-1-yl or piperazin-1-yl optionally substituted on carbon by one or more M; wherein said piperazin-1-yl may be optionally substituted on nitrogen by a group selected from Q;

M is independently selected from fluoro, cyano, hydroxy, methyl, methoxy, ethoxy, dimethylamino, methoxycarbonyl, ethoxycarbonyl, butoxycarbonyl, cyclopropyl, tetrahydrofuryl, pyridyl, imidazolyl, dioxolanyl or morpholino; wherein M may be optionally substituted on carbon by a group selected from P;

P and X are independently selected from hydroxy and methoxy; and

Q is selected from methyl, ethyl, isopropyl, ethylsulphonyl or ethoxycarbonyl; wherein G may be optionally substituted on carbon by one or more X.

Particularly R^3 and R^4 together with the nitrogen to which they are attached form isobutylamino, ethylamino, 2-fluoroethylamino, 3-ethoxypropylamino, butylamino, 2,2,2-trifluoroethylamino, 3-morpholinopropylamino, cyclopropylamino, cyclopropylmethylamino, cyclohexylamino, tetrahydrofur-2-ylmethyl, 2-dimethylaminoethylamino, cyanomethylamino, pyrid-3-ylmethylamino, butoxycarbonylmethylamino, 2-(methoxycarbonyl)ethylamino, 2-hydroxyethylamino, methylamino, 2-propynylamino, 2-methoxyethylamino, 2-imidazol-4-ylethylamino, 2-(2-hydroxyethoxy)ethylamino, 2,3-dihydroxypropylamino, 2,2-dimethyldioxolan-4-ylmethylamino, propylamino, *N*-methyl-*N*-allylamino, *N*-methyl-*N*-ethoxycarbonylmethylamino, *N*-methyl-*N*-(2-cyanoethyl)amino, diethylamino, *N*-methyl-*N*-(2-methoxyethyl)amino, bis-(2-cyanoethyl)amino, *N*-ethyl-*N*-cyclohexylamino, *N*-methyl-*N*-(2,2,2-trifluoroethyl)amino, *N*-methyl-*N*-(2-propynyl)amino, morpholino, 2,6-dimethylmorpholino, 3,5-dimethylpiperidino, piperidino, 4-(2-methoxyethyl)piperazin-1-yl, 4-methylpiperazin-1-yl, 4-isopropylpiperazin-1-yl, 4-ethylsulphonylpiperazin-1-yl, 4-ethoxycarbonylpiperazin-1-yl, 4-(2-hydroxyethyl)piperazin-1-yl, and 3-hydroxypyrrolidin-1-yl.

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

p is 0;

R^2 is sulphamoyl or a group B-E-; wherein

B is selected from C_{1-6}alkyl or (heterocyclic group)C_{1-6}alkyl; wherein said C_{1-6}alkyl or (heterocyclic group)C_{1-6}alkyl are optionally substituted on carbon by one or more D;

E is $-N(R^a)SO_2-$; wherein R^a is hydrogen;

D is independently selected from hydroxy or *N*-(C_{1-6}alkyl)amino;

q is 1;

R^3 is hydrogen or C_{1-6}alkyl; wherein said C_{1-6}alkyl may be optionally substituted by one or more M; and

R^4 is C_{1-6}alkyl or C_{2-6}alkenyl; wherein said C_{1-6}alkyl or C_{2-6}alkenyl may be optionally substituted by one or more M;

or R^3 and R^4 together with the nitrogen to which they are attached form a heterocyclic ring; wherein

M is independently selected from halo, cyano, C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl or a heterocyclic group;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

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

p is 0;

R^2 is sulphamoyl, *N*-(3-hydroxy-2,2-dimethylpropyl)sulphamoyl, *N*-(3-(*N*-isopropylamino)propyl)sulphamoyl or *N*-(tetrahydrofur-2-ylmethyl)sulphamoyl;

q is 1;

R^3 and R^4 together with the nitrogen to which they are attached form morpholino, *i*-butylamino, ethylamino, 2-fluoroethylamino, 3-ethoxypropylamino, butylamino, (*N*-methyl)allylamino, (*N*-methyl)ethoxycarbonylmethylamino, (*N*-methyl)-2-cyanoethylamino, *N,N*-diethylamino, (*N*-methyl)-2-methoxyethylamino, 2,2,2-trifluroethylamino, *N,N*-di-(2-cyanoethyl)amino or 3-morpholinopropylamino;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

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

p is 0;

In another aspect of the invention, preferably R^2 is sulphamoyl or a group B-E-;

B is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or (heterocyclic group)C_{1-6}alkyl; wherein B may be optionally substituted on carbon by one or more D; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from G;

E is $-S(O)_r-$ or $-N(R^a)SO_2-$; wherein R^a is hydrogen or C_{1-6}alkyl and r is 2;

D is independently selected from halo, cyano, hydroxy, amino, C_{1-6}alkyl, C_{1-6}alkoxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino and C_{1-6}alkyl$S(O)_a$ wherein a is 0 to 2; wherein D may be optionally substituted on carbon by a group selected from V;

V is selected from hydroxy and dimethylamino;

G is selected from C_{1-4}alkyl;

q is 1;

R^3 is hydrogen or C_{1-6}alkyl; wherein R^3 may be optionally substituted by one or more M; and

R^4 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{3-8}cycloalkyl; wherein R^4 may be optionally substituted by one or more M;

or R^3 and R^4 together with the nitrogen to which they are attached form a heterocyclic ring optionally substituted on carbon by one or more M; wherein if said heterocyclic ring contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from Q;

M is independently selected from halo, cyano, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkoxycarbonyl, C_{3-8}cycloalkyl or a heterocyclic group; wherein M may be optionally substituted on carbon by a group selected from P;

P and X are independently selected from hydroxy and methoxy;

Q is selected from C_{1-4}alkyl, C_{1-4}alkylsulphonyl or C_{1-4}alkoxycarbonyl; wherein G may be optionally substituted on carbon by one or more X;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

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

p is 0;

R^2 is sulphamoyl or a group B-E-;

B is selected from methyl, ethyl, propyl, butyl, 2,2-dimethylpropyl, pentyl, allyl, 2-propynyl, pyrrolidin-2-ylmethyl, pyrid-3-ylmethyl, 1,4-dioxan-2-ylmethyl, pyrid-2-ylmethyl, 2-morpholinoethyl, 2-1,3,4-triaziol-2-ylethyl, 2-piperidinoethyl, 2-pyrid-2-ylethyl, 2-pyrid-4-ylethyl, 2-pyrrolidin-1-ylethyl, 2-imidazol-4-ylethyl, 3-imidazol-1-ylpropyl, 3-morpholinopropyl, 3-piperidinopropyl or tetrahydrofur-2-ylmethyl; wherein B may be optionally substituted on carbon by one or more D; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from G;

E is -$S(O)_r$- or -$N(R^a)SO_2$-; wherein R^a is hydrogen or C_{1-6}alkyl and r is 2;

D is independently selected from fluoro, cyano, hydroxy, amino, methyl, methoxy, ethoxy, isopropylamino, dimethylamino, diethylamino, acetamido, ethylthio and mesyl; wherein D may be optionally substituted on carbon by a group selected from V;

V is selected from hydroxy and dimethylamino;

G is selected from ethyl;

q is 1;

R^3 is hydrogen, methyl or ethyl; wherein R^3 may be optionally substituted by one or more M; and

R^4 is methyl, ethyl, butyl, isobutyl, propyl, allyl, 2-propynyl, cyclopropyl or cyclohexyl; wherein R^4 may be optionally substituted by one or more M;

or R^3 and R^4 together with the nitrogen to which they are attached form morpholino, piperidino, pyrrolidin-1-yl or piperazin-1-yl optionally substituted on carbon by one or more M; wherein said piperazin-1-yl may be optionally substituted on nitrogen by a group selected from Q;

M is independently selected from fluoro, cyano, hydroxy, methyl, methoxy, ethoxy, dimethylamino, methoxycarbonyl, ethoxycarbonyl, butoxycarbonyl, cyclopropyl, tetrahydrofuryl, pyridyl, imidazolyl, dioxolanyl or morpholino; wherein M may be optionally substituted on carbon by a group selected from P;

P and X are independently selected from hydroxy and methoxy; and

Q is selected from methyl, ethyl, isopropyl, ethylsulphonyl or ethoxycarbonyl; wherein G may be optionally substituted on carbon by one or more X;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

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

p is 0;

R^2 is sulphamoyl, mesyl, ethylsulphonyl, 2-ethoxyethylsulphonyl, propylsulphonyl, 3-isopropylaminopropylsulphonyl, 4-isopropylaminobutylsulphonyl, *N*-(tetrahydrofur-2-ylmethyl)sulphamoyl, *N*-(pyrid-3-ylmethyl)sulphamoyl, *N*-(pyrid-2-ylmethyl)sulphamoyl, *N*-(1,4-dioxan-2-ylmethyl)sulphamoyl, *N*-(methyl)sulphamoyl, *N*-(2-methoxyethyl)sulphamoyl, *N*-(2-ethylthioethyl)sulphamoyl, *N*-(2-morpholinoethyl)sulphamoyl, *N*-(2-piperidinoethyl)sulphamoyl, *N*-(2-pyrid-2-ylethyl)sulphamoyl, *N*-(2-pyrrolidin-1-ylethyl)sulphamoyl, *N*-(2-imidazol-4-ylethyl)sulphamoyl, *N*-(2-isopropylaminoethyl)sulphamoyl,

N-(2-mesylethyl)sulphamoyl, *N*-[2-(2-hydroxyethoxy)ethyl]sulphamoyl, *N*-[2-(1-ethylpyrrolidin-2-yl)ethyl]sulphamoyl, *N*-(2-pyrid-2-ylethyl)sulphamoyl, *N*-(2-diethylaminoethyl)sulphamoyl, *N*-(2-pyrid-4-ylethyl)sulphamoyl, *N*-(2-acetamidoethyl)sulphamoyl, *N*-(2-dimethylaminoethyl)sulphamoyl, *N*-2-[(5-methyl-1,3,4-triazol-2-yl)ethyl]sulphamoyl, *N*-(2-hydroxyethyl)sulphamoyl, *N*-(2-cyanoethyl)sulphamoyl, *N*-(2-diethylaminoethyl)-*N*-(methyl)sulphamoyl, *N*-(2-methoxyethyl)-*N*-(methyl)sulphamoyl, *N*-(2,2,2-trifluoroethyl)sulphamoyl, *N*-(3-hydroxy-2,2-dimethylpropyl)sulphamoyl, *N*-(3-isopropylaminopropyl)sulphamoyl, *N*-(3-methoxypropyl)sulphamoyl, *N*-(3-imidazol-1-ylpropyl)sulphamoyl, *N*-(2-hydroxy-3-aminopropyl)sulphamoyl, *N*-(3-hydroxypropyl)sulphamoyl, *N*-(3-ethoxypropyl)sulphamoyl, *N*-[3-(2-dimethylaminoethyl)propyl]sulphamoyl, *N*-(3-morpholinopropyl)sulphamoyl, *N*-(2-hydroxypropyl)sulphamoyl, *N*-(2-hydroxy-3-piperidinopropyl)sulphamoyl, *N*-(3-piperidinopropyl)-*N*-(methyl)sulphamoyl, *N*-(2-hydroxybutyl)sulphamoyl, *N*-(pentyl)sulphamoyl, *N*-(5-hydroxypentyl)sulphamoyl, *N*-(allyl)sulphamoyl or *N*-(2-propynyl)sulphamoyl;

q is 1 and R^2 is para to the amino group in the aniline of formula (I); and

R^3 and R^4 together with the nitrogen to which they are attached form isobutylamino, ethylamino, 2-fluoroethylamino, 3-ethoxypropylamino, butylamino, 2,2,2-trifluoroethylamino, 3-morpholinopropylamino, cyclopropylamino, cyclopropylmethylamino, cyclohexylamino, tetrahydrofur-2-ylmethyl, 2-dimethylaminoethylamino, cyanomethylamino, pyrid-3-ylmethylamino, butoxycarbonylmethylamino, 2-(methoxycarbonyl)ethylamino, 2-hydroxyethylamino, methylamino, 2-propynylamino, 2-methoxyethylamino, 2-imidazol-4-ylethylamino, 2-(2-hydroxyethoxy)ethylamino, 2,3-dihydroxypropylamino, 2,2-dimethyldioxolan-4-ylmethylamino, propylamino, *N*-methyl-*N*-allylamino, *N*-methyl-*N*-ethoxycarbonylmethylamino, *N*-methyl-*N*-(2-cyanoethyl)amino, diethylamino, *N*-methyl-*N*-(2-methoxyethyl)amino, bis-(2-cyanoethyl)amino, *N*-ethyl-*N*-cyclohexylamino, *N*-methyl-*N*-(2,2,2-trifluoroethyl)amino, *N*-methyl-*N*-(2-propynyl)amino, morpholino, 2,6-dimethylmorpholino, 3,5-dimethylpiperidino, piperidino, 4-(2-methoxyethyl)piperazin-1-yl, 4-methylpiperazin-1-yl, 4-isopropylpiperazin-1-yl, 4-ethylsulphonylpiperazin-1-yl, 4-ethoxycarbonylpiperazin-1-yl, 4-(2-hydroxyethyl)piperazin-1-yl, and 3-hydroxypyrrolidin-1-yl;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

In another aspect of the invention, preferred compounds of the invention are any one

of Examples 1-17 or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

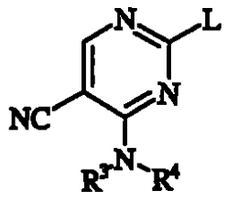
In another aspect of the invention, preferred compounds of the invention are any one of the Examples or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

In an additional aspect of the invention, preferred compounds of the invention are Examples 24, 38, 58, 59, 60, 63, 67, 73, 95 or 126 or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

Preferred aspects of the invention are those which relate to the compound of formula (I) or a pharmaceutically acceptable salt thereof.

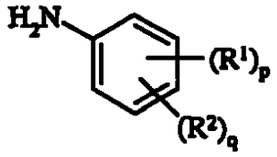
Another aspect of the present invention provides a process for preparing a compound of formula (I) or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof which process (wherein R^1, R^2, R^3, R^4, p and q are, unless otherwise specified, as defined in formula (I)) comprises of:

a) reaction of a pyrimidine of formula (II):



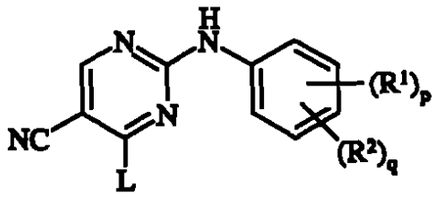
(II)

wherein L is a displaceable group; with an aniline of formula (III):



(III)

b) reacting a pyrimidine of formula (IV):



(IV)

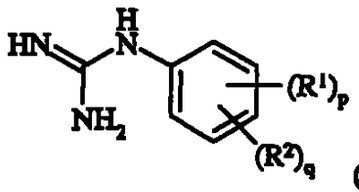
wherein L is a displaceable group; with an amine of formula (V):

R^3R^4NH

(V)

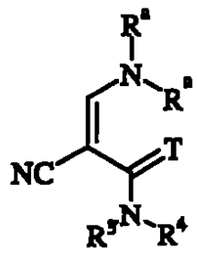
or

c) reacting a compound of formula (VI):



(VI)

with a compound of formula (VII):

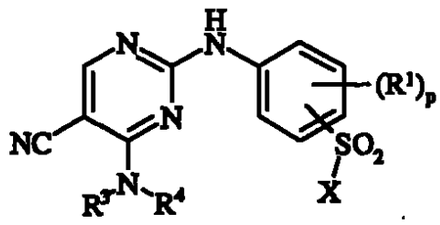


(VII)

wherein T is O or S; R^a may be the same or different and is selected from C_{1-6}alkyl;

d) for compounds of formula (I) where R^2 is sulphamoyl or a group B-E- and E is $-NHSO_2-$;

reacting a pyrimidine of formula (VIII):



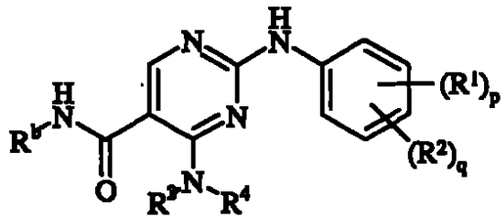
(VIII)

wherein X is a displaceable group; with an amine of formula (IX):

$B\text{-}NH_2$

(IX)

e) by converting a compound of formula (X):



(X)

wherein R^b is hydrogen or *t*-butyl; into a compound of formula (I);

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 or *in vivo* hydrolysable ester.

L is a displaceable group, suitable values for L are for example, a halogeno, (optionally substituted) aryloxy or sulphonyloxy group, for example a chloro, bromo, phenoxy, methanesulphonyloxy or toluene-4-sulphonyloxy group.

X is a displaceable group, suitable values for X are for example, a halogeno group, for example a fluoro, chloro or bromo group. Preferably X is fluoro.

Preferably T is S.

Specific reaction conditions for the above reactions are as follows.

a) and b) Pyrimidines of formula (II) and anilines of formula (III) and pyrimidines of formula (IV) and amines of formula (V) may be reacted together:

i) in the presence of a suitable solvent for example a ketone such as acetone or an alcohol such as ethanol or butanol or an aromatic hydrocarbon such as toluene or *N*-methyl pyrrolidine, optionally in the presence of a suitable acid for example an inorganic acid such as hydrochloric acid or sulphuric acid, or an organic acid such as acetic acid or formic acid (or a suitable Lewis acid) and at a temperature in the range of 0°C to reflux, preferably reflux; or

ii) under standard Buchwald conditions (for example see *J. Am. Chem. Soc.*, 118, 7215; *J. Am. Chem. Soc.*, 119, 8451; *J. Org. Chem.*, 62, 1568 and 6066) for example in the presence of palladium acetate, in a suitable solvent for example an aromatic solvent such as toluene, benzene or xylene, with a suitable base for example an inorganic base such as caesium carbonate or an organic base such as potassium-*t*-butoxide, in the presence of a suitable ligand such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and at a temperature in the range of 25 to 80°C.

Pyrimidines of the formula (II) and (IV) and anilines of formula (III) and amines of formula (V) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

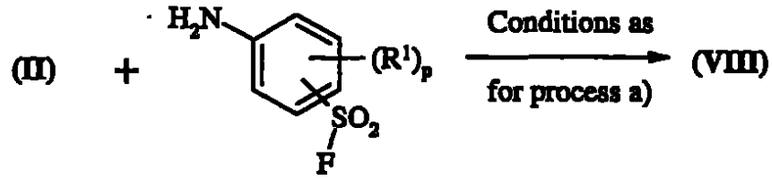
c) Compounds of formula (VI) and compounds of formula (VII) are reacted together in a suitable solvent such as *N*-methylpyrrolidinone or butanol at a temperature in the range of

100-200°C, preferably in the range of 150-170°C. The reaction is preferably conducted in the presence of a suitable base such as, for example, sodium methoxide or potassium carbonate.

Compounds of formula (VI) and (VII) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

d) Compounds of formula (VIII) and compounds of formula (IX) may be reacted together in the presence of a base for example an inorganic base such as caesium carbonate in the presence of an inert solvent such as toluene or tetrahydrofuran, or in the presence of an organic base such as excess (IX) and at a temperature in the range of 25 to 80°C.

Compounds of formula (VIII) wherein X is fluoro may be prepared according to the following scheme:

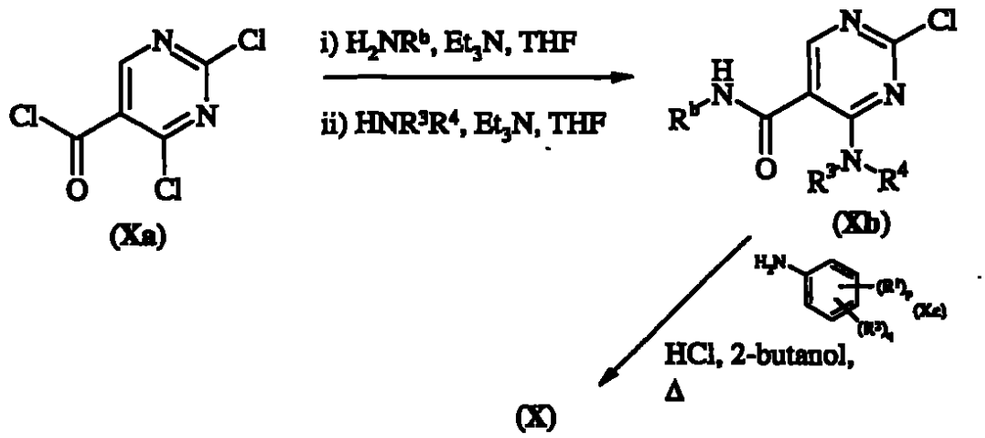


(VIIIa)

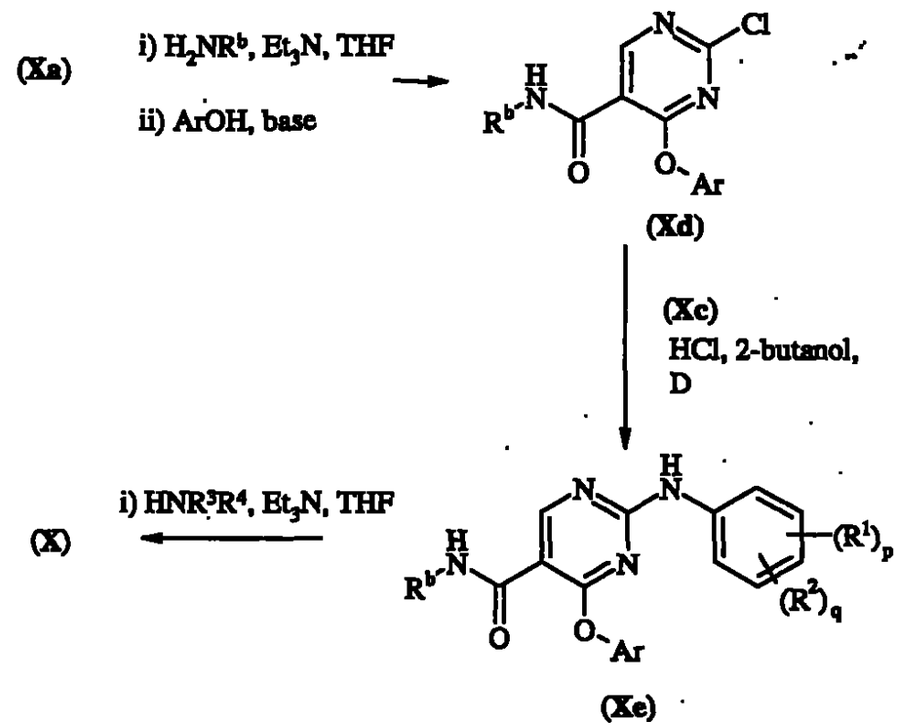
Compounds of formula (VIIIa) and (IX) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

e) Compounds of formula (X) may be converted into compounds of formula (I) under standard conditions, for example in the presence of trifluoroacetic anhydride (where R^b is hydrogen) or thionyl chloride at a temperature in the range of 25 to 100°C.

Compounds of formula (X) may be prepared according to scheme 1 or scheme 2:



Scheme 1



Scheme 2

wherein Ar is optionally substituted aryl, for example phenyl.

Compounds of formula (Xa) and (Xc) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

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 halogeno 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.

As stated hereinbefore the compounds defined in the present invention possesses anti-cell-proliferation activity such as anti-cancer activity which is believed to arise from the CDK inhibitory activity of the compound. These properties may be assessed, for example, using the procedure set out below:-

Assay

The following abbreviations have been used :-

HEPES is *N*-[2-Hydroxyethyl]piperazine-*N*'-[2-ethanesulfonic acid]

DTT is Dithiothreitol

PMSF is Phenylmethylsulphonyl fluoride

The compounds were tested in an *in vitro* kinase assay in 96 well format using Scintillation Proximity Assay (SPA - obtained from Amersham) for measuring incorporation of [γ-33-P]-Adenosine Triphosphate into a test substrate (GST-Retinoblastoma protein; GST-Rb). In each well was placed the compound to be tested (diluted in DMSO and water to correct concentrations) and in control wells either roscovitine as an inhibitor control or DMSO as a positive control.

Approximately 0.2µl of CDK2/Cyclin E partially-purified enzyme (amount dependent on enzyme activity) diluted in 25µl incubation buffer was added to each well then 20µl of GST-Rb/ATP/ATP33 mixture (containing 0.5µg GST-Rb and 0.2µM ATP and 0.14µCi [γ-33-P]-Adenosine Triphosphate in incubation buffer), and the resulting mixture shaken gently, then incubated at room temperature for 60 minutes.

To each well was then added 150µL stop solution containing (0.8mg/well of Protein A-PVT SPA bead (Amersham)), 20pM/well of Anti-Glutathione Transferase, Rabbit IgG (obtained from Molecular Probes), 61mM EDTA and 50mM HEPES pH 7.5 containing 0.05% sodium azide.

The plates were sealed with Topseal-S plate sealers, left for two hours then spun at 2500rpm, 1124xg., for 5 minutes. The plates were read on a Topcount for 30 seconds per well.

The incubation buffer used to dilute the enzyme and substrate mixes contained 50mM HEPES pH7.5, 10mM $MnCl_2$, 1mM DTT, 100µM Sodium vanadate, 100µM NaF, 10mM Sodium Glycerophosphate, BSA (1mg/ml final).

Test substrate

In this assay only part of the retinoblastoma protein (Science 1987 Mar13;235 (4794):1394-1399; Lee W.H., Bookstein R., Hong F., Young L.J., Shew J.Y., Lee E.Y.) was used, fused to a GST tag. PCR of retinoblastoma gene encoding amino acids 379-928 (obtained from retinoblastoma plasmid ATCC pLRbRNL) was performed, and the sequence cloned into pGEX 2T fusion vector (Smith D.B. and Johnson, K.S. Gene 67, 31 (1988); which contained a tac promoter for inducible expression, internal lac I^q gene for use in any E.Coli host, and a coding region for thrombin cleavage - obtained from Pharmacia Biotech) which was used to amplify amino acids 792-928. This sequence was again cloned into pGEX 2T.

The retinoblastoma 792-928 sequence so obtained was expressed in E.Coli (BL21 (DE3) pLysS cells) using standard inducible expression techniques, and purified as follows.

E.coli paste was resuspended in 10ml/g of NETN buffer (50mM Tris pH 7.5, 120mM NaCl, 1mM EDTA, 0.5%v/v NP-40, 1mM PMSF, 1ug/ml leupeptin, 1ug/ml aprotinin and 1ug/ml pepstatin) and sonicated for 2 x 45 seconds per 100ml homogenate. After centrifugation, the supernatant was loaded onto a 10ml glutathione Sepharose column (Pharmacia Biotech, Herts, UK), and washed with NETN buffer. After washing with kinase buffer (50mM HEPES pH 7.5, 10mM MgCl2, 1mM DTT, 1mM PMSF, 1ug/ml leupeptin, 1ug/ml aprotinin and 1ug/ml pepstatin) the protein was eluted with 50mM reduced glutathione in kinase buffer. Fractions containing GST-Rb(792-927) were pooled and dialysed overnight against kinase buffer. The final product was analysed by Sodium Dodeca Sulfate (SDS) PAGE (Polyacrylamide gel) using 8-16% Tris-Glycine gels (Novex, San Diego, USA).

CDK2 and Cyclin E

The open reading frames of CDK2 and Cyclin E were isolated by reverse transcriptase-PCR using HeLa cell and activated T cell mRNA as a template and cloned into the insect expression vector pVL1393 (obtained from Invitrogen 1995 catalogue number: V1392-20). CDK2 and cyclin E were then dually expressed [using a standard virus

Baculogold co-infection technique] in the insect SF21 cell system (Spodoptera Frugiperda cells derived from ovarian tissue of the Fall Army Worm - commercially available).

Example production of Cyclin E/CDK2

The following Example provides details of the production of Cyclin E/CDK2 in SF21 cells (in TC100 + 10% FBS(TCS) + 0.2% Pluronic) having dual infection MOI 3 for each virus of Cyclin E & CDK2.

SF21 cells grown in a roller bottle culture to 2.33 x 10^6 cells/ml were used to inoculate 10 x 500 ml roller bottles at 0.2 x 10E6 cells/ml. The roller bottles were incubated on a roller rig at 28°C.

After 3 days (72 hrs.) the cells were counted, and the average from 2 bottles found to be 1.86 x 10E6 cells/ml. (99% viable). The cultures were then infected with the dual viruses at an MOI 3 for each virus.

The viruses were mixed together before addition to the cultures, and the cultures returned to the roller rig 28°C.

After 2 days (48 hrs.) post infection the 5 Litres of culture was harvested. The total cell count at harvest was 1.58 x 10E6 cells/ml.(99% viable). The cells were spun out at 2500rpm, 30 mins., 4°C in Heraeus Omnifuge 2.0 RS in 250 ml. lots. The supernatant was discarded.

Partial co-purification of Cdk2 and Cyclin E

Sf21 cells were resuspended in lysis buffer (50mM Tris pH 8.2, 10mM $MgCl_2$, 1mM DTT, 10mM glycerophosphate, 0.1mM sodium orthovanadate, 0.1mM NaF, 1mM PMSF, 1ug/ml leupeptin and 1ug/ml aprotinin) and homogenised for 2 minutes in a 10ml Dounce homgeniser. After centrifugation, the supernatant was loaded onto a Poros HQ/M 1.4/100 anion exchange column (PE Biosystems, Hertford, UK). Cdk2 and Cyclin E were coeluted at the beginning of a 0-1M NaCl gradient (run in lysis buffer minus protease inhibitors) over 20 column volumes. Co-elution was checked by western blot using both anti-Cdk2 and anti-Cyclin E antibodies (Santa Cruz Biotechnology, California, US).

By analogy, assays designed to assess inhibition of CDK4 and CDK6 may be constructed. CDK2 (EMBL Accession No. X62071) may be used together with Cyclin A or Cyclin E (see EMBL Accession No. M73812), and further details for such assays are contained in PCT International Publication No. WO99/21845, the relevant Biochemical & Biological Evaluation sections of which are hereby incorporated by reference.

Although the pharmacological properties of the compounds of the formula (I) vary

with structural change, in general activity possessed by compounds of the formula (I) may be demonstrated at IC_{50} concentrations or doses in the range 250μM to 1nM.

When tested in the above in-vitro assay the CDK2 inhibitory activity of Example 1 was measured as $IC_{50} = 0.148\mu M$.

The *in vivo* activity of the compounds of the present invention may be assessed by standard techniques, for example by measuring inhibition of cell growth and assessing cytotoxicity.

Inhibition of cell growth may be measured by staining cells with Sulforhodamine B (SRB), a fluorescent dye that stains proteins and therefore gives an estimation of amount of protein (i.e. cells) in a well (see Boyd, M.R.(1989) Status of the NCI preclinical antitumour drug discovery screen. Prin. Prac Oncol 10:1-12). Thus, the following details are provided of measuring inhibition of cell growth:-

Cells were plated in appropriate medium in a volume of 100□l in 96 well plates; media was Dulbecco's Modified Eagle media for MCF-7, SK-UT-1B and SK-UT-1. The cells were allowed to attach overnight, then inhibitor compounds were added at various concentrations in a maximum concentration of 1% DMSO (v/v). A control plate was assayed to give a value for cells before dosing. Cells were incubated at 37°C, (5% CO_2) for three days.

At the end of three days TCA was added to the plates to a final concentration of 16% (v/v). Plates were then incubated at 4°C for 1 hour, the supernatant removed and the plates washed in tap water. After drying, 100□l SRB dye (0.4% SRB in 1% acetic acid) was added for 30 minutes at 37°C. Excess SRB was removed and the plates washed in 1% acetic acid. The SRB bound to protein was solubilised in 10mM Tris pH7.5 and shaken for 30 minutes at room temperature. The ODs were read at 540nm, and the concentration of inhibitor causing 50% inhibition of growth was determined from a semi-log plot of inhibitor concentration versus absorbance. The concentration of compound that reduced the optical density to below that obtained when the cells were plated at the start of the experiment gave the value for toxicity.

Typical IC_{50} values for compounds of the invention when tested in the SRB assay are in the range 1mM to 1nM.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a pyrimidine derivative of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester 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 5-5000 mg per square meter body area of the animal, i.e. approximately 0.1-100 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-50 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 or *in vivo* hydrolysable ester 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 or *in vivo* hydrolysable ester thereof, are effective cell cycle inhibitors (anti-cell proliferation agents), which property is believed to arise from their CDK 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 CDK enzymes, i.e. the compounds may be used to produce a CDK inhibitory effect in a warm-blooded animal in need of such treatment. Thus the compounds of the present invention provide a method for treating the proliferation of malignant cells characterised by inhibition of CDK enzymes, i.e. the compounds may be used to produce an anti-proliferative effect mediated alone or in part by the inhibition of CDKs. Such a compound of the invention is expected to possess a wide range of anti-cancer properties as CDKs have been implicated in many common human cancers such as leukaemia and breast, lung, colon, rectal, stomach, prostate, bladder, pancreas and ovarian cancer. Thus it is expected that a compound of the invention will possess anti-cancer activity against these cancers. It is in addition expected that a compound of the present invention will possess activity against a range of leukaemias,

lymphoid malignancies and solid tumours such as carcinomas and sarcomas in tissues such as the liver, kidney, prostate and pancreas. In particular such compounds of the invention are expected to slow advantageously the growth of primary and recurrent solid tumours of, for example, the colon, breast, prostate, lungs and skin. More particularly such compounds of the invention, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, are expected to inhibit the growth of those primary and recurrent solid tumours which are associated with CDKs, especially those tumours which are significantly dependent on CDKs for their growth and spread, including for example, certain tumours of the colon, breast, prostate, lung, vulva and skin.

It is further expected that a compound of the present invention will possess activity against other cell-proliferation diseases in a wide range of other disease states including leukaemias, fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

Thus according to this aspect of the invention there is provided a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore for use as a medicament; and the use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of a cell cycle inhibitory (anti-cell-proliferation) effect in a warm-blooded animal such as man. Particularly, an inhibitory effect is produced by preventing entry into or progression through the S phase by inhibition of CDK2, CDK4 and/or CDK6, especially CDK2.

According to a further feature of the invention, there is provided a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before in the manufacture of a medicament for use in the treatment of cancers (solid tumours and leukaemias), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation, particularly in the treatment of cancers.

According to a further feature of this aspect of the invention there is provided a method for producing a cell cycle inhibitory (anti-cell-proliferation) 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 as defined immediately above. Particularly, an inhibitory effect is produced by preventing entry into or progression through the S phase by inhibition of CDK2, CDK4 and/or CDK6, especially CDK2.

According to a further feature of this aspect of the invention there is provided a method for producing a cell cycle inhibitory (anti-cell-proliferation) 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 or *in vivo* hydrolysable ester thereof as defined herein before. Particularly, an inhibitory effect is produced by preventing entry into or progression through the S phase by inhibition of CDK2, CDK4 and/or CDK6, especially CDK2.

According to an additional feature of this aspect of the invention there is provided a method of treating cancers (solid tumours and leukaemias), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation, 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 or *in vivo* hydrolysable ester thereof as defined herein before.

Particularly there is provided a method of treating cancer 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 or in vivo hydrolysable ester 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 or *in vivo* hydrolysable ester thereof, as defined herein before in association with a pharmaceutically-acceptable diluent or carrier for use in the production of a cell cycle inhibitory (anti-cell-proliferation) 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 or *in vivo* hydrolysable ester thereof, as defined herein before in association with a pharmaceutically-acceptable diluent or carrier for use in the treatment of cancers (solid

tumours and leukaemias), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation, 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 or *in vivo* hydrolysable ester thereof, as defined herein before in association with a pharmaceutically-acceptable diluent or carrier for use in the treatment of cancer in a warm-blooded animal such as man.

Preventing cells from entering DNA synthesis by inhibition of essential S-phase initiating activities such as CDK2 initiation may also be useful in protecting normal cells of the body from toxicity of cycle-specific pharmaceutical agents. Inhibition of CDK2 or 4 will prevent progression into the cell cycle in normal cells which could limit the toxicity of cycle-specific pharmaceutical agents which act in S-phase, G2 or mitosis. Such protection may result in the prevention of hair loss normally associated with these agents.

Therefore in a further aspect of the invention there is provided a compound of formula (I) as defined above or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof for use as a cell protective agent.

Therefore in a further aspect of the invention there is provided a compound of formula (I) as defined above or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof for use in preventing hair loss arising from the treatment of malignant conditions with pharmaceutical agents.

Examples of pharmaceutical agents for treating malignant conditions that are known to cause hair loss include alkylating agents such as ifosfamide and cyclophosphamide; antimetabolites such as methotrexate, 5-fluorouracil, gemcitabine and cytarabine; vinca alkaloids and analogues such as vincristine, vinbalstine, vindesine, vinorelbine; taxanes such as paclitaxel and docetaxel; topoisomerase I inhibitors such as irintotecan and topotecan; cytotoxic antibiotics such as doxorubicin, daunorubicin, mitoxantrone, actinomycin-D and mitomycin; and others such as etoposide and tretinoin.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, may be administered in association with a

one or more of the above pharmaceutical agents. In this instance the compound of formula (I) may be administered by systemic or non systemic means. Particularly the compound of formula (I) my may administered by non-systemic means, for example topical administration.

Therefore in an additional feature of the invention, there is provided a method of preventing hair loss during treatment for one or more malignant conditions with pharmaceutical agents, in a warm-blooded animal, such as man, which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

In an additional feature of the invention, there is provided a method of preventing hair loss during treatment for one or more malignant conditions with pharmaceutical agents, in a warm-blooded animal, such as man, which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof in simultaneous, sequential or separate administration with an effective amount of said pharmaceutical agent.

According to a further aspect of the invention there is provided a pharmaceutical composition for use in preventing hair loss arising from the treatment of malignant conditions with pharmaceutical agents which comprises a compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, and said pharmaceutical agent, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, and a pharmaceutical agent for treating malignant conditions that is known to cause hair loss.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, in a first unit dosage form;

b) a pharmaceutical agent for treating malignant conditions that is known to cause hair loss; in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof,

in the manufacture of a medicament for the prevention of hair loss during treatment of malignant conditions with pharmaceutical agents.

According to a further aspect of the present invention there is provided a combination treatment for the prevention of hair loss comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of a pharmaceutical agent for treatment of malignant conditions to a warm-blooded animal, such as man.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular cell-proliferation disease will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. A unit dose in the range, for example, 1-100 mg/kg, preferably 1-50 mg/kg is envisaged.

The CDK inhibitory activity defined hereinbefore may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment in addition to the cell cycle inhibitory treatment defined hereinbefore may be: surgery, radiotherapy or chemotherapy. Such chemotherapy may cover three main categories of therapeutic agent:

(i) other cell cycle inhibitory agents that work by the same or different mechanisms from those defined hereinbefore;

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

example platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors); and

(iii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as antimetabolites (for example antifolates like methotrexate, fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); antitumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa); antimitotic agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere); topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan). According to this aspect of the invention there is provided a pharmaceutical product comprising a compound of the formula (I) as defined hereinbefore and an additional anti-tumour substance as defined hereinbefore for the conjoint treatment of cancer.

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 cell cycle activity 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, that is, at a temperature in the range of 18-25°C;

(ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30mmHg) with a bath temperature of up to 60°C;

(iii) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates;

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

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

(vi) 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 300 MHz using perdeuterio dimethyl sulphoxide (DMSO-d_6) as solvent unless otherwise indicated;

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

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

(x) 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 $(MH)^+$;

(xi) unless stated otherwise compounds containing an asymmetrically substituted carbon and/or sulphur atom have not been resolved;

(xii) 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;

(xvi) the following abbreviations have been used:

THF	tetrahydrofuran;
SM	starting material;
NMP	*N*-methylpyrrolidinone;
DCM	dichloromethane; and
DMSO	dimethylsulphoxide.

Example 1

5-Cyano-4-morpholino-2-{4-[*N*-(3-isopropylaminopropyl)sulphamoyl]anilino}pyrimidine

2-Chloro-5-cyano-4-morpholinopyrimidine (Method 55; 425mg, 1.90mmol), 4-[*N*-(3-isopropylaminopropyl)sulphamoyl]aniline (Method 1; 514mg, 1.90mmol) and 1M ethereal hydrogen chloride (189□l, 3.79mmol) in 2-butanol (2ml) was heated at 95°C for 15 hours. The mixture was allowed to cool, silica was added and the volatiles were evaporated. The residue was purified by chromatography eluting with DCM /methanolic ammonia (100:0) increasing in polarity to (92:8) and the product was recrystallized from methanol to give the title compound (164mg, 19%). NMR: 0.89 (d, 6H), 1.44 (m, 2H), 2.40 (t, 2H), 2.56 (m, 1H), 2.76 (t, 2H), 3.68-3.74 (m, 4H), 3.83-3.90 (m, 4H), 7.69 (d, 2H), 7.83 (d, 2H), 8.49 (s, 1H), m/z: 460.

Examples 2-11

Following the procedure of Example 1 using 4-[*N*-(3-isopropylaminopropyl) sulphamoyl]aniline (Method 1) and the appropriate 4-substituted pyrimidine starting material the following compounds were prepared.

Ex	Compound Name	NMR	m/z	SM
2	5-Cyano-4-(2-methylpropyl-amino)-2-{4-[*N*-(3-isopropylaminopropyl) sulphamoyl]anilino} pyrimidine	0.86 (d, 6H), 0.90 (d, 6H), 1.44 (m, 2H), 1.99 (m, 1H), 2.40 (t, 2H), 2.56 (m, 1H), 2.76 (t, 2H), 3.23 (t, 2H), 7.66 (d, 2H), 7.92 (d, 2H), 7.97 (m, 1H), 8.37 (s, 1H), 10.13 (brs, 1H)	446	Meth 57
3	5-Cyano-4-ethylamino-2-{4-[*N*-(3-isopropylaminopropyl) sulphamoyl]anilino} pyrimidine	0.89 (d, 6H), 1.17 (t, 3H), 1.45 (m, 2H), 2.41 (t, 2H), 2.56 (m, 1H), 2.76 (t, 2H), 3.45 (m, 2H), 7.67 (d, 2H), 7.84 (brt, 1H), 7.94 (d, 2H), 8.38 (s, 1H), 10.13 (brs, 1H)	418	Meth 56
4	5-Cyano-4-(2-fluoroethyl-amino)-2-{4-[*N*-(3-isopropylaminopropyl) sulphamoyl]anilino} pyrimidine	0.90 (d, 6H), 1.44 (m, 2H), 2.41 (t, 2H), 2.57 (m, 1H), 2.75 (t, 2H), 3.69 (m, 1H), 3.78 (m, 1H), 4.53 (t, 1H), 4.69 (t, 1H), 7.68 (d, 2H), 7.88 (d, 2H), 7.98 (m, 1H), 8.42 (s, 1H), 10.18 (brs, 1H)	436	Meth 58

5	5-Cyano-4-(3-ethoxypropyl-amino)-2-{4-[*N*-(3-isopropylaminopropyl) sulphamoyl]anilino} pyrimidine	0.89 (d, 6H), 1.09 (t, 3H), 1.44 (m, 2H), 1.82 (m, 2H), 2.41 (t, 2H), 2.56 (m, 1H), 2.76 (t, 2H), 3.36-3.53 (m, 6H), 7.67 (d, 2H), 7.80 (t, 1H), 7.94 (d, 2H), 8.38 (s, 1H), 10.15 (brs, 1H)	476	Meth 59
6	5-Cyano-4-butylamino-2-{4-[*N*-(3-isopropylaminopropyl) sulphamoyl]anilino} pyrimidine	0.86-0.94 (m, 9H), 1.34 (m, 2H), 1.46 (m, 2H), 1.57 (m, 2H), 2.41 (t, 2H), 2.58 (m, 1H), 2.75 (t, 2H), 3.41 (m, 2H), 7.66 (d, 2H), 7.89 (t, 1H), 7.93 (d, 2H), 8.37 (s, 1H), 10.14 (brs, 1H)	446	Meth 60
7	5-Cyano-4-(*N*-(methyl)-allylamino)-2-{4-[*N*-(3-isopropylaminopropyl) sulphamoyl]anilino} pyrimidine	0.89 (d, 6H), 1.44 (m, 2H), 2.41 (t, 2H), 2.57 (m, 1H), 2.76 (t, 2H), 3.25 (s, 3H), 4.34 (d, 2H), 5.19 (m, 2H), 5.90 (m, 1H), 7.68 (d, 2H), 7.86 (d, 2H), 8.44 (s, 1H), 10.18 (brs, 1H)	444	Meth 61
8	5-Cyano-4-(*N*-(methyl)-ethoxycarbonylmethylamino) -2-{4-[*N*-(3-isopropylaminopropyl) sulphamoyl]anilino} pyrimidine	0.89 (d, 6H), 1.14 (t, 3H), 1.45 (m, 2H), 2.41 (t, 2H), 2.58 (m, 1H), 2.76 (t, 2H), 3.38 (s, 3H), 4.09 (q, 2H), 4.50 (s, 2H), 7.66 (d, 2H), 7.79 (d, 2H), 8.49 (s, 1H), 10.24 (brs, 1H)	490	Meth 62
9	5-Cyano-4-(*N*-(methyl)-2-cyanoethylamino)-2-{4-[*N*-(3-isopropylaminopropyl) sulphamoyl]anilino} pyrimidine	0.89 (d, 6H), 1.44 (m, 2H), 2.41 (t, 2H), 2.58 (m, 1H), 2.77 (t, 2H), 2.93 (t, 2H), 3.38 (s, 3H), 3.99 (t, 2H), 7.70 (d, 2H), 7.85 (d, 2H), 8.49 (s, 1H), 10.24 (brs, 1H)	457	Meth 63
10	5-Cyano-4-diethylamino-2-{4-[*N*-(3-isopropylamino-propyl)sulphamoyl]anilino} pyrimidine	0.93 (d, 6H), 1.21 (t, 6H), 1.51 (m, 2H), 2.49 (m, 2H), 2.65-2.80 (m, 3H), 3.69 (m, 4H), 7.69 (d, 2H), 7.88 (d, 2H), 8.40 (s, 1H), 10.14 (brs, 1H)	446	Meth 64

11	5-Cyano-4-(*N*-(methyl)-2-methoxyethylamino)-2-{4-[*N*-(3-isopropylaminopropyl) sulphamoyl]anilino} pyrimidine	0.89 (d, 6H), 1.46 (m, 2H), 2.41 (t, 2H), 2.56 (m, 1H), 2.76 (t, 2H), 3.25 (s, 3H), 3.31 (s, 3H), 3.59 (t, 2H), 3.90 (t, 2H), 7.68 (d, 2H), 7.86 (d, 2H), 8.42 (s, 1H), 10.17 (brs, 1H)	462	Meth 65

Example 12

5-Cyano-4-(3-morpholinopropylamino)-2-{4-[*N*-(tetrahydrofur-2-ylmethyl)sulphamoyl] anilino}pyrimidine

2-Chloro-5-cyano-4-(3-morpholinopropylamino)pyrimidine (Method 66; 525mg, 1.87mmol), 4-[*N*-(tetrahydrofur-2-ylmethyl)sulphamoyl]aniline (Method 2; 430mg, 1.68mmol) and 1M ethereal hydrogen chloride (1.87ml, 1.87mmol) in 2-butanol (3ml) was heated at 90°C for 3 hours. The mixture was allowed to cool, the resulting precipitate was collected by filtration and was washed with ethyl acetate. The crude solid was purified by chromatography eluting with DCM/methanolic ammonia/ (100:0) increasing in polarity to (97:3). The product was recrystallized from methanol to give the title compound (111 mg). NMR: 1.50 (m, 1H), 1.67-1.88 (m, 5H), 2.28-2.40 (m, 6H), 2.73 (t, 2H), 3.48 (m, 2H), 3.51-3.60 (m, 5H), 3.67 (m, 1H), 3.77 (m, 1H), 7.50 (t, 1H), 7.69 (d, 2H), 7.91 (d, 2H), 7.93 (s, 1H), 8.38 (s, 1H), 10.13 (brs, 1H); m/z: 502.

Examples 13-19

Following the procedure of Example 12 using 4-[*N*-(tetrahydrofur-2-ylmethyl) sulphamoyl]aniline (Method 2) and the appropriate 4-substituted pyrimidine starting material the following compounds were prepared.

Ex	Compound Name	NMR	m/z	SM
13	5-Cyano-4-(diethylamino)-2-{4-[*N*-(tetrahydrofur-2-ylmethyl)sulphamoyl] anilino}pyrimidine	1.24 (t, 6H), 1.52 (m, 1H), 1.70-1.90 (m, 3H), 2.75 (t, 2H), 3.56 (m, 1H), 3.60-3.84 (m, 6H), 7.56 (t, 1H), 7.71 (d, 2H), 7.88 (d, 2H), 8.43 (s, 1H), 10.18 (s, 1H)	431	Meth 64

14	5-Cyano-2-{4-[*N*-(tetrahydrofur-2-ylmethyl)sulphamoyl] anilino}-4-(2-methyl-propylamino)pyrimidine	1.52 (m, 1H), 1.70-1.90 (m, 3H), 2.00 (m, 1H), 3.24 (t, 2H), 3.58 (m, 1H), 3.67 (m, 1H), 3.78 (q, 1H), 7.58 (t, 1H), 7.70 (d, 2H), 7.95 (d, 2H), 8.02 (brt, 1H), 8.40 (s, 1H), 10.18 (s, 1H)	431	Meth 57
15	5-Cyano-4-[*N*-(methyl)allylamino]-2-{4-[*N*-(tetrahydrofur-2-ylmethyl)sulphamoyl] anilino}pyrimidine	1.52 (m, 1H), 1.65-1.90 (m, 3H), 2.74 (t, 2H), 3.28 (s, 3H), 3.58 (m, 1H), 3.67 (m, 1H), 3.79 (q, 1H), 4.35 (d, 2H), 5.24 (m, 2H), 5.92 (m, 1H), 7.57 (t, 1H), 7.70 (d, 2H), 7.89 (d, 2H), 8.48 (s, 1H), 10.22 (s, 1H)	429	Meth 61
16	5-Cyano-4-(2-fluoroethylamino)-2-{4-[*N*-(tetrahydrofur-2-ylmethyl)sulphamoyl] anilino}pyrimidine	1.50 (m, 1H), 1.74 (m, 2H), 1.80 (m, 1H), 2.76 (m, 2H), 3.54 (m, 1H), 3.68 (m, 2H), 3.78 (m, 2H), 4.55 (t, 1H), 4.68 (t, 1H), 7.51 (t, 1H), 7.70 (d, 2H), 7.89 (d, 2H), 7.99 (t, 1H), 8.42 (s, 1H), 10.19 (s, 1H)	421	Meth 58
17	5-Cyano-4-[*N*-(methyl)-2-cyanoethylamino]-2-{4-[*N*-(tetrahydrofur-2-ylmethyl)sulphamoyl] anilino}pyrimidine	1.52 (m, 1H), 1.70-1.90 (m, 3H), 2.78 (t, 2H), 2.94 (t, 2H), 3.38 (s; 3H), 3.57 (q, 1H), 3.68 (q, 1H), 3.78 (q, 1H), 4.00 (t, 2H), 7.54 (t, 1H), 7.74 (d, 2H), 7.85 (d, 2H), 8.50 (s, 1H), 10.25 (s, 1H)	442	Meth 63
18	5-Cyano-4-[2-(dimethylamino)ethyl amino]-2-{4-[*N*-(tetrahydrofur-2-ylmethyl) sulphamoyl]anilino} pyrimidine	1.52 (m, 1H), 1.70-1.90 (m, 3H), 2.20 (s, 6H), 2.48 (m, 2H), 2.75 (t, 2H), 3.54 (m, 3H), 3.68 (q, 1H), 3.79 (quin, 1H), 7.52 (t, 1H), 7.67 (m, 3H), 7.93 (d, 2H), 8.40 (s, 1H), 10.16 (s, 1H)	446	Meth 97

19	5-Cyano-4-(cyanomethylamino)-2-{4-[*N*-(tetrahydrofur-2-ylmethyl)sulphamoyl]anilino}pyrimidine	1.50 (m, 1H), 1.68-1.88 (m, 3H), 2.74 (t, 2H), 3.54 (m, 1H), 3.65 (m, 1H), 3.78 (quintet, 1H), 4.38 (d, 2H), 7.52 (t, 1H), 7.71 (d, 2H), 7.94 (d, 2H), 8.45 (t, 1H), 8.52 (s, 1H), 10.39 (s, 1H)	414	Meth 100

Examples 20-28

Following the procedure of Example 12 using 4-[*N*-(2-methoxyethyl)sulphamoyl] aniline (Method 5) and the appropriate 4-substituted pyrimidine starting material the following compounds were prepared.

Ex	Compound Name	NMR	m/z	SM
20	5-Cyano-4-[*N*-(methyl)-2-methoxyethylamino]-2-{4-[*N*-(2-methoxyethyl) sulphamoyl]anilino} pyrimidine	2.89 (q, 2H), 3.15 (s, 3H), 3.30 (2 x s, m, 8H), 3.60 (t, 2H), 3.92 (t, 2H), 7.52 (t, 1H), 7.72 (d, 2H), 7.87 (d, 2H), 8.45 (s, 1H), 10.18 (s, 1H)	421	Meth 65
21	5-Cyano-4-(2,6-dimethylmorpholino)-2-{4-[*N*-(2-methoxyethyl) sulphamoyl]anilino} pyrimidine (*cis* and *trans* isomers)	1.15 (d, 6H), 2.74-2.94 (q and m, 4H), 3.18 (s, 3H), 3.29 (m, 2H), 3.65 (m, 2H *cis* and *trans* isomers), 3.98 (dd) and 4.08 (m) (*cis* and *trans* isomers, 1H), 4.52 (d, 2H), 7.53 (brt, 1H), 7.72 (d, 2H), 7.84 (d, 2H), 8.51 (s, 1H), 10.23 (s, 1H)	447	Meth 98
22	5-Cyano-4-(*cis*-2,6-dimethylmorpholino)-2-{4-[*N*-(2-methoxyethyl) sulphamoyl]anilino} pyrimidine	1.15 (d, 6H), 2.74 (m 2H), 2.88 (q, 2H), 3.18 (s, 3H), 3.29 (m, 2H), 3.65 (m, 2H), 4.52 (d, 2H), 7.53 (brt, 1H), 7.72 (d, 2H), 7.84 (d, 2H), 8.51 (s, 1H), 10.24 (s, 1H)	447	Meth 99

23 [1]	5-Cyano-4-(3,5-dimethylpiperidino)-2-{4-[*N*-(2-methoxyethyl) sulphamoyl]anilino} pyrimidine	0.89 (7H, d + m), 1.68 (m, 2H), 1.81 (brd, 1H), 2.61 (t, 2H), 2.88 (m, 2H), 3.15 (s, 3H), 3.29 (m, 2H), 4.60 (dxq, 2H), 7.54 (t, 1H), 7.71 (d, 2H), 7.85 (d, 2H), 8.44 (s, 1H), 10.18 (s, 1H)	445	Meth 101
24	5-Cyano-4-ethylamino-2-{4-[*N*-(2-methoxyethyl) sulphamoyl]anilino} pyrimidine	1.19 (t, 3H), 2.88 (m, 2H), 3.15 (s, 3H), 3.28 (m, 2H), 3.45 (m, 2H), 7.50 (t, 1H), 7.70 (d, 2H), 7.86 (t, 1H), 7.92 (d, 2H), 8.49 (s, 1H), 10.14 (s, 1H)	377	Meth 56
25	5-Cyano-4-[4-(2-methoxyethyl)piperazin-1-yl]-2-{4-[*N*-(2-methoxyethyl)sulphamoyl] anilino}pyrimidine	2.56 (m, 4H), 2.50 (m, 2H), 2.89 (m, 2H), 3.15 (s, 3H), 3.23 (s, 3H), 3.27 (m, 2H), 3.46 (m, 2H), 3.86 (m, 4H), 7.51 (t, 1H), 7.72 (d, 2H), 7.84 (d, 2H), 8.50 (s, 1H), 10.21 (s, 1H)	476	Meth 102
26	5-Cyano-2-{4-[*N*-(2-methoxyethyl)sulphamoyl] anilino}-4-(4-methyl-piperazin-1-yl)pyrimidine	2.20 (s, 3H), 2.43 (m, 4H), 2.89 (m, 2H), 3.15 (s, 3H), 3.28 (m, 2H), 3.87 (m, 4H), 7.50 (t, 1H), 7.72 (d, 2H), 7.84 (d, 2H), 8.49 (s, 1H), 10.21 (s, 1H)	432	Meth 103
27	5-Cyano-4-(4-isopropylpiperazin-1-yl)-2-{4-[*N*-(2-methoxyethyl) sulphamoyl]anilino} pyrimidine	0.99 (d, 6H), 2.56 (m, 4H), 2.69 (m, 1H), 2.89 (q, 2H), 3.17 (s, 3H), 3.29 (m, 2H), 3.87 (m, 4H), 7.52 (t, 1H), 7.72 (d, 2H), 7.84 (d, 2H), 8.48 (s, 1H), 10.21 (s, 1H)	460	Meth 104
28	5-Cyano-4-[4-(ethylsulphonyl)piperazin-1-yl]-2-{4-[*N*-(2-methoxyethyl)sulphamoyl] anilino}pyrimidine	1.21 (t, 3H), 2.89 (q, 2H), 3.12 (q, 2H), 3.17 (s, 3H), 3.29 (m, 2H), 3.36 (t, 4H), 3.94 (t, 4H), 7.51 (t, 1H), 7.74 (d, 2H), 7.85 (d, 2H), 8.54 (s, 1H), 10.30 (s, 1H)	510	Meth 105

[1] *cis* and *trans* isomers in 80:20 mixture (by NMR).

Examples 29-34

Following the procedure of Example 12 using 4-[*N*-(3-methoxypropyl)sulphamoyl] aniline (Method 4) and the appropriate 4-substituted pyrimidine starting material the following compounds were prepared.

Ex	Compound Name	NMR	m/z	SM
29	5-Cyano-4-(4-ethoxycarbonylpiperazin-1-yl)-2-{4-[*N*-(3-methoxypropyl) sulphamoyl]anilino} pyrimidine	1.22 (t, 3H), 1.59 (m, 2H), 2.78 (m, 2H), 3.16 (s, 3H), 3.28 (t, 2H), 3.58 (m, 4H), 3.91 (m, 4H), 4.08 (q, 2H), 7.40 (t, 1H), 7.74 (d, 2H), 7.88 (d, 2H), 8.54 (s, 1H), 10.29 (s, 1H)	504	Meth 106
30	5-Cyano-2-{4-[*N*-(3-methoxypropyl)sulphamoyl] anilino}-4-methylamino pyrimidine	1.60 (m, 2H), 2.78 (m, 2H), 2.95 (d, 3H), 3.16 (s, 3H), 3.29 (m, 2H), 7.40 (t, 1H), 7.82 (m, 1H), 7.70 (d, 2H), 7.98 (d, 2H), 8.40 (s, 1H), 10.18 (s, 1H)	377	Meth 107
31	5-Cyano-2-{4-[*N*-(3-methoxypropyl)sulphamoyl] anilino}-4-(2-propynylamino)pyrimidine	1.59 (m, 2H), 2.78 (m, 2H), 3.17 (s, 3H), 3.18 (t, 1H), 3.28 (m, 2H), 4.15 (m, 2H), 7.40 (t, 1H), 8.02 (d, 2H), 8.32 (t, 1H), 8.48 (s, 1H), 8.70 (d, 2H), 10.31 (s, 1H)	401	Meth 108
32	5-Cyano-4-cyanomethylamino-2-{4-[*N*-(3-methoxypropyl) sulphamoyl]anilino} pyrimidine	1.54 (m, 2H), 2.72 (m, 2H), 3.12 (s, 3H), 3.22 (m, 2H), 4.36 (d, 2H), 7.39 (t, 1H), 7.68 (d, 2H), 7.92 (t, 2H), 8.42 (t, 1H), 8.51 (s, 1H), 10.39 (s, 1H)	402	Meth 100
33	5-Cyano-2-{4-[*N*-(3-methoxypropyl)sulphamoyl] anilino}-4-[*N*-(methyl)-2,2,2-trifluoroethylamino] pyrimidine	1.58 (m, 2H), 2.76 (m, 2H), 3.18 (s, 3H), 3.26 (m, 2H), 3.47 (s, 3H), 4.70 (m, 2H), 7.42 (t, 1H), 7.72 (d, 2H), 7.84 (t, 2H), 8.59 (s, 1H), 10.35 (s, 1H)	459	Meth 109

34	5-Cyano-4-(2-methoxyethylamino)-2-{4-[*N*-(3-methoxypropyl) sulphamoyl]anilino} pyrimidine	1.57 (m, 2H), 2.74 (m, 2H), 3.14 (s, 3H), 3.24 (s & m, 3H & 2H), 3.52 (m, 2H), 3.58 (m, 2H), 7.38 (brt, 1H), 7.68 (d, 2H), 7.84 (brt, 1H), 7.91 (d, 2H), 8.40 (s, 1H), 10.18 (s, 1H)	421	Meth 110

Examples 35-39

Following the procedure of Example 12 starting from 4-*n*-butylamino-2-chloro-5-cyanopyrimidine (Method 60) and the appropriate aniline starting material the following compounds were prepared.

Ex	Compound Name	NMR	m/z	SM
35	5-Cyano-4-*n*-butylamino-2-{4-[*N*-(2-methoxyethyl) sulphamoyl]anilino} pyrimidine	0.90 (t, 3H), 1.30 (m, 2H), 1.55 (m, 2H), 2.85 (m, 2H), 3.13 (s, 3H), 3.30 (t, 2H), 3.40 (m, 2H), 5.00 (brs, 1H), 7.50 (brs, 1H), 7.70 (d, 2H), 7.9 (d, 3H), 8.40 (s, 1H)	404	Meth 5
36	5-Cyano-4-*n*-butylamino-2-{4-[*N*-(*n*-pentyl) sulphamoyl]anilino} pyrimidine	0.80 (t, 3H), 0.90 (t, 3H), 1.20 (m, 4H), 1.30 (m, 4H), 1.55 (m, 2H), 2.70 (t, 2H), 3.40 (m, 2H), 7.40 (brs, 1H), 7.70 (d, 2H), 7.90 (d, 2H), 8.10 (brs, 1H), 8.40 (s, 1H)	416	Meth 8
37	5-Cyano-4-*n*-butylamino-2-{4-[*N*-(3-methoxypropyl) sulphamoyl]anilino} pyrimidine	0.90 (t, 3H), 1.30 (m, 2H), 1.55 (m, 4H), 2.75 (t, 2H), 3.10 (s, 3H), 3.25 (t, 2H), 3.40 (m, 2H), 7.40 (brs, 1H), 7.65 (d, 2H), 7.90 (d, 2H), 8.10 (brs, 1H), 8.40 (s, 1H)	418	Meth 4
38	5-Cyano-4-*n*-butylamino-2-(4-mesylanilino)pyrimidine	0.90 (t, 3H), 1.35 (m, 2H), 1.60 (m, 2H), 3.15 (s, 3H), 3.40 (m, 2H), 7.80 (d, 2H), 7.95 (d, 2H), 8.15 (brs, 1H), 8.45 (s, 1H)	345	Com Av

Example 39-40

Following the procedure of Example 12 starting from 2-chloro-5-cyano-4-(2,2,2-trifluoroethylamino)pyrimidine (Method 95) and the appropriate aniline starting material the following compounds were prepared.

Ex	Compound Name	NMR	m/z	SM
39	5-Cyano-4-(2,2,2-trifluoroethylamino)-2-{4-[*N*-(3-methoxypropyl) sulphamoyl]anilino} pyrimidine	1.55 (m, 2H), 2.75 (q, 2H), 3.10 (s, 3H), 3.30 (t, 2H), 4.22 (m, 2H), 7.40 (t, 1H), 7.65 (d, 2H), 7.90 (d, 2H), 8.40 (t, 1H), 8.50 (s, 1H)	m/z: 444	Meth 4
40	5-Cyano-4-(2,2,2-trifluoroethylamino)-2-{4-[*N*-(2-methoxyethyl) sulphamoyl]anilino} pyrimidine	2.90 (q, 2H), 3.15 (s, 3H), 3.30 (t, 2H), 4.25 (m, 2H), 7.50 (t, 1H), 7.70 (d, 2H), 7.85 (d, 2H), 8.40 (t, 1H), 8.50 (s, 1H)	430	Meth 5

Examples 41-42

Following the procedure of Example 12 starting from 2-chloro-5-cyano-4-ethylaminopyrimidine (Method 56) and the appropriate aniline starting material the following compounds were prepared.

Ex	Compound Name	NMR	m/z
41	5-Cyano-4-ethylamino-2-(4-mesylanilino)pyrimidine	1.20 (t, 3H), 3.15 (s, 3H), 3.45 (m, 2H), 7.80 (d, 2H), 8.00 (m, 3H), 8.40 (s, 1H)	317
42 [1]	5-Cyano-4-ethylamino-2-[4-(*N*-allylsulphamoyl) anilino]pyrimidine	1.18 (t, 3H), 3.37 (d, 2H), 3.50 (m, 2H), (d, 1H), 5.10 (d, 1H), 5.63 (m, 1H), (brs, 1H), 7.70 (d, 2H), 7.90 (d, 2H), 8.10 (brs, 1H), 8.42 (s, 1H), 10.65 (brs, 1H)	359

1 Aniline - Method 6

Example 43

5-Cyano-4-butylamino-2-{4-[*N*-(tetrahydrofur-2-ylmethyl)sulphamoyl]anilino}pyrimidine

4-Butylamino-5-*N*-*t*-butylcarbamoyl-2-{4-[*N*-(tetrahydrofur-2-ylmethyl)sulphamoyl] anilino}pyrimidine (Method 67; 200mg, 0.40mmol) in thionyl chloride (1ml) was heated at 90°C for 12 hours. The mixture was allowed to cool and then was evaporated onto silica. The residue was purified by chromatography eluting with DCM / methanol (100:0) increasing in polarity to (97:3). The product was recrystallized from methanol to give the title compound (33 mg). NMR: 0.90 (t, 3H), 1.34 (m, 2H), 1.41-1.63 (m, 3H), 1.66-1.88 (m, 3H), 2.73 (t, 2H), 3.40 (m, 2H), 3.53 (m, 1H), 3.64 (m, 1H), 3.77 (m, 1H), 7.51 (t, 1H), 7.67 (d, 2H), 7.88 (brs, 1H), 7.91 (d, 2H), 8.37 (s, 1H), 10.13 (brs, 1H); m/z: 431.

Example 44-54

Following the procedure of Example 43 using the appropriate 4-substituted amidopyrimidine starting material the following compounds were prepared.

Ex	Compound Name	NMR	m/z	SM
44 [1]	5-Cyano-4-(2,2,2-trifluoro-ethylamino)-2-{4-[*N*-(tetrahydrofur-2-ylmethyl) sulphamoyl]anilino}pyrimidine	1.50 (m, 1H), 1.68-1.89 (m, 3H), 2.74 (t, 2H), 3.54 (m, 1H), 3.63 (m, 1H), 3.76 (m, 1H), 4.22 (m, 2H), 7.54 (t, 1H), 7.69 (d, 2H), 7.86 (d, 2H), 8.39 (t, 1H), 8.51 (s, 1H), 10.31 (brs, 1H)	457	Meth 68
45 [1,2]	5-Cyano-4-[bis-(2-cyanoethyl) amino]-2-{4-[*N*-(tetrahydrofur-2-ylmethyl)sulphamoyl] anilino}pyrimidine	1.50 (m, 1H), 1.65-1.88 (m, 3H), 2.74 (t, 2H), 2.95 (t, 4H), 3.54 (m, 1H), 3.65 (m, 1H), 3.77 (m, 1H), 3.98-4.09 (m, 4H), 7.52 (t, 1H), 7.72 (d, 2H), 7.82 (d, 2H), 8.54 (s, 1H), 10.31 (brs, 1H)	481	Meth 69

46 [3]	5-Cyano-4-(cyclopropylamino)-2-{4-[*N*-(tetrahydrofur-2-ylmethyl)sulphamoyl]anilino}pyrimidine	0.68 (m, 2H), 0.80 (m, 2H), 1.50 (m, 1H), 1.69-1.88 (m, 3H), 2.73 (t, 2H), 2.87 (m, 1H), 3.54 (m, 1H), 3.65 (m, 1H), 3.76 (m, 1H), 7.47 (t, 1H), 7.69 (d, 2H), 8.02 (s, 1H), 8.06 (d, 2H), 8.38 (s, 1H), 10.20 (brs, 1H).	415	Meth 70
47 [3]	5-Cyano-4-(cyclopropylmethylamino)-2-{4-[*N*-(tetrahydrofur-2-ylmethyl)sulphamoyl]anilino}pyrimidine	0.02 (m, 2H), 0.19 (m, 2H), 0.91 (m, 1H), 1.26 (m, 1H), 1.44-1.64 (m, 3H), 2.50 (t, 2H), 3.05 (t, 2H), 3.31 (m, 1H), 3.38-3.58 (m, 2H), 7.29 (t, 1H), 7.44 (d, 2H), 7.66 (d, 2H), 7.78 (t, 1H), 8.17 (s, 1H), 9.93 (s, 1H).	429	Meth 71
48 [3]	5-Cyano-4-(cyclohexylamino)-2-{4-[*N*-(tetrahydrofur-2-ylmethyl)sulphamoyl]anilino}pyrimidine	1.08-1.56 (m, 6H), 1.60-1.93 (m, 8H), 2.72 (brs, 2H), 3.54 (m, 1H), 3.65 (m, 1H), 3.77 (m, 1H), 3.95 (brs, 1H), 7.54 (brs, 1H), 7.64 (brs, 1H), 7.70 (d, 2H), 7.90 (d, 2H), 8.38 (s, 1H), 10.20 (brs, 1H).	457	Meth 72
49 [3]	5-Cyano-4-(tetrahydrofur-2-ylmethylamino)-2-{4-[*N*-(tetrahydrofur-2-ylmethyl)sulphamoyl]anilino}pyrimidine	1.50 (m, 1H), 1.63 (m, 1H), 1.70-1.96 (m, 6H), 2.73 (t, 2H), 3.36-3.60 (m, 3H), 3.64 (m, 2H), 3.77 (m, 2H), 4.09 (m, 1H), 7.51 (t, 1H), 7.67 (d, 2H), 7.84 (t, 1H), 7.91 (d, 2H), 8.39 (s, 1H), 10.15 (brs, 1H)	459	Meth 73

50 [4]	5-Cyano-4-(pyrid-3-ylmethylamino)-2-{4-[*N*-(tetrahydrofur-2-ylmethyl) sulphamoyl]anilino}pyrimidine	1.50 (m, 1H), 1.65-1.87 (m, 3H), 2.70 (m, 2H), 3,46-3.82 (m, 3H), 4.63 (d, 2H), 7.34 (m, 1H), 7.50 (m, 1H), 7.6 (m, 2H), 7.72 (m, 3H), 8.4 (m, 2H), 8.50 (m, 1H), 8.58 (s, 1H), 10.14 (brs, 1H)	466	Meth 74
51 [4]	5-Cyano-4-(piperidino)-2-{4-[*N*-(tetrahydrofur-2-ylmethyl) sulphamoyl]anilino}pyrimidine	1.42 (m, 10H), 2.73 (t, 2H), 3.54 (m, 1H), 3.65 (m, 1H), 3.72-3.90 (m, 9H), 7.50 (t, 1H), 7.69 (d, 3H), 7.83 (d, 2H), 8.44 (s, 1H), 10.15 (brs, 1H)	443	Meth 75
52 [4]	5-Cyano-4-[*N*-(ethyl)-cyclohexylamino]-2-{4-[*N*-(tetrahydrofur-2-ylmethyl) sulphamoyl]anilino}pyrimidine	1.20 (t, 3H), 1.25-1.86 (m, 14H), 2.73 (t, 2H), 3.48-3.80 (m, 5H), 4.58 (m, 1H), 7.54 (t, 1H), 7.68 (d, 2H), 7.84 (d, 2H), 8.40 (s, 1H), 10.13 (brs, 1H)	485	Meth 76
53 [5]	5-Cyano-4-(*n*-butoxycarbonyl methylamino)-2-{4-[*N*-(tetrahydrofur-2-ylmethyl)sulphamoyl] anilino}pyrimidine	0.78 (t, 3H), 1.20 (m, 2H), 1.38 (m, 2H), 1.64-1.92 (m, 3H), 3.73 (m, 2H), 3.48-3.80 (m, 4H), 4.00 (t, 2H), 4.12 (d, 2H), 7.52 (m, 1H), 7.65 (d, 2H), 7.80 (d, 2H), 8.23 (m, 1H), 8.46 (s, 1H), 10.22 (brs, 1H)	489	Meth 77
54 [5]	5-Cyano-4-(2-methoxycarbonyl ethylamino)-2-{4-[*N*-(tetrahydrofur-2-ylmethyl)sulphamoyl] anilino}pyrimidine	1.50 (m, 1H), 1.67-1.9 (m, 3H), 2.70 (m, 4H), 3.48-3.80 (m, 6H), 4.02 (m, 2H), 7.54 (m, 1H), 7.66 (d, 2H), 7.89 (d, 2H), 8.50 (s, 1H), 8.95 (m, 1H), 10.18 (brs, 1H)	461	Meth 78

[1] Reaction mixture was heated at 90°C for 3 hours.

[2] Chromatography eluent was isohexane/ethyl acetate (100:0) increasing in polarity to (0:100).

[3] Reaction mixture was heated at 90°C for 6 hours.

[4] Reaction mixture was heated at 95°C for 3 hours.

[5] Reaction mixture was heated at 95°C for 4 hours.

Examples 55-56

Following the procedure of Example 1, 2-chloro-5-cyano-4-morpholinopyrimidine (Method 55) was treated with the appropriate aniline to give the following compounds.

Ex	Compound Name	NMR	m/z	SM
55	5-Cyano-4-morpholino-2-(4-sulphamoylanilino)pyrimidine	3.70 (t, 4H), 3.86 (m, 4H), 7.20 (s, 2H), 7.73 (d, 2H), 7.80 (d, 2H), 8.50 (s, 1H), 10.22 (s, 1H)	359 $(MH)^-$	Com Av
56	5-Cyano-4-morpholino-2-{4-[*N*-(3-hydroxy-2,2-dimethylpropyl)sulphamoyl] anilino}pyrimidine	0.73 (s, 6H), 2.50 (d, 2H), 3.07 (s, 1H), 3.70 (t, 4H), 3.87 (t, 4H), 7.22 (t, 1H), 7.70 (d, 2H), 7.83 (d, 2H), 8.50 (s, 1H), 10.25 (s, 1H)	447	Meth 3

Example 57

4-[4-(2-Hydroxyethyl)piperazin-1-yl]-5-cyano-2-{4-[*N*-(3-methoxypropyl)sulphamoyl] anilino}pyrimidine

4-[4-(2-Acetoxyethylpiperazin-1-yl)]-5-cyano-2-{4-[*N*-(3-methoxypropyl) sulphamoyl]anilino}pyrimidine (Method 119; 290mg) was dissolved in methanol (3ml), 35% ammonia (1.5 ml) was added and the reaction was stirred at room temperature for 2 hours. The volatiles were evaporated and the residue purified by chromatography on silica gel, eluting with DCM/methanol (98:2) increasing in polarity to (95:5). The resulting solid was triturated with ethyl acetate / diethyl ether and collected by filtration to yield the title compound (19 mg) NMR: 1.55 (m, 2H), 2.45 (2H), 2.55 (brt, 4H), 2.75 (q, 2H), 3.14 (s, 3H), 3.26 (2H), 3.50 (q, 2H), 3.88 (brt, 4H), 4.42 (t, 1H), 7.35 (t, 1H), 7.68 (d, 2H), 7.84 (d, 2H), 8.48 (s, 1H), 10.21 (s, 1H); m/z: 476.

Example 58

5-Cyano-4-cyclopropylamino-2-{4-[*N*-(2-methoxyethyl)sulphamoyl]anilino}pyrimidine

2-Chloro-5-cyano-4-cyclopropylaminopyrimidine (Method 96; 295mg, 1.28mmol) was dissolved in hot 2-butanol (3ml). A hot solution of 4-[*N*-(2-methoxyethyl)sulphamoyl] aniline (Method 5; 207mg, 0.90mmol) in 2-butanol (3ml) was added and the reaction was

stirred and heated at 90°C for 1 hour. The reaction mixture was cooled and the volatiles evaporated to give a solid. The solid residue was triturated with hot ethyl acetate, cooled, and the resultant solid collected by filtration to give the title compound (270mg, 77%). NMR: 0.68 (m, 2H), 0.80 (m, 2H), 2.88 (m, 3H), 3.14 (s, 3H), 3.28 (m, 2H), 7.48 (brs, 1H), 7.70 (d, 2H), 8.05 (d, 2H), 8.12 (brs, 1H) 8.41 (s, 1H), 10.31 (s, 1H); m/z: 389.

Examples 59-72

The following examples were prepared using the procedure of Example 58 starting from 2-chloro-5-cyano-4-cyclopropylaminopyrimidine (Method 96) and the appropriate aniline.

Ex	Compound Name	NMR	m/z	SM
59	5-Cyano-4-cyclopropylamino-2-{4-[*N*-(3-methoxypropyl) sulphamoyl]anilino} pyrimidine	0.68 (m, 2H), 0.80 (m, 2H), 1.57 (m, 2H), 2.74 (m, 2H), 2.88 (m, 1H), 3.12 (s, 3H), 3.25 (m, 2H), 7.48 (brs, 1H), 7.70 (d, 2H), 8.05 (d, 2H), 8.12 (brs, 1H) 8.41 (s, 1H), 10.31 (s, 1H)	403	Meth 4
60	5-Cyano-4-cyclopropylamino-2-[4-(ethylsulphonyl) anilino]pyrimidine	0.68 (m, 2H), 0.83 (m, 2H), 1.08 (t, 3H), 2.88 (m, 1H), 3.20 (q, 2H), 7.78 (d, 2H), 8.12 (d and s, 3H), 8.41 (s, 1H), 10.37 (brs, 1H)	344	Ref [1]
61	5-Cyano-4-cyclopropylamino-2-{4-[(2-ethoxyethyl)sulphonyl] anilino}pyrimidine	0.68 (m, 2H), 0.82 (m, 2H), 0.90 (t, 3H), 2.86 (m, 1H), 3.28 (q, 2H),), 3.46 (m, 2H), 3.60 (m, 2H), 7.78 (d, 2H), 8.10 (d, 2H), 8.15 (brs, 1H), 8.41 (s, 1H), 10.37 (brs, 1H)	388	Ref [2]
62	5-Cyano-4-cyclopropylamino-2-[4-(propylsulphonyl) anilino]pyrimidine	0.68 (m, 2H), 0.82 (m, 2H), 0.88 (t, 3H), 1.52 (m, 2H), 2.86 (m, 1H), 3.18 (m, 2H), 7.79 (d, 2H), 8.13 (s and d, 3H), 8.42 (s, 1H), 10.39 (brs, 1H)	358	Ref [1]

63	5-Cyano-4-cyclopropylamino-2-(4-mesyl anilino)pyrimidine	0.68 (m, 2H), 0.82 (m, 2H), 0.88 (t, 3H), 2.86 (m, 1H), 3.12 (s, 3H), 7.82 (d, 2H), 8.10 (d, 2H), 8.17 (brs, 1H), 8.42 (s, 1H), 10.40 (brs, 1H)	330	Com Av
64	5-Cyano-4-cyclopropyl-amino-2-{4-[2-(diethylamino) ethylsulphonyl]anilino) pyrimidine	0.68 (m, 2H), 0.82 (m, 8H), 2.33 (m, 4H), 2.68 (m, 2H), 2.85 (m, 1H), 3.30 (m, 2H), 7.81 (d, 2H), 8.10 (s, 1H), 8.14 (d, 2H), 8.41 (s, 1H), 10.31 (s, 1H)	415	Com Av
65	5-Cyano-4-cyclopropylamino-2-{4-[*N*-(2-diethylaminoethyl) sulphamoyl]anilino} pyrimidine	0.71 (m, 2H), 0.82 (m, 2H), 0.87 (t, 6H), 2.38 (m, 6H), 2.78 (m, 2H), 2.88 (m, 1H), 7.21 (brs, 1H), 7.71 (d, 2H), 8.08 (d and s, 3H), 8.41 (s, 1H), 10.24 (s, 1H)	430	Meth 17
66	5-Cyano-4-cyclopropylamino-2-{4-[*N*-(2-diethylaminoethyl)-*N*-(methyl)sulphamoyl]anilino} pyrimidine	0.68 (m, 2H), 0.85 (m, 2H), 0.93 (t, 6H), 2.45 (m, 6H), 2.70 (s, 3H), 2.88 (m, 1H), 3.00 (m, 2H), 7.71 (d, 2H), 8.09 (brs, 1H), 8.14 (d, 2H), 8.43 (s, 1H), 10.28 (s, 1H)	444	Meth 18
67	5-Cyano-4-cyclopropylamino-2-{4-[*N*-(2-methoxyethyl)-*N*-(methyl)sulphamoyl]anilino} pyrimidine	0.68 (m, 2H), 0.82 (m, 2H), 2.68 (s, 3H), 2.88 (m, 1H), 3.08 (t, 2H), 3.20 (s, 3H), 3.42 (t, 2H), 7.68 (d, 2H), 8.09 (d, 3H), 8.40 (s, 1H), 10.38 (brs, 1H)	403	Meth 16
68	5-Cyano-4-cyclopropylamino-2-(4-{*N*-[2-(piperidino)ethyl] sulphamoyl}anilino) pyrimidine	0.68 (m, 2H), 0.78 (m, 2H), 1.30 (m, 2H), 1.40 (m, 4H), 2.18 (m, 4H), 2.23 (t, 2H), 2.80 (t, 2H), 2.85 (m, 1H), 7.19 (brs, 1H), 7.70 (d, 2H), 8.02 (s, 1H), 8.08 (d, 2H), 8.38 (s, 1H), 10.19 (brs, 1H)	442	Meth 7

69	5-Cyano-4-cyclopropylamino-2-{4-[3-(isopropylamino)propyl sulphonyl]anilino}pyrimidine	0.69 (m, 2H), 0.82 (m, 2H), 1.18 (d, 6H), 1.90 (brquin, 2H), 2.90 (m, 3H), 3.19 (m, 1H), 3.40 (m, 2H), 7.80 (d, 2H), 8.12 (brs, 1H), 8.19 (d, 2H), 8.25 - 8.90 (brs, 1H), 8.41 (s, 1H), 10.35 (s, 1H)	415	Meth 30
70	5-Cyano-4-cyclopropylamino-2-{4-[4-(isopropylamino)butyl sulphonyl]anilino}pyrimidine	0.68 (m, 2H), 0.82 (m, 2H), 1.20 (d, 6H), 1.60 (m, 2H), 1.68 (m, 2H), 2.83 (m, 3H), 3.17 (m, 1H), 3.28 (m, 2H), 7.80 (d, 2H), 8.10 (s, 1H), 8.16 (d, 2H), 8.41 (s, 1H), 8.68 (brs, 2H), 10.34 (s, 1H)	429	Meth 29
71	5-Cyano-4-cyclopropylamino-2-{4-[*N*-(3-piperidinopropyl) sulphamoyl]anilino} pyrimidine hydrochloride	0.68 (m, 2H), 0.81 (m, 2H), 1.21 (t, 1H), 1.35 (m, 1H), 1.68 (m, 1H), 1.72 (m, 4H), 1.80 (m, 2H), 2.78 (m, 4H), 2.86 (m, 1H), 2.95 (m, 2H), 3.06 (m, 1H), 7.58 (t, 1H), 7.71 (d, 2H), 8.08 (d, 3H), 8.40 (s, 1H), 9.92 (brs, 1H), 10.19 (brs, 1H)	456	Meth 19
72	5-Cyano-4-cyclopropylamino-2-{4-[*N*-(methyl)-*N*-(3-piperidino propyl)sulphamoyl]anilino} pyrimidine hydrochloride	0.68 (m, 2H), 0.82 (m, 2H), 1.37 (brm, 1H), 1.73 (m, 4H), 1.92 (brm, 5H), 2.18 (m, 4H), 2.64 (s, 3H), 2.83 (m, 3H), 2.98 (m, 4H), 3.37 (brt, 2H), 7.69 (d, 2H), 8.08 (s, 1H), 8.13 (d, 2H), 8.40 (s, 1H), 9.96 (brs, 1H), 10.28 (brs, 1H)	470	Meth 20

[1] Helv. Chim. Acta, 66(4) 1046-52 (1983)

[2] Kogyo Kagaku Zasshi, 62 825-8 (1959)

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Example 73

5-Cyano-4-ethylamino-2-{4-[*N*-(3-methoxypropyl)sulphamoyl]anilino}pyrimidine

5-Cyano-4-ethylamino-2-[(4-fluorosulphonyl)anilino]pyrimidine (Method 111; 50mg, 0.16mmol), 3-methoxypropylamine (28mg, 0.31mmol) and polymer supported 4-(dimethylamino)pyridine (supplied by Argonout Technologies Inc; 1.45mmol/l) (218mg, 0.31mmol) in NMP (1ml) were heated at 100°C for 18 hours. Volatiles were removed by evaporation and the residue was triturated with ether. The resultant solid was purified by reverse phase chromatography (Waters xterra 19x50mm column) (0.1% formic acid in a gradient of 0-95% acetonitrile in water) to give the title compound (16mg, 26%). NMR: 1.18 (t, 3H), 1.57 (m, 2H), 2.75 (m, 2H), 3.13 (s, 3H), 3.25 (m, 2H), 3.43 (m, 2H), 7.35 (m, 1H), 7.65 (d, 2H), 7.82 (m, 1H), 7.94 (d, 2H), 8.39 (s, 1H), 10.13 (s, 1H), m/z: 391.

Examples 74-100

Following the procedure of Example 73, 5-Cyano-4-ethylamino-2-[(4-fluorosulphonyl)anilino]pyrimidine (Method 111) was treated with the appropriate amine to give the following compounds.

Ex	Compound Name	m/z
74	5-Cyano-4-ethylamino-2-{4-[*N*-(3-ethoxypropyl)sulphamoyl]anilino}pyrimidine	405
75	5-Cyano-4-ethylamino-2-{4-[*N*-(3-imidazolylpropyl)sulphamoyl]anilino} pyrimidine	427
76	5-Cyano-4-ethylamino-2-(4-{*N*-[3-(2-dimethylaminoethoxy)propyl] sulphamoyl}anilino)pyrimidine	448
77	5-Cyano-4-ethylamino-2-{4-[*N*-(3-morpholinopropyl)sulphamoyl]anilino} pyrimidine	446
78	5-Cyano-4-ethylamino-2-{4-[*N*-(2-pyrrolidinylethyl)sulphamoyl]anilino} pyrimidine	416
79	5-Cyano-4-ethylamino-2-(4-{*N*-[2-(1-ethylpyrrolidin-2-yl)ethyl]sulphamoyl} anilino)pyrimidine	430
80	5-Cyano-4-ethylamino-2-{4-[*N*-(2-pyridin-2-ylethyl)sulphamoyl]anilino} pyrimidine	424

81	5-Cyano-4-ethylamino-2-{4-[*N*-(pyridin-3-ylmethyl)sulphamoyl]anilino} pyrimidine	410
82	5-Cyano-4-ethylamino-2-{4-[*N*-(2-piperidinoethyl)sulphamoyl]anilino} pyrimidine	430
83	5-Cyano-4-ethylamino-2-{4-[*N*-(2-diethylaminoethyl)sulphamoyl]anilino} pyrimidine	418
84	5-Cyano-4-ethylamino-2-{4-[*N*-(2-pyridin-4-ylethyl)sulphamoyl]anilino} pyrimidine	424
85	5-Cyano-4-ethylamino-2-{4-[*N*-(pyridin-2-ylmethyl)sulphamoyl]anilino} pyrimidine	410
86	5-Cyano-4-ethylamino-2-{4-[*N*-(2-acetamidoethyl)sulphamoyl]anilino} pyrimidine	404
87	5-Cyano-4-ethylamino-2-{4-[*N*-(2-isopropylaminoethyl)sulphamoyl]anilino} pyrimidine	404
88	5-Cyano-4-ethylamino-2-{4-[*N*-(2-dimethylaminoethyl)sulphamoyl]anilino} pyrimidine	390
89	5-Cyano-4-ethylamino-2-{4-[*N*-(2-morpholinoethyl)sulphamoyl]anilino} pyrimidine	432
90	5-Cyano-4-ethylamino-2-{4-[*N*-(dioxan-2-ylmethyl)sulphamoyl]anilino} pyrimidine	419
91	5-Cyano-4-ethylamino-2-{4-[*N*-(tetrahydrofur-2-ylmethyl)sulphamoyl]anilino} pyrimidine	403
92	5-Cyano-4-ethylamino-2-{4-[*N*-(2-hydroxypropyl)sulphamoyl]anilino} pyrimidine	377
93	5-Cyano-4-ethylamino-2-{4-[*N*-(2-propynyl)sulphamoyl]anilino}pyrimidine	418
94	5-Cyano-4-ethylamino-2-{4-[*N*-(3-hydroxy-2,2-dimethylpropyl)sulphamoyl] anilino}pyrimidine	405
95	5-Cyano-4-ethylamino-2-[4-(*N*-methylsulphamoyl)anilino]pyrimidine	333
96	5-Cyano-4-ethylamino-2-(4-{*N*-[2-(2-hydroxyethyl)ethoxy]sulphamoyl} anilino)pyrimidine	407

97	5-Cyano-4-ethylamino-2-{4-[*N*-(2-hydroxyethyl)sulphamoyl]anilino}pyrimidine	363
98	5-Cyano-4-ethylamino-2-{4-[*N*-(5-hydroxypentyl)sulphamoyl]anilino} pyrimidine	405
99	5-Cyano-4-ethylamino-2-{4-[*N*-(2-hydroxybutyl)sulphamoyl]anilino}pyrimidine	391
100	5-Cyano-4-ethylamino-2-{4-[*N*-(2-cyanoethyl)sulphamoyl]anilino}pyrimidine	377

Example 101

5-Cyano-4-*n*-butylamino-2-{4-[*N*-(ethylthioethyl)sulphamoyl]anilino}pyrimidine

5-Cyano-4-butylamino-2-[(4-fluorosulphonyl)anilino]pyrimidine (Method 112; 200mg, 0.57mmol), 2-(ethylthio)ethylamine (480mg, 4.56mmol), triethylamine (58mg, 0.57mmol) and 4-(dimethylamino)pyridine (7mg, 0.06mmol) in 1-butanol (6ml) was heated at 95°C for 24 hours. The mixture was allowed to cool and the solvent was removed by evaporation. The resulting solid was recrystallized from ethanol to give the title compound (130mg). NMR: 0.90 (t, 3H), 1.10 (t, 3H), 1.35 (m, 2H), 1.59 (m, 2H), 2.40-2.60 (m, 4H), 2.90 (t, 2H), 3.40 (q, 2H), 7.70 (d, 2H), 7.80-8.88 (m, 3H), 8.40 (s, 1H); m/z:434.

Example 102-108

Starting from 5-cyano-4-butylamino-2-[(4-fluorosulphonyl)anilino]pyrimidine (Method 112) and the appropriate amines the following compounds were prepared using the procedure in Example 101.

Ex	Compound Name	NMR	m/z
102	5-Cyano-4-*n*-butylamino-2-{4-[*N*-(2-morpholinoethyl) sulphamoyl]anilino} pyrimidine	0.90 (t, 3H), 1.35 (m, 2H), 1.59 (m, 2H), 2.30 (m, 6H), 2.81 (t, 2H), 3.39-3.60 (m, 6H), 7.75 (d, 2H), 7.90 (m, 3H), 8.39 (s, 1H)	459
103	5-Cyano-4-*n*-butylamino-2-{4-[*N*-(3-imidazol-1-ylpropyl)sulphamoyl] anilino}pyrimidine	0.95 (t, 3H), 1.35 (m, 2H), 1.59 (m, 2H), 1.80 (m, 2H), 2.65 (t, 2H), 3.40 (q, 2H), 3.90 (t, 2H), 6.81 (s, 1H), 7.05 (s, 1H), 7.50 (s, 1H), 7.65 (d, 2H), 7.90 (m, 3H), 8.39 (s, 1H)	454

104	5-Cyano-4-*n*-butylamino-2-{4-[*N*-(2-piperidinoethyl) sulphamoyl]anilino} pyrimidine	0.95 (t, 3H), 1.20-1.50 (m, 8H), 1.55 (m, 2H), 2.20 (brm, 6H), 2.80 (t, 2H), 3.40 (q, 2H), 7.25 (brs, 1H), 7.65 (d, 2H), 7.90 (m, 3H), 8.40 (s, 1H)	457
105	5-Cyano-4-*n*-butylamino-2-{4-[*N*-(2-pyrid-2-ylethyl)sulphamoyl] anilino}pyrimidine	0.95 (t, 3H), 1.30 (m, 2H), 1.60 (m, 2H), 2.80 (t, 3H), 3.10 (m, 2H), 3.40 (q, 2H), 7.20 (m, 2H), 7.50 (brs, 1H), 7.65 (m, 3H), 7.90 (m, 3H), 8.35 (s, 1H), 8.40 (d, 1H)	451
106	5-Cyano-4-*n*-butylamino-2-{4-[*N*-(2-pyrrolidin-1-ylethyl)sulphamoyl] anilino}pyrimidine	0.90 (t, 3H), 1.35 (m, 2H), 1.60 (m, 6H), 2.20-2.40 (m, 6H), 2.80 (t, 2H), 3.40 (q, 2H), 7.30 (brs, 1H), 7.70 (d, 2H), 7.9 (m, 3H), 8.38 (s, 1H)	443
107	5-Cyano-4-*n*-butylamino-2-{4-[*N*-(3-amino-2-hydroxypropyl)sulphamoyl] anilino}pyrimidine	0.90 (t, 3H), 1.40 (m, 2H), 1.60 (m, 2H), 2.40 (m, 1H), 2.60 (m, 1H), 2.70 (m, 1H), 2.80 (m, 1H). 3.45 (m, 2H), 7.70 (d, 1H), 7.90 (m, 3H), 8.40 (s, 1H), 10.15 (brs, 1H)	419
108	5-Cyano-4-*n*-butylamino-2-{4-[*N*-(2-isopropylamino-ethyl)sulphamoyl] anilino}pyrimidine	0.90 (m, 9H), 1.40 (m, 2H), 1.60 (m, 2H), 2.60 (m, 1H), 2.80 (t, 2H), 3.45 (q, 2H), 7.70 (d, 2H), 7.9 (m, 3H), 8.40 (s, 1H), 10.20 (s, 1H)	431

Example 109

5-Cyano-4-(2,2,2-trifluoroethylamino)-2-{4-[*N*-(2-imidazo-4-ylethyl)sulphamoyl]anilino} pyrimidine

5-Cyano-4-(2,2,2-trifluoroethylamino)-2-[(4-fluorosulphonyl)anilino]pyrimidine (Method 113; 200mg, 0.53mmol), histamine (466mg, 4.24mmol), triethylamine (54mg, 0.53mmol) and 4-(dimethylamino)pyridine (7mg, 0.05mmol) in 2-butanol (6ml) was heated at 95°C for 48 hours. The mixture was allowed to cool and the solvent was removed by evaporation. The resulting solid was recrystallized from ethanol to give the title compound (80mg). NMR: 2.70 (m, 2H), 3.10 (t, 2H), 4.30 (m, 2H), 6.70 (s, 1H), 7.40 (s, 1H), 7.70 (d, 2H), 7.90 (d, 2H), 8.50 (s, 1H); m/z:466

Example 110-114

Starting from 5-cyano-4-(2,2,2-trifluoroethylamino)-2-[(4-fluorosulphonyl)anilino] pyrimidine (Method 113) and the appropriate amines the following compounds were prepared using the procedure of Example 109.

Ex	Compound Name	NMR	m/z
110	5-Cyano-4-(2,2,2-trifluoroethylamino)-2-{4-[*N*-(2-mesylethyl)sulphamoyl]anilino} pyrimidine	2.99 (s, 3H), 3.00-3.40 (m, 7H), 4.25 (m, 2H), 7.70 (d, 2H), 7.90 (d, 2H), 8.40 (brs, 1H), 8.50 (s, 1H)	478
111	5-Cyano-4-(2,2,2-trifluoroethylamino)-2-(4-{*N*-[2-(2-hydroxyethoxy)ethyl]sulphamoyl} anilino)pyrimidine	2.90 (q, 2H), 3.40-3.60 (m, 6H), 4.25 (m, 2H), 4.55 (t, 1H), 7.55 (t, 1H), 7.70 (d, 2H), 7.90 (d, 2H), 8.40 (t, 1H), 8.55 (s, 1H), 10.40 (s, 1H)	460
112	5-Cyano-4-(2,2,2-trifluoroethylamino)-2-{4-[*N*-(3-hydroxypropyl)sulphamoyl] anilino}pyrimidine	1.50 (m, 2H), 2.80 (t, 2H), 3.35 (m, 2H), 4.30 (q, 2H), 4.45 (t, 1H), 7.40 (brs, 1H), 7.75 (d, 2H), 7.90 (d, 2H), 8.40 (brs, 1H), 8.55 (s, 1H), 10.40 (brs, 1H)	430
113	5-Cyano-4-(2,2,2-trifluoroethylamino)-2-{4-[*N*-(2-methyl-1,3,4-triazol-5-yl)sulphamoyl]anilino}pyrimidine	2.20 (brm, 3H), 2.75 (brm, 2H), 3.00 (brm, 2H), 4.20 (q, 2H), 7.50 (brs, 1H), 7.75 (d, 2H), 7.90 (d, 2H), 8.40 (t, 1H), 8.50 (s, 1H)	481
114	5-Cyano-4-(2,2,2-trifluoroethylamino)-2-{4-[*N*-(2-hydroxyethyl)sulphamoyl]anilino} pyrimidine	2.80 (q, 2H), 3.40 (t, 2H), 4.25 (m, 2H), 7.40 (t, 1H), 7.70 (d, 2H), 7.90 (d, 2H), 8.40 (t, 1H), 8.55 (s, 1H), 10.40 (brs, 1H)	416

Example 115

5-Cyano-4-(2,3-dihydroxypropylamino)-2-{4-[*N*-(3-methoxypropyl)sulphamoyl]anilino} pyrimidine

A suspension of 2-chloro-4-(4-chlorophenoxy)-5-cyanopyrimidine (Method 115; 179mg, 0.68mmol) and 4-[*N*-(3-methoxypropyl)sulphamoyl]aniline (Method 4; 149mg, 0.61mmol) in 2-butanol (6ml) was heated and stirred at 50°C for 5 hours. 3-Amino-1,2-

propanediol (309mg, 3.4mmol) was then added and the temperature was raised to 90°C and the reaction was stirred at this temperature for a further 18 hours. The solvent was removed by evaporation and the resulting solid was recrystallized from ethanol to give the title compound (104mg, 39%). NMR: 1.55 (m, 2H), 2.75 (m, 2H), 3.15 (s, 3H), 3.25 (m, 2H), 3.40 (m, 3H), 3.60 (m, 1H), 3.75 (m, 1H), 4.70 (t, 1H), 5.85 (m, 1H), 7.35 (t, 1H), 7.55 (brs, 1H), 7.70 (d, 2H), 7.95 (d, 2H), 8.40 (s, 1H), 10.20 (s, 1H); m/z:436.

Example 116-129

Starting from 2-chloro-4-(4-chlorophenoxy)-5-cyanopyrimidine (Method 115), the appropriate anilino sulphonamide/sulphone (see column SM) and the appropriate amines following the procedure in Example 115 the following compounds were prepared.

Ex	Compound Name	NMR	m/z	SM
116	5-Cyano-4-(3-hydroxypyrrolidin-1-yl)-2-{4-[*N*-(2-methoxyethyl) sulphamoyl]anilino} pyrimidine	1.95 (brs, 2H), 2.90 (q, 2H), 3.15 (s, 3H), 3.25 (m, 2H), 3.60-3.90 (brm, 4H), 4.40 (brs, 1H), 5.05 (brs, 1H), 7.50 (brs, 1H), 7.75 (d, 2H), 7.90 (d, 2H), 8.40 (s, 1H)	418	Meth 5
117	5-Cyano-4-[*N*-methyl-*N*-(2-propynyl)amino]-2-{4-[*N*-(3-methoxypropyl)sulphamoyl] anilino}pyrimidine	1.55 (m, 2H), 2.75 (m, 2H), 3.15 (s, 3H), 3.25 (m, 2H), 3.30 (s, 1H), 3.70 (s, 3H), 4.50 (s, 2H), 7.40 (t, 1H), 7.70 (d, 2H), 7.90 (d, 2H), 8.50 (s, 1H)	414	Meth 4
118	5-Cyano-4-(2,2-dimethyldioxolan-4-ylmethylamino)-2-{4-[*N*-(3-methoxypropyl)sulphamoyl] anilino}pyrimidine	1.21 (s, 3H), 1.35 (s, 3H), 1.58 (m, 2H), 2.75 (m, 2H), 3.10 (s, 3H), 3.25 (m, 2H), 3.55 (m, 2H), 3.76 (m, 1H), 3.95 (m, 1H), 4.30 (m, 1H), 7.40 (t, 1H), 7.65 (d, 2H), 7.85 (t, 1H), 7.9 (d, 2H), 8.40 (s, 1H)	476	Meth 4
119	5-Cyano-4-(2-imidazol-4-ylethylamino)-2-{4-[*N*-(3-methoxypropyl)sulphamoyl] anilino}pyrimidine	1.65 (m, 2H), 2.80-3.00 (m, 4H), 3.20 (s, 3H), 3.35 (t, 2H), 3.75 (m, 2H), 6.82 (brs, 1H), 7.02 (brs, 1H), 7.50 (s, 1H), 7.55 (brs, 1H), 7.70 (d, 2H), 7.95 (d, 2H), 8.35 (s, 1H), 9.80 (brs, 1H)	456	Meth 4

120	5-Cyano-4-[2-(2-hydroxyethoxy)ethylamino]-2-{4-[*N*-(3-methoxypropyl) sulphamoyl]anilino} pyrimidine	1.60 (m, 2H), 2.75 (q, 2H), 3.10 (s, 3H), 3.25 (m, 2H), 3.50 (m, 4H), 3.60 (brs, 4H), 4.55 (t, 1H), 7.35 (t, 1H), 7.65 (d, 2H), 7.75 (brs, 1H), 7.90 (d, 2H), 8.40 (s, 1H)	450	Meth 4
121[1]	5-Cyano-4-(2-hydroxyethylamino)-2-{4-[*N*-(3-methoxypropyl) sulphamoyl]anilino} pyrimidine	1.55 (m, 2H), 2.75 (m 2H), 3.10 (s, 3H), 3.25 (m, 2H), 3.50 (m, 2H), 3.60 (m, 2H), 4.75 (t, 1H), 7.35 (t, 1H), 7.65 (d, 2H), 7.90 (d, 2H), 8.40 (s, 1H)	406	Meth 4
122	5-Cyano-4-(2-hydroxyethylamino)-2-(4-mesylanilino)pyrimidine	3.12 (s, 3H), 3.50 (m, 2H), 3.60 (m, 2H), 4.80 (t, 1H), 7.70 (t, 1H), 7.80 (d, 2H), 8.00 (d, 2H), 8.40 (s, 1H)	333	Com Av
123	5-Cyano-4-(isobutylamino)-2-(4-mesylanilino) pyrimidine	0.95 (d, 6H), 2.00 (m, 1H), 3.25 (m, 2H), 3.30 (s, 3H), 7.80 (d, 2H), 8.00 (d, 2H), 8.40 (s, 1H), 10.25 (s, 1H)	345	Com Av
124	5-Cyano-4-(cyclopropylmethylamino)-2-(4-mesylanilino) pyrimidine	0.30 (m, 2H), 0.50 (m, 2H), 1.20 (m, 1H), 3.20 (s, 3H), 3.35 (m, 2H), 7.85 (d, 2H), 8.00 (d, 3H), 8.45 (s, 1H), 10.25 (s, 1H)	343	Com Av
125	5-Cyano-4-(cyclopropylamino)-2-{4-[*N*-(2,2,2-trifluoroethyl) sulphamoyl]anilino} pyrimidine	0.65 (m, 2H), 0.80 (m, 2H), 2.85 (m, 1H), 3.65 (m, 2H), 7.70 (d, 2H), 8.10 (d, 3H), 8.35 (brs, 1H), 8.40 (s, 1H)	412	Meth 9
126	5-Cyano-4-(ethylamino)-2-(4-ethylsulphonylanilino) pyrimidine	1.10 (t, 3H), 1.20 (t, 3H), 3.20 (m, 2H), 3.45 (m, 2H), 7.80 (d, 2H), 7.90 (m, 2H), 8.00 (d, 2H), 8.40 (s, 1H)	331	Ref[2]
127	5-Cyano-4-(ethylamino)-2-{4-[*N*-(2,2,2-trifluoroethyl) sulphamoyl]anilino} pyrimidine	1.20 (t, 3H), 3.45 (m, 2H), 3.65 (m, 2H), 7.75 (d, 2H), 7.85 (t, 1H), 7.95 (d, 2H), 8.35 (m, 2H)	400	Meth 9

128	5-Cyano-4-(methylamino)-2-(4-mesylanilino)pyrimidine	2.90 (d, 3H), 3.10 (s, 3H), 7.80 (d, 3H), 8 .00 (d, 2H), 8.40 (s, 1H)	303	Com Av
129	5-Cyano-4-(propylamino)-2-(4-mesylanilino)pyrimidine	0.90 (t, 3H), 1.60 (m, 2H), 3.10 (s, 3H), 3.40 (m, 2H), 7.80 (d, 2H), 7.90 (t, 1H), 8.00 (d, 2H), 8.40 (s, 1H)	331	Ref [2]

[1] In this case the intermediate 2-anilino-4-phenoxy-5-cyanopyrimidine was isolated and purified before treatment with ethanolamine.

[2] Helv. Chim. Acta, 66(4) 1046-52 (1983)

Example 130

5-Cyano-4-ethylamino-2-{4-[*N*-(2-hydroxy-3-piperidinopropyl)sulphamoyl]anilino} pyrimidine

4-[*N*-(2-Hydroxy-3-piperidinopropyl)sulphamoyl]aniline (Method 118; 200mg, 0.64mmol) was dissolved in methanol (4ml). 1M Ethereal hydrogen chloride (1.28ml, 1.28mmol) was added and the mixture gently warmed to give a solution. The volatiles were partially evaporated to give a volume of approx. 1.5ml. 2-Butanol (5ml) was added and the cloudy solution warmed to 50°C. 2-Chloro-5-cyano-4-ethylaminopyrimidine (Method 56; 233mg, 1.28mmol) was added in portions and the reaction was then heated at 95°C for 20 hours. The hot supernatant was decanted from the solid residue and the solution allowed to cool. The resulting precipitate was collected by filtration, washed with diethyl ether and suspended in water (approx. 35ml). The suspension was adjusted to pH>10 with 2M aqueous sodium hydroxide solution and extracted with ethyl acetate (3 x 15ml). The extracts were dried, the volatiles evaporated and the residue purified by chromatography on silica eluting with DCM/ methanolic ammonia (100:0) increasing in polarity to (85:15). The product was triturated with diethyl ether and collected by filtration to give the title compound (30mg, 10%). NMR : 1.15 (t, 3H), 1.35 (m, 2H), 1.43 (m, 4H), 2.10-2.35 (m, 6H), 2.68 (m, 1H), 2.83 (m, 1H), 3.48 (quin, 2H), 3.56 (m, 1H), 4.59 (s, 1H) 7.36 (brt, 1H), 7.70 (d, 2H), 7.88 (t, 1H), 7.95 (d, 2H), 8.40 (s, 1H) 10.16 (s, 1H); m/z: 460.

Examples 131-132

The following compounds were prepared starting from 4-[*N*-(2-hydroxy-3-piperidinopropyl)sulphamoyl]aniline (Method 118) using the procedure of Example 130 and the appropriate pyrimidine starting material.

Ex	Compound Name	NMR	m/z	SM
131	5-Cyano-4-cyclopropylamino-2-{4-[*N*-(2-hydroxy-3-piperidino-propyl)sulphamoyl]anilino} pyrimidine	0.70 (m, 2H), 0.84 (m, 2H), 1.30-1.52 (m, 6H), 2.10-2.30 (m, 6H), 2.67 (m, 1H), 2.90 (m, 2H), 3.58 (m, 1H), 4.60 (brs, 1H), 7.37 (t, 1H) 7.70 (d, 2H), 8.05 (d, 3H), 8.40 (s, 1H), 10.23 (brs, 1H)	472	Meth 96
132	5-Cyano-4-(2,2,2-trifluoroethylamino)-2-{4-[*N*-(2-hydroxy-3-piperidino-propyl)sulphamoyl]anilino} pyrimidine	1.25-1.85 (m, 6H), 2.10-2.80 (m, 8H), 3.80 (brs, 1H), 4.25 (m, 2H), 4.60 (brs, 1H), 7.60 (brs, 1H), 7.71 (d, 2H), 7.91 (d, 2H), 8.42 (t, 1H), 8.55 (s, 1H), 10.35 (brs, 1H)	514	Meth 95

Preparation of Starting Materials

The starting materials for the above Examples are either commercially available or are readily prepared by standard methods from known materials. For example the following reactions are illustrations but not limitations of the preparation of some of the starting materials used in the above reactions.

Method 1

4-[*N*-(3-Isopropylaminopropyl)sulphamoyl]aniline.

Sulphanilyl fluoride (6.5g, 37.1mmol), *N*-isopropyl-1,3-propanediamine (5.71ml, 40.8mmol) and triethylamine (5.69ml, 40.8mmol) in *N*-butanol (15ml) was heated at reflux for 10 hours. The mixture was allowed to cool, silica was added and the volatiles were evaporated. The residue was purified by chromatography eluting with DCM / methanolic ammonia (100:0) increasing in polarity to (90:10) to give the title compound as a clear oil which crystallized on standing (8.81g, 88%). NMR: 0.89 (d, 6H), 1.43 (m, 2H), 2.41 (t, 2H), 2.58 (m, 1H), 2.68 (t, 2H), 3.16 (s, 2H), 5.85 (s, 2H), 6.58 (d, 2H), 7.38 (d, 2H); m/z: 272.

Methods 2-9

The following compounds were prepared using the procedure of Method 1.

Meth	Compound Name	m/z
2	4-[*N*-(tetrahydrofur-2-ylmethyl)sulphamoyl]aniline	257

Meth	Compound Name	NMR	m/z
3	4-[*N*-(3-hydroxy-2,2-dimethylpropyl)sulphamoyl] aniline	0.72 (s, 6H), 2.45 (d, 2H), 3.06 (d, 2H), 4.37 (t, 1H), 5.83 (s, 2H), 6.57 (d, 2H), 6.85 (t, 1H), 7.40 (d, 2H)	259
4	4-[*N*-(3-methoxypropyl) sulphamoyl]aniline	1.60 (m, 2H), 2.95 (q, 2H), 3.20 (s, 3H), 3.30 (t, 2H), 4.10 (brs, 2H), 4.90 (brt, 1H), 6.60 (d, 2H), 7.55 (d, 2H)	244
5	4-[*N*-(2-methoxyethyl) sulphamoyl]aniline	2.80 (q, 2H), 3.15 (s, 3H), 3.30 (t, 2H), 5.85 (brs, 2H), 6.60 (d, 2H), 7.10 (t, 1H), 7.40 (d, 2H)	230
6	4-(*N*-allylsulphamoyl)aniline	3.30 (t, 2H), 5.00 (d, 1H), 5.10 (d, 1H), 5.65 (m, 1H), 5.85 (s, 2H), 6.40 (d, 2H), 7.20 (t, 1H), 7.40 (d, 2H)	212
7	4-[*N*-(2-piperidinoethyl) sulphamoyl]aniline	1.30 (brm, 2H), 1.40 (brm, 4H), 2.25 (brm, 6H), 2.70 (brt, 2H), 5.85 (s, 2H), 6.60 (d, 2H), 6.80 (brs, 1H), 7.40 (d, 2H)	283
8	4-(*N*-*n*-pentylsulphamoyl) aniline	0.80 (t, 3H), 1.20 (brm, 4H), 1.35 (brm, 2H), 2.80 (q, 2H), 4.10 (brs, 2H), 4.40 (t, 1H), 6.60 (d, 2H), 7.45 (d, 2H)	242
9	4-[*N*-(2,2,2-trifluoroethyl) sulphamoyl]aniline	3.50 (m, 2H), 5.90 (brs, 2H), 6.60 (d, 2H), 7.40 (d, 2H), 8.00 (brt, 1H)	254

Method 10

N-(2-Methoxyethyl)-*N*-methyl-4-nitrobenzenesulphonamide

A stirred solution of triethylamine (2.4ml, 17.23mmol) and *N*-(2-methoxyethyl) methylamine (1.5g, 16.85mmol) in DCM (20ml) was cooled in an ice/water bath. A solution of 4-nitrobenzenesulphonyl chloride (3.2g, 14.45mmol) in DCM (20ml) was added dropwise.

The reaction was stirred for one hour the cooling bath was removed and the mixture stirred for further 3 hours. The reaction mixture was washed with 1M hydrochloric acid (40ml), water (30ml) and then brine. The volatiles were evaporated to give the title compound (3.8g). M/z: 245.

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Methods 11 - 14

Using the procedure of Method 10 starting from 4-nitrobenzenesulphonyl chloride and the appropriate commercially available amine the following compounds were prepared.

Meth	Compound Name	m/z
11	*N*-(2-Diethylaminoethyl)-4-nitrobenzenesulphonamide	302
12	*N*-(2-Diethylaminoethyl)-*N*-methyl-4-nitrobenzenesulphonamide	316

Meth	Compound Name	NMR	m/z
13	4-Nitro-*N*-(2-piperidinoethyl) benzenesulphonamide	1.35 (brs, 1H), 1.72 (brm, 5H), 2.85 (brs, 2H), 3.09 (brt, 2H), 3.26 (brq, 2H), 3.35 (brm, 2H), 8.10 (d, 2H), 8.41 (d, 2H), 8.55 (brt, 1H)	314
14	4-Nitro-*N*-(3-piperidinopropyl) benzenesulphonamide	1.33 (brt, 2H), 1.40 (m, 4H), 1.51 (m, 2H), 2.18 (brt, 6H), 2.82 (t, 2H), 8.02 (d, 2H), 8.41 (d, 2H)	328

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Method 15

N-Methyl-4-nitro-*N*-(3-piperidinopropyl)benzenesulphonamide

4-Nitro-*N*-(3-piperidinopropyl)benzenesulphonamide (Method 14; 1g, 3.06 mmol) was stirred under nitrogen at ambient temperature. Sodium hydride (60% dispersion in mineral oil) 15 (122mg, 3.05mmol) was added in portions. The reaction was stirred for 10 minutes, then iodomethane (210µl, 3.38mmol) was added dropwise. After 2 hours, added extra sodium hydride (<30mg) was added, and the reaction was stirred for 15 minutes, then stood overnight. Volatiles were removed by evaporation, water (20ml) was added and the solution was extracted with ethyl acetate (2x 30ml). The organic layers were combined, washed with water 20 and the volatiles evaporated to give the title compound (830 mg). NMR: 1.34 (m, 2H), 1.45 (m, 4H), 1.60 (quintet, 2H), 2.19 (m, 2H), 2.24 (m, 4H), 2.72 (s, 3H), 3.02 (t, 2H), 8.02 (d, 2H), 8.40 (d, 2H); m/z: 342.

Method 16

4-[*N*-(2-Methoxyethyl)-*N*-(methyl)sulphamoyl]aniline

N-(2-Methoxyethyl)-*N*-methyl-4-nitrobenzenesulphonamide (Method 10; 3.8g) was reduced by hydrogenation in ethanol (100ml)over 10% palladium on carbon (400mg) at 3 bar pressure. The catalyst was removed by filtration and the volatiles evaporated to give the title compound (3.2g). M/z: 245.

Methods 17-20

The following compounds were prepared using the procedure of Method 16.

Meth	Compound Name	m/z	SM
17	4-[*N*-(2-Diethylaminoethyl)sulphamoyl]aniline	272	Meth 11
18	4-[*N*-(2-Diethylaminoethyl)-*N*-(methyl)sulphamoyl]aniline	286	Meth 12
19 [1]	4-[*N*-(3-Piperidinopropyl)sulphamoyl]aniline (hydrochloride)	298	Meth 14
20 [1]	4-[*N*-(Methyl)-*N*-(3-piperidinopropyl)sulphamoyl]aniline (hydrochloride)	312	Meth 15

[1] Reduced in 1M hydrochloric acid / ethanol

Method 21

1-Nitro-4-[4-(phthalimido)butylsulphide]phenyl

4-Nitrothiophenol (1.9g, 12.26 mmol) was stirred in DMF under nitrogen and cooled (ice/water bath). Sodium hydride (60% dispersion in oil: 400mg, 10mmol) was added in portions and the mixture stirred for 10 minutes. *N*-(4-bromobutyl)phthalimide (2.8g, 9.93 mmol) in DMF (10ml) was added and the reaction was heated at 90°C for 1.5 hours, cooled to room temperature and stood overnight at ambient temperature. Volatiles were removed by evaporation, water (20 ml) was added and the solution was extracted into ethyl acetate (50 + 25 ml). The organic layers were combined, washed with water (20ml) and brine, dried and the volatiles evaporated. The resulting gum was triturated twice with isohexane. The solvent was decantated to give the title compound as a solid (3.8g). NMR: 1.64 (m, 2H), 1.74 (m, 2H), 3.12 (t, 2H), 3.60 (t, 2H), 7.45 (d, 2H), 7.81 (m, 4H), 8.06 (d, 2H).

Method 22

The following compound was prepared using the procedure of Method 21

Meth	Compound Name	NMR	M/z
22	1-Nitro-4-[3-(phthalimido) propylsulphide]phenyl	1.97 (quin, 2H), 3.18 (t, 2H), 3.71 (t, 2H), 7.49 (d, 2H), 7.71 (m, 4H), 8.10 (d, 2H)	342 (EI)

Method 23

1-Nitro-4-[4-(phthalimido)butylsulphonyl]phenyl

A solution of chromium(VI)oxide (3.5g, 35.0 mmol) in water (3ml) and glacial acetic acid (12.5 ml) was added dropwise over 15 to 20 minutes to a solution of 1-nitro-4-[4-(phthalimido)butylsulphide]phenyl (Method 21; 3.5g, 9.83 mmol) in glacial acetic acid (17.5ml) heated at 90-100°C. The mixture was then heated at 100°C for 3.5 hours. The reaction was cooled and poured onto crushed ice (250g). The solid was collected by filtration and washed with water. The solid was dried by azeotroping with methanol 3 times to give the title compound (3.4g). M/z: 389.

Method 24

1-Nitro-4-[3-(phthalimido)propylsulphonyl]phenyl

1-Nitro-4-[3-(phthalimido)propylsulphide]phenyl (Method 22; 600mg) was dissolved in DCM (20ml) and methanol (1ml). 3-Chloroperbenzoic acid (70%; 1.4g) was added in portions over 10 minutes. After 75 minutes DCM (10ml), saturated sodium bicarbonate solution (10ml) and water (10 ml) was added and the solution was stirred for 20 minutes before additional saturated sodium. T and the organic layer was separated and washed with water and brine, dried and evaporated to dryness to give the title compound (795mg). NMR: 1.90 (m, 2H), 3.55 (m, 2H), 3.64 (t, 2H), 7.81 (s, 4H), 8.17 (d, 2H), 8.41 (d, 2H)

Method 25

1-Nitro-4-(4-aminobutylsulphonyl)phenyl

1-Nitro-4-[4-(phthalimido)butylsulphonyl]phenyl (Method 23; 3g, 7.73 mmol) was heated at 90°C in acetonitrile (30ml) and methanol (10ml). Hydrazine hydrate (0.76ml, 15.7 mmol) was added and the reaction was heated for 1.5 hours, then cooled, and stood overnight at ambient temperature. The resulting solid was removed by filtration and washed with

methanol. The combined filtrates were evaporated to give the title compound (2.3g). M/z: 259.

Method 26

4-(3-Aminopropyl-sulphonyl)-1-nitrophenyl

The title compound was prepared from Method 24 using the procedure of Method 25.

Method 27

1-Nitro-4-[4-(isopropylamino)butylsulphonyl]phenyl

1-Nitro-4-(4-aminobutylsulphonyl)phenyl (Method 25; 2g, 7.75mmol) was stirred in methanol (20ml) and acetone (2.3ml) was added. Sodium cyanoborohydride (730mg, 11.62mmol) was added in portions over 5 minutes and the reaction was stirred for 2.5 hours. Water (15ml) was added, and the organic solvents were removed by evaporation more water was added and the solution was extracted with ethyl acetate (130ml). The organic layers were washed with water (25ml) and brine. The volatiles were evaporated and the residue was purified by chromatography on neutral alumina (activity II), eluting with DCM increasing polarity to methanol : DCM (3:97) to give the title compound (1.26g). m/z: 301.

Method 28

The following compound was prepared using the procedure of Method 27.

Meth	Compound Name	NMR	m/z	SM
28	4-[3-(Isopropylamino) propylsulphonyl]-1-nitrophenyl	1.08 (d, 6H), 1.96 (quin, 2H), 2.77 (m, 2H), 2.81 (m, 1H), 3.30 (m, 2H), 8.12 (d, 2H), 8.39 (d, 2H)	287	Meth 26

Method 29

4-[4-(Isopropylamino)butylsulphonyl]aniline

1-Nitro-4-[4-(isopropylamino)butylsulphonyl]phenyl (Method 27; 1.2g, 4mmol) was dissolved in ethanol (20ml) and 1M hydrochloric acid (6ml) and hydrogenated at 1 atmosphere over 10% palladium on carbon (400mg) for 4 hours at 1 atmosphere. The catalyst was removed by filtration and the volatiles evaporated to give the title compound as a foam. M/z: 271.

Method 30

The following compound was prepared using the procedure of Method 29.

Meth	Compound Name	NMR	m/z	SM
30	4-[3-(Isopropylamino) propylsulphonyl]aniline	1.19 (d, 6H), 1.89 (quintet, 2H), 2.89 (m, 2H), 3.28 (t, 2H), 6.70 (d, 2H), 7.48 (d, 2H), 9.00 (brs, 2H)	257	Meth 28

Method 31

2,4-Dichloro-5-chloroformylpyrimidine

5-Carboxy-2,4-dihydroxypyrimidine (19.0g, 0.12mol), phosphorus pentachloride (83.5g, 0.40mol); and phosphoryl chloride (28.3ml, 0.30mol) were heated at 114°C for 5 hours. The resulting solution was cooled overnight and the volatiles removed by evaporation. The residue was purified by vacuum distillation to yield the title compound as a clear oil (17.85g, 70%). M/z: 211.

Method 32

5-*N*-*t*-Butylcarbamoyl-2-chloro-4-morpholinopyrimidine.

A solution of 2,4-dichloro-5-chloroformylpyrimidine (Method 31; 500mg, 2.36mmol) in dry THF (5ml) was cooled to -15°C. *t*-Butylamine (250□l, 2.36mmol) and triethylamine (330□l, 2.36mmol) in dry THF were added slowly so as to maintain the temperature below -10°C. The resulting mixture was stirred at -10°C for 2 hours, allowed to warm to ambient temperature and stirred for a further 30 minutes. Morpholine (208□l, 2.36mmol) and triethylamine (330□l, 2.36mmol) in dry THF (1ml) were added and the resulting mixture was stirred at room temperature for 12 hours. The precipitate was removed by filtration and the filtrate evaporated to give the title compound as a pale yellow solid (570mg, 78%). NMR: 1.30 (s, 9H), 3.52-3.58 (m, 4H), 3.60-3.67 (m, 4H), 8.00 (s, 1H), 8.21 (brs, 1H); m/z: 299.

Methods 33-54

The following intermediates were prepared using the procedure of Method 32 starting from 2,4-dichloro-5-chloroformylpyrimidine (Method 31), *t*-butylamine and amines.

Meth	Compound Name	m/z
33 [1]	5-*N*-*t*-Butylcarbamoyl-2-chloro-4-(2-methylpropylamino)pyrimidine	285
34 [1]	5-*N*-*t*-Butylcarbamoyl-2-chloro-4-ethylaminopyrimidine	257
35 [1]	5-*N*-*t*-butylcarbamoyl-2-chloro-4-(2-fluoroethylamino)pyrimidine	273
36 [1]	5-*N*-*t*-butylcarbamoyl-2-chloro-4-(3-ethoxypropylamino)pyrimidine	315
37 [1]	5-*N*-*t*-butylcarbamoyl-2-chloro-4-*n*-butylaminopyrimidine	285
38 [1]	5-*N*-*t*-butylcarbamoyl-2-chloro-4-[*N*-(methyl)allylamino]pyrimidine	283
39 [1]	5-*N*-*t*-butylcarbamoyl-2-chloro-4-[*N*-(methyl)-ethoxycarbonylmethylamino]pyrimidine	329
40 [1]	5-*N*-*t*-butylcarbamoyl-2-chloro-4-[*N*-(methyl)-2-cyanoethylamino]pyrimidine	296
41 [1]	5-*N*-*t*-butylcarbamoyl-2-chloro-4-diethylaminopyrimidine	285
42 [1]	5-*N*-*t*-butylcarbamoyl-2-chloro-4-[*N*-(methyl)-2-methoxyethylamino]pyrimidine	301
43	5-*N*-*t*-butylcarbamoyl-2-chloro-4-(2,2,2-trifluoroethylamino)pyrimidine	311
44	5-*N*-*t*-butylcarbamoyl-2-chloro-4-[bis-(2-cyanoethyl)amino]pyrimidine	335
45	5-*N*-*t*-butylcarbamoyl-2-chloro-4-(3-morpholinopropylamino)pyrimidine	356
46	5-*N*-*t*-butylcarbamoyl-2-chloro-4-(cyclopropylamino)pyrimidine	269
47	5-*N*-*t*-butylcarbamoyl-2-chloro-4-(cyclopropylmethylamino)pyrimidine	283
48	5-*N*-*t*-butylcarbamoyl-2-chloro-4-(cyclohexylamino)pyrimidine	311
49	5-*N*-*t*-butylcarbamoyl-2-chloro-4-(tetrahydrofur-2-ylmethylamino)pyrimidine	[2]
50	5-*N*-*t*-butylcarbamoyl-2-chloro-4-(pyrid-3-ylmethylamino)pyrimidine	320
51	5-*N*-*t*-butylcarbamoyl-2-chloro-4-piperidinopyrimidine	297
52	5-*N*-*t*-butylcarbamoyl-2-chloro-4-[*N*-(ethyl)-cyclohexylamino]pyrimidine	339
53	5-*N*-*t*-butylcarbamoyl-2-chloro-4-(ethoxycarbonylmethylamino)pyrimidine	315
54	5-*N*-*t*-butylcarbamoyl-2-chloro-4-(2-methoxycarbonylethylamino)pyrimidine	315

[1] Products were purified by chromatography eluting with DCM/methanol (100:0) increasing in polarity to (95:5).

[2] NMR: 1.35 (s, 9H); 2.5 (m, 2H); 1.8 (m, 2H), 3.35 (m, 1H), 3.54 (m, 1H), 3.65 (m, 1H), 3.77 (m, 1H), 4.0 (m, 1H), 7.95 (s, 1H) 8.48 (s, 1H), 9.96 (m, 1H).

Method 55

2-Chloro-5-cyano-4-morpholinopyrimidine

5-*N*-*t*-Butylcarbamoyl-2-chloro-4-morpholinopyrimidine (Method 32; 560mg, 1.88mmol) in thionyl chloride (4ml) was heated at 90°C for 2 hours. The mixture was cooled to room temperature and the volatiles evaporated, and the residue azeotroped with toluene, to yield the title compound as a brown solid (425mg). NMR: 3.66-3.74 (m, 4H), 3.85-3.93 (m, 4H), 8.63 (s, 1H); m/z: 225, 227.

Method 56

2-Chloro-5-cyano-4-ethylaminopyrimidine.

5-*N*-*t*-Butylcarbamoyl-2-chloro-4-ethylaminopyrimidine (Method 34; 255mg, 1.00mmol) and thionyl chloride (240□l, 3.29mmol) in toluene (2 ml) was heated at 90°C for 15 hours. The mixtures were allowed to cool to room temperature, silica was added and the volatiles were evaporated. The residue was purified by chromatography eluting with DCM/methanol (100:0) increasing in polarity to (97:3) to give the title compound (86mg). NMR: 1.12 (t, 3H), 3.39 (m, 2H), 8.52 (s, 1H), 8.55 (brs, 1H).

Methods 57-66

The following compounds were prepared using the procedure of Method 56 from the appropriate pyrimidine starting material.

Meth	Compound Name	NMR	m/z	SM
57	2-Chloro-5-cyano-4-(2-methylpropylamino)pyrimidine	0.86 (d, 6H), 1.93 (m, 1H), 3.18 (t, 2H), 8.51 (s, 1H), 8.58 (brs, 1H)	211	Meth 33
58	2-Chloro-5-cyano-4-(2-fluoroethylamino)pyrimidine	3.64 (bt, 1H), 3.73 (bt, 1H), 4.49 (t, 1H), 4.64 (t, 1H), 8.57 (s, 1H), 8.70 (brs, 1H)		Meth 35
59	2-Chloro-5-cyano-4-(3-ethoxypropylamino)pyrimidine	1.09 (t, 3H), 1.77 (m, 2H), 3.34-3.48 (m, 6H), 8.46 (brs, 1H), 8.53 (s, 1H)		Meth 36

60	2-Chloro-5-cyano-4-*n*-butylaminopyrimidine	0.89 (t, 3H), 1.29 (m, 2H), 1.51 (m, 2H), 3.36 (m, 2H), 8.51 (s, 1H), 8.54 (brs, 1H)	209 $(MH)^-$	Meth 37
61	2-Chloro-5-cyano-4-[*N*-(methyl)allylamino]pyrimidine	3.25 (s, 3H), 4.33 (d, 2H), 5.20 (m, 2H), 5.85 (m, 1H), 8.59 (s, 1H)		Meth 38
62	2-Chloro-5-cyano-4-[*N*-(methyl)-ethoxycarbonylmethylamino] pyrimidine	1.19 (t, 3H), 3.27 (s, 3H), 4.16 (q, 2H), 4.51 (brs, 2H), 8.68 (s, 1H)		Meth 39
63	2-Chloro-5-cyano-4-[*N*-(methyl)-2-cyanoethylamino]pyrimidine	2.90 (t, 2H), 3.38 (s, 3H), 3.97 (t, 2H), 8.66 (s, 1H)	222	Meth 40
64	2-Chloro-5-cyano-4-diethylaminopyrimidine	1.19 (t, 6H), 3.69 (q, 4H), 8.57 (s, 1H)		Meth 41
65	2-Chloro-5-cyano-4-[*N*-(methyl)-2-methoxyethylamino]pyrimidine	3.26 (s, 3H), 3.32 (s, 3H), 3.57 (t, 2H), 3.90 (t, 2H), 8.59 (s, 1H)		Meth 42
66 [1]	2-Chloro-5-cyano-4-(3-morpholinopropylamino) pyrimidine		282	Meth 45

[1] Prepared by the procedure of Method 55.

Method 67

4-*n*-Butylamino-5-*N*-*t*-butylcarbamoyl-2-{4-[*N*-(tetrahydrofur-2-ylmethyl)sulphamoyl] anilino}pyrimidine

4-*n*-Butylamino-5-*N*-*t*-butylcarbamoyl-2-chloropyrimidine (Method 37; 282mg, 1.0mmol), 4-[*N*-(tetrahydrofur-2-ylmethyl)sulphamoyl]aniline (Method 2; 241mg, 0.95mmol) and 1M ethereal hydrogen chloride (993□l, 1.0mmol) in 2-butanol (2ml) were heated at 90°C for 3 hours. The mixture was cooled, silica was added and the volatiles were evaporated. The residue was purified by chromatography eluting with DCM / methanol (100:0) increasing in polarity to (95:5) to give the title compound as a white solid (372mg). M/z: 505.

Methods 68-78

The following examples were all prepared using the procedure of Method 67 from 4-[*N*-(tetrahydrofur-2-ylmethyl)sulphamoyl]aniline (Method 2) and the appropriate pyrimidine.

Meth	Compound	m/z	SM
68[1]	5-*N*-*t*-Butylcarbamoyl-2-{4-[*N*-(tetrahydrofur-2-ylmethyl) sulphamoyl]anilino}-4-(2,2,2-trifluoroethylamino)pyrimidine	531	Meth 43
69	4-[Bis-(2-cyanoethyl)amino]-5-*N*-*t*-butylcarbamoyl-2-{4-[*N*-(tetrahydrofur-2-ylmethyl)sulphamoyl]anilino}pyrimidine	555	Meth 44
70	4-(Cyclopropylamino)-5-*N*-*t*-butylcarbamoyl-2-{4-[*N*-(tetrahydrofur-2-ylmethyl)sulphamoyl]anilino}pyrimidine	489	Meth 46
71	4-(Cyclopropylmethylamino)-5-*N*-*t*-butylcarbamoyl-2-{4-[*N*-(tetrahydrofur-2-ylmethyl)sulphamoyl]anilino}pyrimidine	503	Meth 47
72	4-(Cyclohexylamino)-5-*N*-*t*-butylcarbamoyl-2-{4-[*N*-(tetrahydrofur-2-ylmethyl)sulphamoyl]anilino}pyrimidine	531	Meth 48
73	5-*N*-*t*-Butylcarbamoyl-2-{4-[*N*-(tetrahydrofur-2-ylmethyl) sulphamoyl]anilino}-4-(tetrahydrofur-2-ylmethylamino)pyrimidine	533	Meth 49
74	5-*N*-*t*-Butylcarbamoyl-4-(pyrid-3-ylmethylamino)-2-{4-[*N*-(tetrahydrofur-2-ylmethyl)sulphamoyl]anilino}pyrimidine	540	Meth 50
75	5-*N*-*t*-Butylcarbamoyl-4-(piperidino)-2-{4-[*N*-(tetrahydrofur-2-ylmethyl)sulphamoyl]anilino}pyrimidine	517	Meth 51
76	5-*N*-*t*-Butylcarbamoyl-4-[*N*-(ethyl)cyclohexylamino]-2-{4-[*N*-(tetrahydrofur-2-ylmethyl)sulphamoyl]anilino}pyrimidine	559	Meth 52
77[2]	4-(*N*-Butoxycarbonylmethylamino)-5-*N*-*t*-butylcarbamoyl-2-{4-[*N*-(tetrahydrofur-2-ylmethyl)sulphamoyl]anilino}pyrimidine	563	Meth 53
78	5-*N*-*t*-Butylcarbamoyl-4-(2-methoxycarbonylethylamino)-2-{4-[*N*-(tetrahydrofur-2-ylmethyl)sulphamoyl]anilino}pyrimidine	535	Meth 54

[1] Chromatography eluent was isohexane/ethyl acetate (100:0) increasing in polarity to (50:50).

[2] Ester exchange occurred.

Method 79

5-*N*-*t*-Butylcarbamoyl-2,4-dichloropyrimidine.

A solution of 2,4-dichloro-5-chloroformylpyrimidine (Method 31; 9.8g, 46.3mmol) in dry THF (50ml) was cooled to -15°C. *t*-Butylamine (5.2ml, 49.3mmol) and triethylamine (6.9ml, 49.5mmol) in dry THF (20ml) were added slowly so as to maintain the temperature below -10°C. The resulting mixture was stirred at -10°C for 2 hours, allowed to warm to ambient temperature and stirred for a further 30 minutes. The precipitate was removed by filtration and the filtrate evaporated to give a viscous oil, and then evaporated under high vacuum to give the title compound as a solid (10.48g, 90%). NMR: 1.49 (s, 9H), 6.19 (brs, 1H), 8.86 (s, 1H); m/z: 248.

Method 80

5-*N*-*t*-Butylcarbamoyl-2-chloro-4-[4-(2-hydroxyethyl)piperazin-1-yl]pyrimidine.

A solution of triethylamine (210µl, 1.5mmol) and 1-(2-hydroxyethyl)piperazine (195 mg, 1.5mmol) in dry THF (3ml) was added to a solution of 5-*N*-*t*-butylcarbamoyl-2,4-dichloropyrimidine (Method 79; 372mg, 1.5mmol) in dry THF (2ml). The mixture was stirred at ambient temperature for 5 hours. The resulting precipitate was removed by filtration, the filter pad washed with dry ether (5ml) and the filtrate evaporated to give the title compound. M/z: 342 (1xCl).

Methods 81-94

The following derivatives were prepared from 5-*N*-*t*-butylcarbamoyl-2,4-dichloropyrimidine (Method 79) and the appropriate amine using the procedure of Method 80.

Meth	Compound Name	m/z
81	5-*N*-*t*-Butylcarbamoyl-2-chloro-4-(2-dimethylaminoethylamino)pyrimidine	300
82	5-*N*-*t*-Butylcarbamoyl-2-chloro-4-(2,6-dimethylmorpholino)pyrimidine	327
83	5-*N*-*t*-Butylcarbamoyl-2-chloro-4-(cis-2,6-dimethylmorpholino)pyrimidine	327
84	5-*N*-*t*-Butylcarbamoyl-2-chloro-4-(cyanomethylamino)pyrimidine	268
85	5-*N*-*t*-Butylcarbamoyl-2-chloro-4-(3,5-dimethylpiperidino)pyrimidine	325
86	5-*N*-*t*-Butylcarbamoyl-2-chloro-4-[4-(2-methoxyethyl)piperazin-1-yl)pyrimidine	356
87	5-*N*-*t*-Butylcarbamoyl-2-chloro-4-(4-methylpiperazin-1-yl)pyrimidine	312

88	5-*N*-*t*-Butylcarbamoyl-2-chloro-4-(4-isopropylpiperazin-1-yl)pyrimidine	340
89	5-*N*-*t*-Butylcarbamoyl-2-chloro-4-[4-(ethylsulphonyl)piperazin-1-yl] pyrimidine	390
90	5-*N*-*t*-Butylcarbamoyl-4-(ethoxycarbonylpiperazin-1-yl)-2-chloropyrimidine	369
91	5-*N*-*t*-Butylcarbamoyl-2-chloro-4-methylaminopyrimidine	243
92	5-*N*-*t*-Butylcarbamoyl-2-chloro-4-(2-propynylamino)pyrimidine	267
93 [1]	5-*N*-*t*-Butylcarbamoyl-2-chloro-4-[*N*-(methyl)-2,2,2-trifluoroethylamino] pyrimidine	325
94	5-*N*-*t*-Butylcarbamoyl-2-chloro-4-(2-methoxyethylamino)pyrimidine	287

[1] Purified by chromatography eluting with DCM/MeOH (98:2).

Method 95

2-Chloro-5-cyano-4-(2,2,2-trifluoroethylamino)pyrimidine

A solution of 5-*N*-t-butylcarbamoyl-2-chloro-4-(2,2,2-trifluoroethylamino)pyrimidine (Method 43; 8.5g, 0.027mol) in thionyl chloride (100ml) was heated at reflux for 4 hours. The thionyl chloride was removed by evaporation and the resulting gum was triturated with isohexane/ethyl acetate (95/5), collected by filtration and dried to give the title compound NMR: 4.20 (m, 2H), 8.70 (s, 1H), 9.10 (brt, 1H); m/z:236

Method 96

2-Chloro-5-cyano-4-cyclopropylaminopyrimidine

5-*N*-*t*-Butylcarbamoyl-2-chloro-4-cyclopropylaminopyrimidine (Method 46; 2.40g, 8.92mmol) was heated at 80-90°C with thionyl chloride (10ml) for 4-6 hours. The thionyl chloride was removed by evaporation, and the residue triturated with ether/ethyl acetate to give the title compound (2.00g), which was used without further purification.

Methods 97-110

The following compounds were prepared using the procedure of Method 96 from the appropriate pyrimidine starting material. Final products were not characterised but were used immediately in subsequent reactions.

Meth	Compound Name	SM
97	2-Chloro-5-cyano-4-(2-dimethylaminoethylamino)pyrimidine	Meth 81
98	2-Chloro-5-cyano-4-(2,6-dimethylmorpholino)pyrimidine	Meth 82
99	2-Chloro-5-cyano-4-(cis-2,6-dimethylmorpholino)pyrimidine	Meth 83
100	2-Chloro-5-cyano-4-(cyanomethylamino)pyrimidine	Meth 84
101	2-Chloro-5-cyano-4-(3,5-dimethylpiperidino)pyrimidine	Meth 85
102	2-Chloro-5-cyano-4-[4-(2-methoxyethyl)piperazin-1-yl]pyrimidine	Meth 86
103	2-Chloro-5-cyano-4-(4-methylpiperazin-1-yl)pyrimidine	Meth 87
104	2-Chloro-5-cyano-4-(4-isopropylpiperazin-1-yl)pyrimidine	Meth 88
105	2-Chloro-5-cyano-4-[(4-ethylsulphonyl)piperazin-1-yl]pyrimidine	Meth 89
106	2-Chloro-4-(4-ethoxycarbonylpiperazin-1-yl)-5-cyanopyrimidine	Meth 90
107	2-Chloro-5-cyano-4-methylaminopyrimidine	Meth 91
108	2-Chloro-5-cyano-4-(2-propynylamino)pyrimidine	Meth 92
109	2-Chloro-5-cyano-4-[*N*-(methyl)-2,2,2-trifluoroethylamino]pyrimidine	Meth 93
110	2-Chloro-5-cyano-4-(2-methoxyethylamino)pyrimidine	Meth 94

Method 111

5-Cyano-4-ethylamino-2-[4-(fluorosulphonyl)anilino]pyrimidine

2-Chloro-5-cyano-4-ethylaminopyrimidine (Method 56; 6.35g, 34.88mmol) and sulphanilyl fluoride (6.11g, 34.88mmol) in 2-butanol (120ml) were heated at 95°C for 4 hours and then stirred at ambient temperatures for 48 hours. The volatiles were evaporated and the residue triturated with ether to give the title compound (10.46g, 93%). NMR: 1.20 (t, 3H), 3.45 (m, 2H), 8.00 (d, 2H), 8.13 (d, 2H), 8.41 (s, 1H), 10.52 (s, 1H); m/z: 321.

Method 112-113

The following compounds were prepared using the procedure of Method 111 from the appropriate pyrimidine starting material.

Meth	Compound Name	NMR	m/z	SM
112	5-Cyano-4-*n*-butylamino-2-[4-(fluorosulphonyl)anilino] pyrimidine	0.9 (t, 3H), 1.35 (m, 2H), 1.6 (m, 2H), 3.42 (m, 2H), 8.00 (d, 2H), 8.14 (d, 2H), 8.50 (s, 1H), 10.6 (s, 1H), 10.87 (brs, 1H)	349	Meth 60
113	5-Cyano-4-(2,2,2-trifluoroethylamino)-2-[4-(fluorosulphonyl)anilino] pyrimidine	4.24 (m, 2H), 8.0 (d, 2H), 8.08 (d, 2H), 8.49 (t, 1H), 8.58 (s, 1H), 10.62 (brs, 1H)	375	Meth 95

Method 114

5-*N*-*t*-Butylcarbamoyl-2-chloro-4-(4-chlorophenoxy)pyrimidine

Sodium hydride (105mg, 2.63mmol) was added to a solution of 4-chlorophenol (338mg, 2.63mmol) in dry THF (10ml). When effervescence had stopped, this solution was slowly added to a solution of 5-*N*-*t*-butylcarbamoyl-2,4-dichloropyrimidine (Method 79; 680mg, 2.74 mmol) in dry THF (15ml). The reaction mixture was stirred at ambient temperature for 2 hours. The solvent was removed by evaporation and the resulting solid was suspended in diethyl ether. The insolubles were removed by filtration and the filtrate was washed with 2M sodium hydroxide solution, citric acid solution, water and brine and then dried. The volatiles were removed by evaporation to give the title compound (880mg, 99%). M/z: 339.

Method 115

2-Chloro-4-(4-chlorophenoxy)-5-cyanopyrimidine

A solution of 5-*N*-*t*-butylcarbamoyl-2-chloro-4-(4-chlorophenoxy)pyrimidine (Method 114; 200mg, 0.59mmol) in thionyl chloride (5ml, 69mmol) was heated at reflux (95°C) for 18 hours. The thionyl chloride was removed by evaporation to give the title compound (210mg). NMR: 7.35 (d, 2H), 7.55 (d, 2H), 9.20 (s, 1H).

Method 116

4-[*N*-(2,3-Epoxypropyl)sulphamoyl]nitrobenzene

p-Nitrobenzene sulphonamide (6.06g, 30mmol) was added portionwise to a solution of sodium hydroxide (1.32g, 33mmol) in water (60ml) at room temperature. Epibromohydrin (4.5g, 33mmol) was added quickly dropwise and the solution stirred at room temperature for 24 hours. The mixture was acidified to pH 1 with 2M hydrochloric acid and extracted with DCM (2 x 30ml). The combined organic extracts were dried with sodium sulphate, filtered and the volatiles removed by evaporation. The resulting yellow oil was purified by chromatography on silica eluting with DCM/methanol (100:0) increasing in polarity to (99:1) to give the title compound as a pale yellow solid (2.5g, 32%); NMR (CDCl3) 2.65 (m, 1H), 2.80 (t, 1H), 3.10 (m, 2H), 3.50 (m, 1H), 5.08 (brs, 1H), 8.08 (d, 2H), 8.38 (d, 2H); m/z: 257.

Method 117

4-[*N*-(2-Hydroxy-3-piperidinopropyl)sulphamoyl]nitrobenzene

4-[*N*-(2,3-Epoxypropyl)sulphamoyl]nitrobenzene (Method 116, 1g, 3.88mmol) and piperidine (0.34g, 4mmol) in 1-propanol (75ml) were heated at reflux for 20 hours. The mixture was cooled and the solvent evaporated. The resulting yellow oil was triturated with diethyl ether collected by filtration and dried under vacuum to give the title compound 1.2g (90%). NMR : 1.26 - 1.50 (m, 6H), 2.10 - 2.28 (m, 6H), 2.70 (dd, 1H), 2.90 (dd, 1H), 3.55 (m, 1H), 8.04 (d, 2H), 8.40 (d, 2H); m/z: 344.

Method 118

4-[*N*-(2-Hydroxy-3-piperidinopropyl)sulphamoyl]aniline

Ammonium formate (1.1g, 17.46mmol) followed by a slurry of 10% palladium on carbon catalyst (0.7g) in ethanol was added in portions to a suspension of 4-[*N*-(2-Hydroxy-3-piperidinopropyl)sulphamoyl]nitrobenzene (Method 117; 1.2g, 3.5mmol) in ethanol (100ml). The mixture was heated at reflux under nitrogen for 2 hours. The mixture was cooled and the catalyst was removed by filtration through diatomaceous earth. The filter pad was washed with ethanol and the combined filtrates were evaporated. The residue was triturated with diethyl ether, collected by filtration and dried, to give the title compound (0.93g, 85%) as a pale green solid. NMR : 1.3 - 1.5 (m, 6H), 2.10-2.32 (m, 6H), 2.60 (m, 1H), 2.75 (m, 1H), 3.52 (m, 1H), 4.50 (brs, 1H), 5.85 (s, 2H), 6.59 (d, 2H), 6.98 (brs, 1H), 7.39 (d, 2H); m/z: 314.

Method 119

4-[4-(2-Acetoxyethylpiperazin-1-yl)]-5-cyano-2-{4-[*N*-(3-methoxypropyl)sulphamoyl] anilino}pyrimidine

Thionyl chloride (1.5 ml) was added to 4-[4-(2-acetoxyethylpiperazin-1-yl)]-5-*N*-*t*-butylcarbamoyl-2-{4-[*N*-(3-methoxypropyl)sulphamoyl]anilino}pyrimidine (Method 120; 570 mg), and the reaction was heated at 80°C for 3 hours. The mixture was cooled, the volatiles evaporated, the residue triturated with ethyl acetate and collected by filtration to give the title compound (290mg). M/z 518.

Method 120

4-[4-(2-Acetoxyethylpiperazin-1-yl)]-5-*N*-*t*-butylcarbamoyl-2-{4-[*N*-(3-methoxypropyl) sulphamoyl]anilino}pyrimidine

5-*N*-*t*-Butylcarbamoyl-4-[4-(2-hydroxyethylpiperazin-1-yl)]-2-{4-[*N*-(3-methoxypropyl)sulphamoyl]anilino}pyrimidine (Method 121; 1g) was dissolved in pyridine (5ml) at room temperature, 4-dimethylaminopyridine (~5mg) was added, followed by dropwise addition of acetic anhydride (0.29ml, 3mmol). The reaction mixture was stirred for 18 hours. The volatiles were evaporated, water added and the reaction extracted with EtOAc (2x20ml), washed with brine, dried and evaporated to give a gum (400mg). The residue was dissolved in DCM (10ml), triethylamine was added (300µl, 4.1mmol) followed by dropwise addition of acetyl chloride (100 µl, 1.15 mmol). The reaction was stirred at room temperature for 4 hours, then the volatiles were evaporated. The residue was suspended in ethyl acetate, the insolubles were removed by filtration and the filtrate evaporated to give the title compound as an oil (570 mg) which was used without further purification.

Method 121

5-*N*-*t*-Butylcarbamoyl-4-[4-(2-hydroxyethylpiperazin-1-yl)]-2-{4-[*N*-(3-methoxypropyl) sulphamoyl]anilino}pyrimidine

5-*N*-*t*-Butylcarbamoyl-2-chloro-4-[4-(2-hydroxyethyl)piperazin-1-yl]pyrimidine (Method 80, 1.5mmol) and 4-[*N*-(3-methoxypropyl)sulphamoyl]aniline (Method 4; 330mg, 1.35mmol) in 2-butanol (5ml) were heated at 95°C for 5 minutes. 1M Ethereal hydrogen chloride (1.5ml, 1.5mmol) was added and heating continued at 95°C for 2 hours. The volatiles

were evaporated, the residue triturated with ethyl acetate and collected by filtration to give the title compound (1g). M/z 550.

Example 133

The following illustrate representative pharmaceutical dosage forms containing the compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof (hereafter compound X), for therapeutic or prophylactic use in humans:-

(a): Tablet I	mg/tablet
Compound X	100
Lactose Ph.Eur	182.75
Croscarmellose sodium	12.0
Maize starch paste (5% w/v paste)	2.25
Magnesium stearate	3.0

(b): Tablet II	mg/tablet
Compound X	50
Lactose Ph.Eur	223.75
Croscarmellose sodium	6.0
Maize starch	15.0
Polyvinylpyrrolidone (5% w/v paste)	2.25
Magnesium stearate	3.0

(c): Tablet III	mg/tablet
Compound X	1.0
Lactose Ph.Eur	93.25
Croscarmellose sodium	4.0
Maize starch paste (5% w/v paste)	0.75
Magnesium stearate	1.0

(d): Capsule	mg/capsule
Compound X	10
Lactose Ph.Eur	488.5
Magnesium stearate	1.5

(e): Injection I	(50 mg/ml)
Compound X	5.0% w/v
1M Sodium hydroxide solution	15.0% v/v
0.1M Hydrochloric acid	(to adjust pH to 7.6)
Polyethylene glycol 400	4.5% w/v
Water for injection	to 100%

(f): Injection II	10 mg/ml
Compound X	1.0% w/v
Sodium phosphate BP	3.6% w/v
0.1M Sodium hydroxide solution	15.0% v/v
Water for injection	to 100%

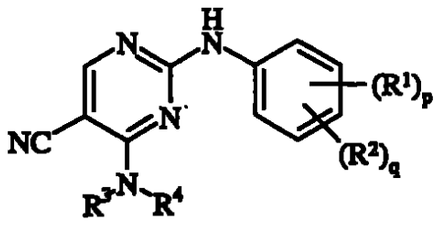
(g): Injection III	(1mg/ml,buffered to pH6)
Compound X	0.1% w/v
Sodium phosphate BP	2.26% w/v
Citric acid	0.38% w/v
Polyethylene glycol 400	3.5% w/v
Water for injection	to 100%

Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

Claims

1. A compound of formula (I):



(I)

wherein:

R^1 is halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl;

p is 0-4; wherein the values of R^1 may be the same or different;

R^2 is sulphamoyl or a group B-E-;

q is 0-2; wherein the values of R^2 maybe the same or different; and wherein p + q = 1-5;

R^3 is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{3-8}cycloalkyl; wherein R^3 may be optionally substituted on carbon by one or more M;

R^4 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl or heterocyclyl; wherein R^4 may be optionally substituted by one or more M; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from Z;

or R^3 and R^4 together with the nitrogen to which they are attached form a heterocyclic ring optionally substituted on carbon by one or more M; wherein if said heterocyclic ring contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from Q;

B is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-6}alkyl, phenyl, a heterocyclic group, phenylC_{1-6}alkyl or (heterocyclic group)C_{1-6}alkyl; wherein B may be optionally substituted on carbon by one or more D; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from G;

E is -C(O)-, -N(R^a)C(O)-, -C(O)N(R^a)-, -S(O)$_r$-, -SO_2N(R^a)- or -N(R^a)SO_2-; wherein R^a is hydrogen or C_{1-6}alkyl optionally substituted by one or more D and r is 1-2;

D is independently selected from halo, nitro, cyano, hydroxy, trifluoromethyl, 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, 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 and *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl; wherein D may be optionally substituted on carbon by one or more V;

M is 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, 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_{3-8}cycloalkyl, phenyl or a heterocyclic group; wherein M may be optionally substituted on carbon by one or more P; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from T;

P, X and V are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, 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, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl; and

G, Q, T and Z are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl wherein G, Q and T may be independently optionally substituted on carbon by one or more X;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

2. A compound of formula (I) as claimed in claim 1 wherein p is 0 or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

3 A compound of formula (I) as claimed in either of claims 1 or 2 wherein R^2 is sulphamoyl or a group B-E-; wherein

B is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or (heterocyclic group)C_{1-6}alkyl; wherein B may be optionally substituted on carbon by one or more D; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from G;

E is $-S(O)_r-$ or $-N(R^a)SO_2-$; wherein R^a is hydrogen or C_{1-6}alkyl and r is 2;

D is independently selected from halo, cyano, hydroxy, amino, C_{1-6}alkyl, C_{1-6}alkoxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino and C_{1-6}alkyl$S(O)_a$ wherein a is 0 to 2; wherein D may be optionally substituted on carbon by a group selected from V;

V is selected from hydroxy and dimethylamino; and

G is selected from C_{1-4}alkyl;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

4. A compound of formula (I) as claimed in any one of claims 1 - 3 wherein q is 1 or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

5. A compound of formula (I) as claimed in any one of claims 1 - 4 wherein R^3 is hydrogen or C_{1-6}alkyl; wherein R^3 may be optionally substituted by one or more M; and

R^4 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{3-8}cycloalkyl; wherein R^4 may be optionally substituted by one or more M;

or R^3 and R^4 together with the nitrogen to which they are attached form a heterocyclic ring optionally substituted on carbon by one or more M; wherein if said heterocyclic ring contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from Q;

M is independently selected from halo, cyano, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkoxycarbonyl, C_{3-8}cycloalkyl or a heterocyclic group; wherein M may be optionally substituted on carbon by a group selected from P;

P and X are independently selected from hydroxy and methoxy; and

Q is selected from C_{1-4}alkyl, C_{1-4}alkylsulphonyl or C_{1-4}alkoxycarbonyl; wherein G may be optionally substituted on carbon by one or more X;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

6. A compound of formula (I) as depicted in claim 1 wherein:

p is 0;

R^2 is sulphamoyl, mesyl, ethylsulphonyl, 2-ethoxyethylsulphonyl, propylsulphonyl, 3-isopropylaminopropylsulphonyl, 4-isopropylaminobutylsulphonyl, *N*-(tetrahydrofur-2-ylmethyl)sulphamoyl, *N*-(pyrid-3-ylmethyl)sulphamoyl, *N*-(pyrid-2-ylmethyl)sulphamoyl, *N*-(1,4-dioxan-2-ylmethyl)sulphamoyl, *N*-(methyl)sulphamoyl, *N*-(2-methoxyethyl)sulphamoyl, *N*-(2-ethylthioethyl)sulphamoyl, *N*-(2-morpholinoethyl)sulphamoyl, *N*-(2-piperidinoethyl)sulphamoyl, *N*-(2-pyrid-2-ylethyl)sulphamoyl, *N*-(2-pyrrolidin-1-ylethyl)sulphamoyl, *N*-(2-imidazol-4-ylethyl)sulphamoyl, *N*-(2-isopropylaminoethyl)sulphamoyl, *N*-(2-mesylethyl)sulphamoyl, *N*-[2-(2-hydroxyethoxy)ethyl]sulphamoyl, *N*-[2-(1-ethylpyrrolidin-2-yl)ethyl]sulphamoyl, *N*-(2-pyrid-2-ylethyl)sulphamoyl, *N*-(2-diethylaminoethyl)sulphamoyl, *N*-(2-pyrid-4-ylethyl)sulphamoyl, *N*-(2-acetamidoethyl)sulphamoyl, *N*-(2-dimethylaminoethyl)sulphamoyl, *N*-2-[(5-methyl-1,3,4-triazol-2-yl)ethyl]sulphamoyl, *N*-(2-hydroxyethyl)sulphamoyl, *N*-(2-cyanoethyl)sulphamoyl, *N*-(2-diethylaminoethyl)-*N*-(methyl)sulphamoyl, *N*-(2-methoxyethyl)-*N*-(methyl)sulphamoyl, *N*-(2,2,2-trifluoroethyl)sulphamoyl, *N*-(3-hydroxy-2,2-dimethylpropyl)sulphamoyl, *N*-(3-isopropylaminopropyl)sulphamoyl, *N*-(3-methoxypropyl)sulphamoyl, *N*-(3-imidazol-1-ylpropyl)sulphamoyl, *N*-(2-hydroxy-3-aminopropyl)sulphamoyl, *N*-(3-hydroxypropyl)sulphamoyl, *N*-(3-ethoxypropyl)sulphamoyl, *N*-[3-(2-dimethylaminoethyl)propyl]sulphamoyl, *N*-(3-morpholinopropyl)sulphamoyl, *N*-(2-hydroxypropyl)sulphamoyl, *N*-(2-hydroxy-3-piperidinopropyl)sulphamoyl, *N*-(3-piperidinopropyl)-*N*-(methyl)sulphamoyl, *N*-(2-hydroxybutyl)sulphamoyl, *N*-(pentyl)sulphamoyl, *N*-(5-hydroxypentyl)sulphamoyl, *N*-(allyl)sulphamoyl or *N*-(2-propynyl)sulphamoyl;

q is 1 and R^2 is para to the amino group in the aniline of formula (I); and

R^3 and R^4 together with the nitrogen to which they are attached form isobutylamino, ethylamino, 2-fluoroethylamino, 3-ethoxypropylamino, butylamino, 2,2,2-trifluoroethylamino, 3-morpholinopropylamino, cyclopropylamino, cyclopropylmethylamino, cyclohexylamino, tetrahydrofur-2-ylmethyl, 2-dimethylaminoethylamino, cyanomethylamino, pyrid-3-ylmethylamino, butoxycarbonylmethylamino, 2-(methoxycarbonyl)ethylamino, 2-hydroxyethylamino, methylamino, 2-propynylamino, 2-methoxyethylamino, 2-imidazol-4-ylethylamino, 2-(2-hydroxyethoxy)ethylamino, 2,3-dihydroxypropylamino, 2,2-dimethyldioxolan-4-ylmethylamino, propylamino, *N*-methyl-*N*-allylamino, *N*-methyl-*N*-

ethoxycarbonylmethylamino, *N*-methyl-*N*-(2-cyanoethyl)amino, diethylamino, *N*-methyl-*N*-(2-methoxyethyl)amino, bis-(2-cyanoethyl)amino, *N*-ethyl-*N*-cyclohexylamino, *N*-methyl-*N*-(2,2,2-trifluoroethyl)amino, *N*-methyl-*N*-(2-propynyl)amino, morpholino, 2,6-dimethylmorpholino, 3,5-dimethylpiperidino, piperidino, 4-(2-methoxyethyl)piperazin-1-yl, 4-methylpiperazin-1-yl, 4-isopropylpiperazin-1-yl, 4-ethylsulphonylpiperazin-1-yl, 4-ethoxycarbonylpiperazin-1-yl, 4-(2-hydroxyethyl)piperazin-1-yl, and 3-hydroxypyrrolidin-1-yl;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

7. A compound of formula (I) selected from:

5-Cyano-4-*n*-butylamino-2-(4-mesylanilino)pyrimidine;

5-Cyano-4-ethylamino-2-{4-[*N*-(2-methoxyethyl)sulphamoyl]anilino}pyrimidine;

5-Cyano-4-ethylamino-2-{4-[*N*-(3-methoxypropyl)sulphamoyl]anilino}pyrimidine;

5-Cyano-4-cyclopropylamino-2-{4-[*N*-(2-methoxyethyl)sulphamoyl]anilino}pyrimidine;

5-Cyano-4-cyclopropylamino-2-{4-[*N*-(3-methoxypropyl)sulphamoyl]anilino}pyrimidine;

5-Cyano-4-cyclopropylamino-2-[4-(ethylsulphonyl)anilino]pyrimidine;

5-Cyano-4-cyclopropylamino-2-(4-mesylanilino)pyrimidine;

5-Cyano-4-ethylamino-2-[4-(*N*-methylsulphamoyl)anilino]pyrimidine;

5-Cyano-4-cyclopropylamino-2-{4-[*N*-(2-methoxyethyl)-*N*-(methyl)sulphamoyl]anilino} pyrimidine; and

5-Cyano-4-(ethylamino)-2-(4-ethylsulphonylanilino) pyrimidine;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

8. A pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1-7 in association with a pharmaceutically-acceptable diluent or carrier.

9. A compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1-7 for use as a medicament.

10. The use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined in any one of claims 1-7 in the manufacture of a

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medicament for use in the production of a cell cycle inhibitory (anti-cell-proliferation) effect in a warm-blooded animal such as man.

11. A method of producing a cell cycle inhibitory (anti-cell-proliferation) 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 or *in vivo* hydrolysable ester thereof as claimed in any one of claims 1-7.

12. A pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1-7 in association with a pharmaceutically-acceptable diluent or carrier for use in the production of a cell cycle inhibitory (anti-cell-proliferation) effect in a warm-blooded animal such as man.

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INTERNATIONAL SEARCH REPORT

Inter al Application No
PCT/GB 01/03084

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/48 C07D403/04 C07D403/12 C07D401/12 A61K31/505 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)
IPC 7 C07D A61K A61P

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)
CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 39101 A (ASTRAZENECA) 6 July 2000 (2000-07-06) page 109; claims; examples 41,145	1,8-12
A	DIANE H. BOSCHELLI ET AL.: "SYNTHESIS A. TYROSINE KINASE INHIBITORY ACTIVITY OF A SERIE OF 2-AMINO-8H-PYRIDO'2,3-D!PYRIMIDINES:" JOURNAL OF MEDICINAL CHEMISTRY., vol. 41, no. 22, 1998, pages 4365-4377, XP002179356 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623 page 4365 -page 4373; example 33	1,8-12

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

☒ Patent family members are listed in 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
5 October 2001	19/10/2001

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, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Francois, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/GB 01/03084

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0039101 A	06-07-2000	AU 1874300 A	31-07-2000
		WO 0039101 A1	06-07-2000

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

08 APR 2002

To:

BRYANT, Tracey
ASTRAZENECA
Global Intellectual Property
P.O.Box 272
Mereside, Alderley Park
Macclesfield, Cheshire, SK10 4GR
GRANDE BRETAGNE

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	28/03/2002
Applicant's or agent's file reference: 100117/WO	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB 01/03084	06/07/2001	11/07/2000

Applicant

ASTRAZENECA AB et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523656 epmu d
Fax: (+49-89) 2399-4465

Authorized officer

LODOLO F

Tel. (+49-89) 2399 2828

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
100117/WO		
International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/GB 01/03084	06/07/2001	11/07/2000
International Patent Classification (IPC) or national classification and IPC		
C07D239/48		
Applicant		
ASTRAZENECA AB et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of _____ sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of _____ sheets.

3. This report contains indications relating to the following items:

I ☒ Basis of the report

II ☐ Priority

III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

IV ☐ Lack of unity of invention

V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

VI ☐ Certain documents cited

VII ☐ Certain defects in the international application

VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15/01/2002	25/03/2002
Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	VERHULST W

Form PCT/IPEA/409 (cover sheet) (July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.PCT/ GB 01/ 03084

I. Basis of the report

The basis of this international preliminary examination is the application as originally filed.

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(e) PCT); see also international search report).

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability

To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:

In light of the documents cited in the international search report, it is considered that the invention as defined in the claims, which have been the subject of an international search report, meets the criteria mentioned in Article 33(1) PCT, i.e. appears to be novel, to involve an inventive step and to be industrially applicable.

WO 02/04429
PCT/GB01/03084

PATENT COOPERATION TREATY

CODE
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From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
BRYANT, Tracey
AstraZeneca
Global Intellectual Property
Alderley Park, Mereside
P.O. Box 272, Macclesfield,
Cheshire SK10 4GR
ROYAUME-UNI

31 JAN 2002

Date of mailing (day/month/year)	
17 January 2002 (17.01.02)	
Applicant's or agent's file reference: 100117/WO	IMPORTANT NOTICE

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/GB01/03084	06 July 2001 (06.07.01)	11 July 2000 (11.07.00)

Applicant
ASTRAZENECA AB et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:
KP,KR,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
AE,AG,AL,AM,AP,AT,AU,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CO,CR,CU,CZ,DE,DK,DM,DZ,EA,EC,
EE,EP,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,
MD,MG,MK,MN,MW,MX,MZ,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 17 January 2002 (17.01.02) under No. WO 02/04429

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and the PCT Applicant's Guide, Volume II.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.91.11

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PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 100117/WO

Box No. I TITLE OF INVENTION

CHEMICAL COMPOUNDS

Box No. II APPLICANT ☐ This person is also inventor

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

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SWEDEN

Telephone No. +44-1625-516485
Facsimile No. +44-1625-510752
Teleprinter No. 669095/669388
Applicant's registration No. with the Office

State *(that is, country)* of nationality: SE

State *(that is, country)* of residence: SE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☒ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

ASTRAZENECA UK LIMITED
15 Stanhope Gate
London
W1Y 6LN
GB

This person is:
☒ applicant only
☐ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☒ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BRYANT, Tracey et al
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Agent's registration No. with the Office

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

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Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

THOMAS, Andrew Peter
Alderley Park
Macclesfield
Cheshire, SK10 4TG
GB

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

NEWCOMBE, Nicholas John
Alderley Park
Macclesfield
Cheshire, SK10 4TG
GB

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

HEATON, David, William
Alderley Park
Macclesfield
Cheshire, SK10 4TG
GB

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

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Box No.V DESIGNATION OF STATES *Mark the applicable check-boxes below; at least one must be marked.*

The following designations are hereby made under Rule 4.9(a):

Regional Patent

- ☒ AP **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ EA **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP **European Patent:** AT Austria, BE Belgium, CH & LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- ☒ AE United Arab Emirates
- ☒ AG Antigua and Barbuda
- ☒ AL Albania
- ☒ AM Armenia
- ☒ AT Austria
- ☒ AU Australia
- ☒ AZ Azerbaijan
- ☒ BA Bosnia and Herzegovina
- ☒ BB Barbados
- ☒ BG Bulgaria
- ☒ BR Brazil
- ☒ BY Belarus
- ☒ BZ Belize
- ☒ CA Canada
- ☒ CH & LI Switzerland and Liechtenstein
- ☒ CN China
- ☒ CO Colombia
- ☒ CR Costa Rica
- ☒ CU Cuba
- ☒ CZ Czech Republic
- ☒ DE Germany
- ☒ DK Denmark
- ☒ DM Dominica
- ☒ DZ Algeria
- ☒ EE Estonia
- ☒ ES Spain
- ☒ FI Finland
- ☒ GB United Kingdom
- ☒ GD Grenada
- ☒ GE Georgia
- ☒ GH Ghana
- ☒ GM Gambia
- ☒ HR Croatia
- ☒ HU Hungary
- ☒ ID Indonesia
- ☒ IL Israel
- ☒ IN India
- ☒ IS Iceland
- ☒ JP Japan
- ☒ KE Kenya
- ☒ KG Kyrgyzstan
- ☒ KP Democratic People's Republic of Korea
- ☒ KR Republic of Korea
- ☒ KZ Kazakhstan
- ☒ LC Saint Lucia
- ☒ LK Sri Lanka
- ☒ LR Liberia
- ☒ LS Lesotho
- ☒ LT Lithuania
- ☒ LU Luxembourg
- ☒ LV Latvia
- ☒ MA Morocco
- ☒ MD Republic of Moldova
- ☒ MG Madagascar
- ☒ MK The former Yugoslav Republic of Macedonia
- ☒ MN Mongolia
- ☒ MW Malawi
- ☒ MX Mexico
- ☒ MZ Mozambique
- ☒ NO Norway
- ☒ NZ New Zealand
- ☒ PL Poland
- ☒ PT Portugal
- ☒ RO Romania
- ☒ RU Russian Federation
- ☒ SD Sudan
- ☒ SE Sweden
- ☒ SG Singapore
- ☒ SI Slovenia
- ☒ SK Slovakia
- ☒ SL Sierra Leone
- ☒ TJ Tajikistan
- ☒ TM Turkmenistan
- ☒ TR Turkey
- ☒ TT Trinidad and Tobago
- ☒ TZ United Republic of Tanzania
- ☒ UA Ukraine
- ☒ UG Uganda
- ☒ US United States of America
- ☒ UZ Uzbekistan
- ☒ VN Viet Nam
- ☒ YU Yugoslavia
- ☒ ZA South Africa
- ☒ ZW Zimbabwe

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

- ☒ Ecuador
- ☐
- ☐
- ☐
- ☐
- ☐

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

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Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

1. If, in any of the Boxes, except Boxes Nos. VIII(i) to (v) for which a special continuation box is provided, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No...." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

(i) If more than two persons are to be indicated as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;

(ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;

(iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;

(iv) if, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;

(v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;

(vi) if, in Box No. VI, there are more than five earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.

2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.

Continuation of Box II:

ASTRAZENECA AB is applicant for the purposes of:

All designated states except MG, Madagascar and US, United States of America

Continuation of Box III:

ASTRAZENECA UK LIMITED is applicant for the purpose of:

MG, Madagascar

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Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
		national application: country	regional application:* regional Office	international application: receiving Office
item (1) 11 July 2000 (11/07/2000)	0016877.3	GB		
item (2)				
item (3)				
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office)* identified above as:

☐ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

** Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):* ....

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*:

ISA / EPO

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)*: Number of declarations

☐ Box No. VIII (i)	Declaration as to the identity of the inventor	:
☐ Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:
☐ Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:
☐ Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)	:
☐ Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	:

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:

(a) the following number of sheets in paper form:

request (including declaration sheets)	:	06
description (excluding sequence listing part)	:	79
claims	:	06
abstract	:	01
drawings	:	00
Sub-total number of sheets	:	92
sequence listing part of description *(actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below)*	:	
Total number of sheets	:	92

(b) sequence listing part of description filed in computer readable form

(i) ☐ only (under Section 801(a)(i))

(ii) ☐ in addition to being filed in paper form (under Section 801(a)(ii))

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained *(additional copies to be indicated under item 9(ii), in right column)*: .....

This international application is accompanied by the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item)*: — **Number of items**

1. ☒ fee calculation sheet : 1
2. ☐ original separate power of attorney :
3. ☐ original general power of attorney :
4. ☐ copy of general power of attorney; reference number, if any: ..... :
5. ☐ statement explaining lack of signature :
6. ☒ priority document(s) identified in Box No. VI as item(s): ..... : 1
7. ☐ translation of international application into *(language)*: ..... :
8. ☐ separate indications concerning deposited microorganism or other biological material :
9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))
   - (i) ☐ copy submitted for the purposes of international search under Rule 13*ter* only (and not as part of the international application) :
   - (ii) ☐ *(only where check-box (b)(i) or (b)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter* :
   - (iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column :
10. ☐ other *(specify)*: ..... :

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

T. Bryant

BRYANT, Tracey et al

For receiving Office use only

1. Date of actual receipt of the purported international application:
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

0038

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This sheet is not part of and does not count as a sheet of the international application.

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International Application No.

Date stamp of the receiving Office

Applicant's or agent's file reference: 100117/WO

Applicant: ASTRAZENECA AB ET AL

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE . . . . . GBP 55.00 [T]

2. SEARCH FEE . . . . . 624.00 [S]

International search to be carried out by _____

(If two or more International Searching Authorities are competent to carry out the international search, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

Where item (b) of Box No. IX applies, enter Sub-total number of sheets / Where item (b) of Box No. IX does not apply, enter Total number of sheets: 92

[b1] first 30 sheets . . . . . 264.00 [b1]

[b2] 62 (number of sheets in excess of 30) x 6 (fee per sheet) = 372.00 [b2]

[b3] additional component (only if sequence listing part of description is filed in computer readable form under Section 801(a)(i), or both in that form and on paper, under Section 801(a)(ii)):

400 x _____ (fee per sheet) = _____ [b3]

Add amounts entered at b1, b2 and b3 and enter total at B . . . . 636.00 [B]

Designation Fees

The international application contains 88 designations.

6 (number of designation fees payable *(maximum 6)*) x 56.00 (amount of designation fee) = 336.00 [D]

Add amounts entered at B and D and enter total at I . . . . . 972.00 [I]

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT *(if applicable)* . . . . . 22.00 [P]

5. TOTAL FEES PAYABLE . . . . . 1673.00 TOTAL

Add amounts entered at T, S, I and P, and enter total in the TOTAL box

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

☐ authorization to charge deposit account (see below) ☐ postal money order ☐ cash ☐ coupons

☒ cheque ☐ bank draft ☐ revenue stamps ☐ other *(specify)*:

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

(This mode of payment may not be available at all receiving Offices)

Receiving Office: RO/ GB

Deposit Account No.: D02934

Date: 5 July 2001

Name: Joanne M Marshall

Signature: JMarshall

☐ Authorization to charge the total fees indicated above.

☒ *(This check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit)* Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

☒ Authorization to charge the fee for priority document.

005962

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03001210 00000000 Folios: 62
Fecha (AAMM): 2003-01-10 16:15:11
Tramite : 011 PCT-PATENT 370 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN MODELO DE UTILIDAD	( )	( )
- Indicación de que se solicita la concesión de una patente.	( )	( )
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
- Descripción de la invención.	( )	( )
- Dibujos de ser estos pertinentes.	( )	( )
- Comprobante de Pago de las tasas establecidas.		
COMPLETA ( ) INCOMPLETA	( )	( )
DISEÑO INDUSTRIAL ( )		
- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta	( )	( )
- la solicitud.		
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )
ESQUEMA DE TRAZADO ( )		
- Indicación de que solicita el registro de un Esquema de trazado.	( )	( )
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )

Firma Responsable:

Fecha:

PETITORIO

AS- 00 064

Industria y Comercio
SUPERINTENDENCIA 03 001310 00

SUPERINTENDENCIA : COMERCIO
Radicacion : 03001310 00000000 Folios: 00
Fecha Sol.: 2003-01-28 16:55:11
Tramite : 611 PCT-PATENT 579 FASE NACI 411 PRESENTAC
Presentado: 2003-01-28 16:55:11 DE PATENTES (PRESENCIAL)

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FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☐ Capítulo I. ☒ Capítulo II.

2 SOLICITANTE (71)	**Nombre:** ASTRAZENECA AB **Dirección:** S-151 85 Sodertalje, Suecia **Nacionalidad o Domicilio:** Suecia **Lugar de Constitución:** Suecia **Teléfono:** **Fax:** **E-mail**	**IDENTIFICACION** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número
3 REPRESENTANTE O APODERADO	**Nombre:** RAMIRO CASTRO DUQUE **Dirección:** Cra. 7 No. 16-56 Piso 9 **Teléfono:** 380-2200 **Fax:** 380-2700 **E-mail:**	**IDENTIFICACION** C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número 170.322 TP 1003
4 INVENTOR (ES) (72)	**Nombre:** Andrew Peter Thomas, Nicholas John Newcombe, David William Heaton **Dirección:** Alderley Park, Macclesfield, Cheshire SK10 4TG, Reino Unido; Alderley Park, Macclesfield, Cheshire SK10 4TG, Reino Unido; Alderley Park, Macclesfield, Cheshire SK10 4TG, Reino Unido (Respectivamente) **Nacionalidad o Domicilio:** Reino Unido (Respectivamente)	

5 PCT (86)
Solicitud Internacional No. PCT/GB01/03084 Fecha 06-07-2001
Publicación Internacional No. WO 02/04429 A1 Fecha 17-01-2002

9 Título (54): DERIVADOS DE PIRIMIDINA

7 Clasificación Internacional (51) A61K 31/505 ; C07D 239/48

8 Prioridad SI ☒ NO ☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	GB	11-07-2000	0016877.3

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

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Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá, D.C.,

Doctor: **Oficio N°** 08193
Ramiro Castro Duque
Apoderado
Astrazeneca AB.

ASUNTO:	Radicación N°	03-1310
	Solicitud internacional	PCT/GB2001/03084
	Fecha inicio fase nacional	11/02/2003
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento el el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- La solicitud nacional no contiene la traducción de la solicitud internacional tal como fue presentada. (Numeral 5.2.5, capítulo quinto del título décimo de la Circular Única de la SIC).
- La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486).
- La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha 03 OCT. 2003.

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