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REF: Expediente No. 02 116.483 - Solicitud de Patente FASE NACIONAL
a nombre de ASTRAZENECA AB Titulada: DERIVADOS DE
QUINAZOLINA SUSTITUIDOS Y SU USO COMO INHIBIDORES

RAMIRO CASTRO DUQUE, vecino de Bogotá, portador de la tarjeta profesional No. 1003, obrando como apoderado de la Sociedad ASTRAZENECA AB, según lo acredita el documento de Poder presentado en esa División, me permito anexar al presente escrito los siguientes documentos:

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De la señora jefe atentamente,



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Patentanmeldung Nr. Patent application No. Demande de brevet n°

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Der Präsident des Europäischen Patentamts:
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
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The present invention relates to certain quinazoline derivatives for use in the treatment of certain diseases in particular to proliferative disease such as cancer and in the preparation of medicaments for use in the treatment of proliferative disease, to novel quinazoline compounds and to processes for their preparation, as well as pharmaceutical compositions containing them as active ingredient.

Cancer (and other hyperproliferative disease) is characterised by uncontrolled cellular proliferation. This loss of the normal regulation of cell proliferation often appears to occur as the result of genetic damage to cellular pathways that control progress through the cell cycle.

In eukaryotes, the cell cycle is largely controlled by an ordered cascade of protein phosphorylation. Several families of protein kinases that play critical roles in this cascade have now been identified. The activity of many of these kinases is increased in human tumours when compared to normal tissue. This can occur by either increased levels of expression of the protein (as a result of gene amplification for example), or by changes in expression of co activators or inhibitory proteins.

The first identified, and most widely studied of these cell cycle regulators have been the cyclin dependent kinases (or CDKs). Activity of specific CDKs at specific times is essential for both initiation and coordinated progress through the cell cycle. For example, the CDK4 protein appears to control entry into the cell cycle (the G0-G1-S transition) by phosphorylating the retinoblastoma gene product pRb. This stimulates the release of the transcription factor E2F from pRb, which then acts to increase the transcription of genes necessary for entry into S phase. The catalytic activity of CDK4 is stimulated by binding to a partner protein, Cyclin D. One of the first demonstrations of a direct link between cancer and the cell cycle was made with the observation that the Cyclin D1 gene was amplified and cyclin D protein levels increased (and hence the activity of CDK4 increased) in many human tumours (Reviewed in Sherr, 1996, Science 274: 1672-1677; Pines, 1995, Seminars in Cancer Biology 6: 63-72). Other studies (Loda et al., 1997, Nature Medicine 3(2): 231-234; Gemma et al., 1996, International Journal of Cancer 68(5): 605-11; Elledge et al. 1996, Trends in Cell Biology 6: 388-392) have shown that negative regulators of CDK function are frequently down regulated or deleted in human tumours again leading to inappropriate activation of these kinases.

More recently, protein kinases that are structurally distinct from the CDK family have been identified which play critical roles in regulating the cell cycle and which also appear to be important in oncogenesis. These include the newly identified human homologues of the *Drosophila* aurora and *S.cerevisiae* Ipl1 proteins. *Drosophila* aurora and *S.cerevisiae* Ipl1, which are highly homologous at the amino acid sequence level, encode serine/threonine protein kinases. Both aurora and Ipl1 are known to be involved in controlling the transition from the G2 phase of the cell cycle through mitosis, centrosome function, formation of a mitotic spindle and proper chromosome separation / segregation into daughter cells. The two human homologues of these genes, termed aurora1 and aurora2, encode cell cycle regulated protein kinases. These show a peak of expression and kinase activity at the G2/M boundary (aurora2) and in mitosis itself (aurora1). Several observations implicate the involvement of human aurora proteins, and particularly aurora2 in cancer. The aurora2 gene maps to chromosome 20q13, a region that is frequently amplified in human tumours including both breast and colon tumours. Aurora2 may be the major target gene of this amplicon, since aurora2 DNA is amplified and aurora2 mRNA overexpressed in greater than 50% of primary human colorectal cancers. In these tumours aurora2 protein levels appear greatly elevated compared to adjacent normal tissue. In addition, transfection of rodent fibroblasts with human aurora2 leads to transformation, conferring the ability to grow in soft agar and form tumours in nude mice (Bischoff et al., 1998, The EMBO Journal. 17(11): 3052-3065). Other work (Zhou et al., 1998, Nature Genetics. 20(2): 189-93) has shown that artificial overexpression of aurora2 leads to an increase in centrosome number and an increase in aneuploidy.

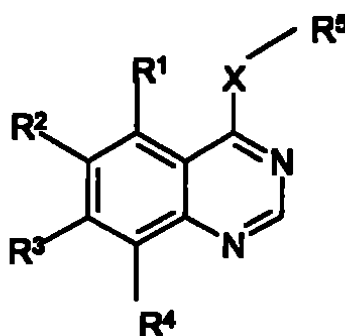
Importantly, it has also been demonstrated that abrogation of aurora2 expression and function by antisense oligonucleotide treatment of human tumour cell lines (WO 97/22702 and WO 99/37788) leads to cell cycle arrest in the G2 phase of the cell cycle and exerts an antiproliferative effect in these tumour cell lines. This indicates that inhibition of the function of aurora2 will have an antiproliferative effect that may be useful in the treatment of human tumours and other hyperproliferative diseases.

A number of quinazoline derivatives have been proposed hitherto for use in the inhibition of various kinases. Examples of such proposals are included in WO 92/20642 and EP-B-584222 which relates to bicyclic compounds which inhibit epidermal growth factor (EGF) and platelet-derived growth factor (PDGF) receptor tyrosine kinase, WO 95/15758 which describes the use of bis ring systems for the selective inhibition of CSF-1R tyrosine

kinase activity, and WO 99/09016, WO 97/03069 and US 570158 which describe the use of certain quinazoline compounds as tyrosine kinase inhibitors in other contexts.

The applicants have found a series of compounds which inhibit the effect of the aurora2 kinase and which are thus of use in the treatment of proliferative disease such as cancer, in particular in such diseases such as colorectal or breast cancer where aurora 2 kinase is known to be active.

The present invention provides the use of a compound of formula (I)



(I)

or a salt, ester or amide thereof;

where X is O, or S, S(O) or S(O)₂ or NR⁶ where R⁶ is hydrogen or C₁₋₄alkyl;

R⁵ is an optionally substituted 5-membered heteroaromatic ring,

R¹, R², R³, R⁴ are independently selected from, halo, cyano, nitro, trifluoromethyl, C₁₋₃alkyl, -NR⁷R⁸ (wherein R⁷ and R⁸, which may be the same or different, each represents hydrogen or C₁₋₃alkyl), or -X¹R⁹ (wherein X¹ represents a direct bond, -O-, -CH₂-, -OCO-, carbonyl, -S-, -SO-, -SO₂-, -NR¹⁰CO-, -CONR¹¹-, -SO₂NR¹²-, -NR¹³SO₂- or -NR¹⁴- (wherein R¹⁰, R¹¹, R¹², R¹³ and R¹⁴ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl), and R⁹ is selected from one of the following groups:

1) hydrogen or C₁₋₃alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro or amino,

2) C₁₋₃alkylX²COR¹⁵ (wherein X² represents -O- or -NR¹⁶- (in which R¹⁵ represents hydrogen,

C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹⁶ represents C₁₋₃alkyl, -NR¹⁷R¹⁸ or -OR¹⁹ (wherein R¹⁷, R¹⁸ and R¹⁹ which may be the same or different each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl));

- 3) $C_{1,3}\text{alkyl}X^3R^{20}$ (wherein X^3 represents -O-, -S-, -SO-, -SO₂-, -OCO-, -NR²¹CO-, -CONR²²-, -SO₂NR²³-, -NR²⁴SO₂- or -NR²⁵- (wherein R²¹, R²², R²³, R²⁴ and R²⁵ each independently represents hydrogen, C_{1,3}alkyl or C_{1,3}alkoxyC_{2,3}alkyl) and R²⁰ represents hydrogen, C_{1,3}alkyl, cyclopentyl, cyclohexyl or a 5-6-membered saturated heterocyclic group with 1-2
- 5 heteroatoms, selected independently from O, S and N, which C_{1,3}alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1,4}alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1,4}alkyl, C_{1,4}hydroxyalkyl and C_{1,4}alkoxy);
- 4) $C_{1,3}\text{alkyl}X^4C_{1,3}\text{alkyl}X^5R^{26}$ (wherein X^4 and X^5 which may be the same or different are each -
- 10 O-, -S-, -SO-, -SO₂-, -NR²⁷CO-, -CONR²⁸-, -SO₂NR²⁹-, -NR³⁰SO₂- or -NR³¹- (wherein R²⁷, R²⁸, R²⁹, R³⁰ and R³¹ each independently represents hydrogen, C_{1,3}alkyl or C_{1,3}alkoxyC_{2,3}alkyl) and R²⁶ represents hydrogen or C_{1,3}alkyl);
- 5) R³² (wherein R³² is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic
- 15 group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1,4}alkyl, C_{1,4}hydroxyalkyl, C_{1,4}alkoxy, C_{1,4}alkoxyC_{1,4}alkyl and C_{1,4}alkylsulphonyl(C_{1,4}alkyl));
- 6) C_{1,3}alkylR³² (wherein R³² is as defined hereinbefore);
- 7) C_{2,3}alkenylR³² (wherein R³² is as defined hereinbefore);
- 8) C_{2,3}alkynylR³² (wherein R³² is as defined hereinbefore);
- 20 9) R³³ (wherein R³³ represents a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-3 heteroatoms selected from O, N and S, which pyridone, phenyl or aromatic heterocyclic group may carry up to 5 substituents on an available carbon atom selected from hydroxy, halogeno, amino, C_{1,4}alkyl, C_{1,4}alkoxy, C_{1,4}hydroxyalkyl, C_{1,4}aminoalkyl, C_{1,4}alkylamino, C_{1,4}hydroxyalkoxy, carboxy,
- 25 trifluoromethyl, cyano, -CONR³⁴R³⁵ and -NR³⁶COR³⁷ (wherein R³⁴, R³⁵, R³⁶ and R³⁷, which may be the same or different, each represents hydrogen, C_{1,4}alkyl or C_{1,3}alkoxyC_{2,3}alkyl));
- 10) C_{1,3}alkylR³³ (wherein R³³ is as defined hereinbefore);
- 11) C_{2,3}alkenylR³³ (wherein R³³ is as defined hereinbefore);
- 12) C_{2,3}alkynylR³³ (wherein R³³ is as defined hereinbefore);
- 30 13) $C_{1,3}\text{alkyl}X^6R^{33}$ (wherein X^6 represents -O-, -S-, -SO-, -SO₂-, -NR³⁸CO-, -CONR³⁹-, -SO₂NR⁴⁰-, -NR⁴¹SO₂- or -NR⁴²- (wherein R³⁸, R³⁹, R⁴⁰, R⁴¹ and R⁴² each independently represents hydrogen, C_{1,3}alkyl or C_{1,3}alkoxyC_{2,3}alkyl) and R³³ is as defined hereinbefore);

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- 14) $C_{2,3}alkenylX^7R^{33}$ (wherein X^7 represents -O-, -S-, -SO-, -SO₂-, -NR⁴³CO-, -CONR⁴⁴-, -SO₂NR⁴⁵-, -NR⁴⁶SO₂- or -NR⁴⁷- (wherein R⁴³, R⁴⁴, R⁴⁵, R⁴⁶ and R⁴⁷ each independently represents hydrogen, C_{1,3}alkyl or C_{1,3}alkoxyC_{2,3}alkyl) and R³³ is as defined hereinbefore);
- 15) $C_{2,3}alkynylX^8R^{33}$ (wherein X^8 represents -O-, -S-, -SO-, -SO₂-, -NR⁴⁸CO-, -CONR⁴⁹-, -SO₂NR⁵⁰-, -NR⁵¹SO₂- or -NR⁵²- (wherein R⁴⁸, R⁴⁹, R⁵⁰, R⁵¹ and R⁵² each independently represents hydrogen, C_{1,3}alkyl or C_{1,3}alkoxyC_{2,3}alkyl) and R³³ is as defined hereinbefore);
- 16) $C_{1,3}alkylX^9C_{1,3}alkylR^{33}$ (wherein X^9 represents -O-, -S-, -SO-, -SO₂-, -NR⁵³CO-, -CONR⁵⁴-, -SO₂NR⁵⁵-, -NR⁵⁶SO₂- or -NR⁵⁷- (wherein R⁵³, R⁵⁴, R⁵⁵, R⁵⁶ and R⁵⁷ each independently represents hydrogen, C_{1,3}alkyl or C_{1,3}alkoxyC_{2,3}alkyl) and R³³ is as defined hereinbefore); and
- 17) $C_{1,3}alkylX^9C_{1,3}alkylR^{33}$ (wherein X^9 and R³³ are as defined hereinbefore):

in the preparation of a medicament for use in the inhibition of aurora 2 kinase. In particular, such medicaments are useful in the treatment of proliferative disease such as cancer, and in particular cancers where aurora 2 is upregulated such as colon or breast cancers.

In this specification the term 'alkyl' when used either alone or as a suffix includes straight chained, branched structures. Unless otherwise stated, these groups may contain up to 10, preferably up to 6 and more preferably up to 4 carbon atoms. Similarly the terms "alkenyl" and "alkynyl" refer to unsaturated straight or branched structures containing for example from 2 to 10, preferably from 2 to 6 carbon atoms. Cyclic moieties such as cycloalkyl, cycloalkenyl and cycloalkynyl are similar in nature but have at least 3 carbon atoms. Terms such as "alkoxy" comprise alkyl groups as is understood in the art.

The term "halo" includes fluoro, chloro, bromo and iodo. References to aryl groups include aromatic carbocyclic groups such as phenyl and naphthyl. The term "heterocyclyl" includes aromatic or non-aromatic rings, for example containing from 4 to 20, suitably from 5 to 8 ring atoms, at least one of which is a heteroatom such as oxygen, sulphur or nitrogen. Examples of such groups include furyl, thienyl, pyrrolyl, pyrrolidinyl, imidazolyl, triazolyl, thiazolyl, tetrazolyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, quinoliny, isoquinoliny, quinoxaliny, benzothiazolyl, benzoxazolyl, benzothienyl or benzofuryl.

"Heteroaryl" refers to those groups described above which have an aromatic character.

The term "aralkyl" refers to aryl substituted alkyl groups such as benzyl.

Other expressions used in the specification include "hydrocarbyl" which refers to any structure comprising carbon and hydrogen atoms. For example, these may be alkyl, alkenyl, alkynyl, aryl, heterocyclyl, alkoxy, aralkyl, cycloalkyl, cycloalkenyl or cycloalkynyl.

The term "functional group" refers to reactive substituents such as nitro, cyano, halo, oxo, $=CR^7R^8$, $C(O)_xR^7$, OR^7 , $S(O)_yR^7$, NR^7R^8 , $C(O)NR^7R^8$, $OC(O)NR^7R^8$, $=NOR^7$, $-NR^7C(O)_xR^8$, $-NR^7CONR^7R^8$, $-N=CR^7R^8$, $S(O)_yNR^7R^8$ or $-NR^7S(O)_yR^8$ where R^7 , R^8 and R^9 are independently selected from hydrogen or optionally substituted hydrocarbyl, or R^7 and R^8 together form an optionally substituted ring which optionally contains further heteroatoms such as S(O), oxygen and nitrogen, x is an integer of 1 or 2, y is 0 or an integer of 1-3.

Suitable optional substituents for hydrocarbyl groups R^7 , R^8 and R^9 include halo, perhaloalkyl such as trifluoromethyl, mercapto, hydroxy, carboxy, alkoxy, heteroaryl, heteroaryloxy, alkenyloxy, alkynyloxy, alkoxyalkoxy, aryloxy (where the aryl group may be substituted by halo, nitro, or hydroxy), cyano, nitro, amino, mono- or di-alkyl amino, oximino or S(O), where y is as defined above.

Preferably R^4 is hydrogen.

Suitably R^1 is hydrogen or a group set out for R^2 or R^3 below. Frequently, R^1 is hydrogen.

In a preferred embodiment, at least one group R^1 , R^2 or R^3 , preferably R^3 , comprises a chain of at least 3 and preferably at least 4 optionally substituted carbon atoms or heteroatoms such as oxygen, nitrogen or sulphur. Most preferably the chain is substituted by a polar group which assists in solubility.

Suitably R^3 is a group X^1R^9 . Preferably in this case, X^1 is oxygen and R^9 is selected from a group of formula (1) or (10) above. Particular groups R^9 are those in group (1) above, especially alkyl such as methyl or halo substituted alkyl, or those in group (10) above. In one preferred embodiment, at least one of R^2 or R^3 is a group $-OC_{1-3}alkylR^{13}$ and R^{13} is a heterocyclic ring such as an N-linked morpholine ring such as 3-morpholinopropoxy.

Suitably R^2 is selected from, halo, cyano, nitro, trifluoromethyl, $C_{1-3}alkyl$, $-NR^9R^{10}$ (wherein R^9 and R^{10} , which may be the same or different, each represents hydrogen or $C_{1-3}alkyl$), or a group $-X^1R^{11}$. Preferred examples of $-X^1R^{11}$ for R^2 include those listed above in relation to R^1 .

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Other examples for R^2 and R^3 include methoxy or 3,3,3-trifluoroethoxy.

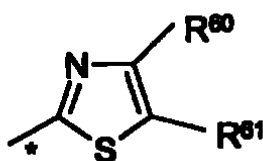
Preferably X is NH or O and is most preferably NH.

Examples of 5-membered aromatic rings R^4 include rings containing one or more heteroatoms selected from sulphur, oxygen and nitrogen. Such rings include pyrrole, pyrazole, pyrazolone, imidazole, oxazole, furan, tetrazole, triazole, thiazole, thiophene, or thiadiazole, any of which may be optionally substituted. In particular, R^4 includes at least one nitrogen or sulphur heteroatoms. Preferred rings for R^4 include pyrrole, pyrazole, imidazole, triazole, thiazole, thiophene, or thiadiazole.

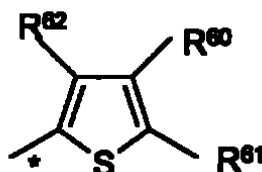
In a particular embodiment, R^4 is a sulphur containing ring. Suitably R^4 is optionally substituted thiazole, optionally substituted thiophene or optionally substituted thiadiazole and preferably, optionally substituted thiazole or optionally substituted thiophene.

More preferably, R^4 is a substituted thiazole or substituted thiophene group.

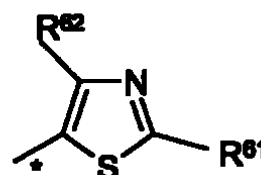
In particular, R^4 is a group of formula (a), (b), (c) or (d) and preferably (a) or (b):



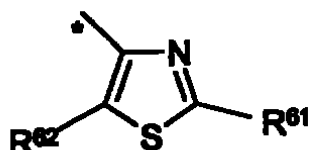
(a)



(b)



(c)



(d)



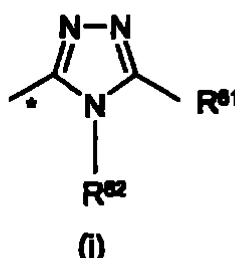
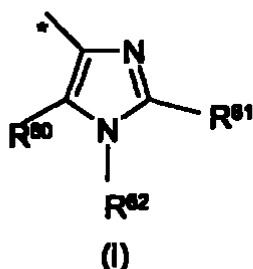
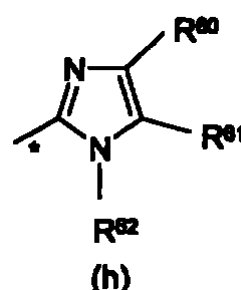
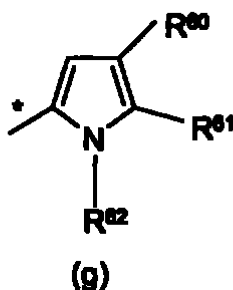
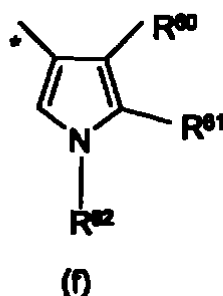
(e)

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where R^{60} , R^{61} and R^{62} are independently selected from hydrogen or a substituent group and * indicates the point of attachment to the group X in formula (I). In particular, one of R^{60} , R^{61} or R^{62} is a substituent group and the others are either hydrogen or a small substituent such as C_{1-3} alkyl, for instance methyl. Suitably R^{62} is hydrogen. Preferably R^{61} is other than

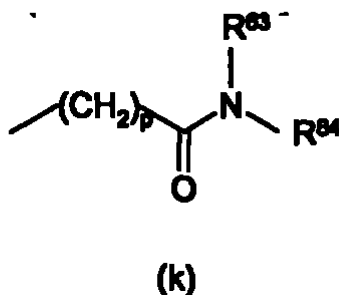
20 hydrogen,

Alternatively, R^3 is an optionally substituted nitrogen containing ring such as a group of formula (f), (g), (h), (i) or (j):



- 5 Suitable substituents for groups R^3 include optionally substituted hydrocarbyl, optionally substituted heterocyclyl or a functional group as defined above.

In particular, R^0 , R^1 or R^2 is a group of sub-formula (k)



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where p is 0 or 1 and R^3 and R^4 are independently selected from hydrogen, optionally substituted hydrocarbyl or optionally substituted heterocyclyl, or R^3 and R^4 together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring.

- 15 Examples of groups for R^3 and R^4 include the group $-(CH_2)_q R^5$ where q and R^5 are as defined below in relation to formula (II).

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Suitably one of R^{63} or R^{64} is hydrogen, or methyl, ethyl or propyl optionally substituted with hydroxy and preferably one of R^{63} or R^{64} is hydrogen. In this case, the other is suitably a larger substituent for example of at least 4 carbon or heteroatoms, and is optionally substituted hydrocarbyl or optionally substituted heterocyclyl. Particular

5 optionally substituted hydrocarbyl groups for R^{63} or R^{64} include alkyl, cycloalkyl, alkenyl, or aryl any of which is optionally substituted with a functional group as defined above, or in the case of aryl groups, with an alkyl group and in the case of alkyl group, with an aryl or heterocyclic group either of which may themselves be optionally substituted with alkyl or a functional group. Examples of optionally substituted aryl groups R^{63} or R^{64} include phenyl

10 optionally substituted with one or more groups selected from C_{1-4} alkyl group such as methyl or ethyl (either of which may be optionally substituted with a functional group such as hydroxy), or a functional group as defined above (such as halo like fluoro, chloro or bromo, hydroxy, alkoxy such as methoxy, trifluoromethyl, nitro, cyano, trifluoromethoxy, $CONH_2$, $C(O)CH_3$, amino, or dimethylamino).

15 When R^{63} or R^{64} is an optionally substituted alkyl group, it is suitably a C_{1-6} alkyl group, optionally substituted with one or more functional groups (such as cyano, hydroxy, alkoxy, in particular methoxy, COO alkyl such as $COOCH_3$), or aryl optionally substituted with a functional group as defined above (in particular in relation to R^{63} or R^{64} themselves, or an optionally substituted heterocyclic group such as N-methyl pyrrole.

20 When R^{63} and R^{64} is optionally substituted cycloalkyl, it is suitable cyclohexyl optionally substituted with a functional group such as hydroxy.

When R^{63} and R^{64} is optionally substituted alkenyl, it is suitably prop-2-enyl.

When R^{63} or R^{64} is optionally substituted heterocyclyl, or R^{63} and R^{64} together form a heterocyclic group, then this may be aromatic or non-aromatic and includes in particular,

25 piperidine, piperazine, morpholino, pyrrolidine or pyridine any of which may be optionally substituted with a functional group such as hydroxy, alkoxy such as methoxy, or alkyl such as methyl which may itself be substituted with for instance a hydroxy group.

Alternatively at least one of R^{60} , R^{61} or R^{62} is a functional group, and in particular, one of R^{60} , R^{61} or R^{62} is a functional group a group of formula $C(O)_x R^{77}$ where x and R^{77} are as

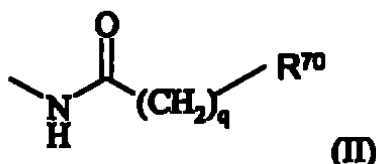
30 defined above, and in particular x is 2 and R^{77} is hydrogen or alkyl such as methyl.

Alternatively, R^5 is substituted by one or more groups selected from nitro, halo, C_{1-6} alkyl, optionally substituted C_{1-4} alkoxy, C_{1-4} alkoxymethyl, $di(C_{1-4}$ alkoxy)methyl, C_{1-6}

alkanoyl, trifluoromethyl, cyano, amino, C₂₋₆alkenyl, C₂₋₆alkynyl, a phenyl group, a benzyl group or a 5-6-membered heterocyclic group with 1-3 heteroatoms, selected independently from O, S and N, which heterocyclic group may be aromatic or non-aromatic and may be saturated (linked via a ring carbon or nitrogen atom) or unsaturated (linked via a ring carbon atom), and which phenyl, benzyl or heterocyclic group may bear on one or more ring carbon atoms up to 5 substituents selected from hydroxy, halogeno, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₄alkanoyloxy, trifluoromethyl, cyano, amino, nitro, C₂₋₄alkanoyl, C₁₋₄alkanoylamino, C₁₋₄alkoxycarbonyl, C₁₋₄alkylsulphanyl, C₁₋₄alkylsulphinyl, C₁₋₄alkylsulphonyl, carbamoyl, N-C₁₋₄alkylcarbamoyl, N,N-di(C₁₋₄alkyl)carbamoyl, aminosulphonyl, N-C₁₋₄alkylaminosulphonyl, N,N-di(C₁₋₄alkyl)aminosulphonyl, C₁₋₄alkylsulphonylamino, and a saturated heterocyclic group selected from morpholino, thiomorpholino, pyrrolidinyl, piperazinyl, piperidinyl imidazolidinyl and pyrazolidinyl, which saturated heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃alkanoyloxy, trifluoromethyl, cyano, amino, nitro and C₁₋₄alkoxycarbonyl.

Suitably R⁵ is substituted with at least one group which has at least 4 atoms which may be carbon or heteroatoms forming a chain. A particular example of such a substituent is optionally substituted alkoxy. Suitable substituents for the alkoxy group include those listed above in relation to R⁷⁷, R⁷⁸ and R⁷⁹.

A further particular substituent group for R⁵ is a group of sub-formula (II)



where q is 0, 1, 2, 3 or 4;

R⁷⁰ is hydrogen, hydroxy (other than where q is 0), C₁₋₆alkyl, C₁₋₆alkoxy, amino, N-C₁₋₆alkylamino, N,N-(C₁₋₆alkyl)₂amino, hydroxyC₂₋₆alkoxy, C₁₋₆alkoxyC₂₋₆alkoxy, aminoC₂₋₆alkoxy, N-C₁₋₆alkylaminoC₂₋₆alkoxy, N,N-(C₁₋₆alkyl)₂aminoC₂₋₆alkoxy or C₃₋₇cycloalkyl, or R⁷⁰ is of the Formula (III):

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wherein J is aryl, heteroaryl or heterocyclyl and K is a bond, oxy, imino, *N*-(C₁₋₆alkyl)imino, oxyC₁₋₆alkylene, iminoC₁₋₆alkylene, *N*-(C₁₋₆alkyl)iminoC₁₋₆alkylene, -NHC(O)-, -SO₂NH-,

5 -NHSO₂- or -NHC(O)-C₁₋₆alkylene-,

and any aryl, heteroaryl or heterocyclyl group in a Rⁿ group may be optionally substituted by one or more groups selected from hydroxy, halo, trifluoromethyl, cyano, mercapto, nitro,

amino, carboxy, carbamoyl, formyl, sulphamoyl, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl,

C₁₋₆alkoxy, -O-(C₁₋₃alkyl)-O-, C₁₋₆alkylS(O)_n- (wherein n is 0-2), *N*-C₁₋₆alkylamino,

10 *N,N*-(C₁₋₆alkyl)₂amino, C₁₋₆alkoxycarbonyl, *N*-C₁₋₆alkylcarbamoyl, *N,N*-(C₁₋₆alkyl)₂carbamoyl,

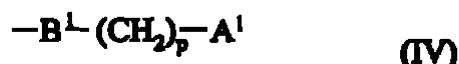
C₂₋₆alkanoyl, C₁₋₆alkanoyloxy, C₁₋₆alkanoylamino, *N*-C₁₋₆alkylsulphamoyl,

N,N-(C₁₋₆alkyl)₂sulphamoyl, C₁₋₆alkylsulphonylamino and C₁₋₆alkylsulphonyl-

N-(C₁₋₆alkyl)amino,

or any aryl, heteroaryl or heterocyclyl group in a Rⁿ group may be optionally substituted with

15 one or more groups of the Formula (IV):



wherein A¹ is halo, hydroxy, C₁₋₆alkoxy, cyano, amino, *N*-C₁₋₆alkylamino,

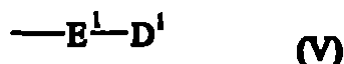
20 *N,N*-(C₁₋₆alkyl)₂amino, carboxy, C₁₋₆alkoxycarbonyl, carbamoyl, *N*-C₁₋₆alkylcarbamoyl or

N,N-(C₁₋₆alkyl)₂carbamoyl, p is 1 - 6, and B¹ is a bond, oxy, imino, *N*-(C₁₋₆alkyl)imino or

-NHC(O)-, with the proviso that p is 2 or more unless B¹ is a bond or -NHC(O)-;

or any aryl, heteroaryl or heterocyclyl group in a Rⁿ group may be optionally substituted with one or more groups of the Formula (V):

25



wherein D¹ is aryl, heteroaryl or heterocyclyl and E¹ is a bond, C₁₋₆alkylene, oxyC₁₋₆alkylene, oxy, imino, *N*-(C₁₋₆alkyl)imino, iminoC₁₋₆alkylene, *N*-(C₁₋₆alkyl)-iminoC₁₋₆alkylene,

30 C₁₋₆alkylene-oxyC₁₋₆alkylene, C₁₋₆alkylene-iminoC₁₋₆alkylene, C₁₋₆alkylene-*N*-(C₁₋₆alkyl)-

iminoC₁₋₆alkylene, -NHC(O)-, -NHSO₂-, -SO₂NH- or -NHC(O)-C₁₋₆alkylene-, and any aryl,

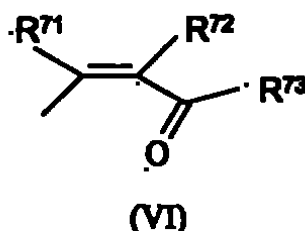
heteroaryl or heterocyclyl group in a substituent on D¹ may be optionally substituted with one or more groups selected from hydroxy, halo, C₁₋₆alkyl, C₁₋₆alkoxy, carboxy, C₁₋₆alkoxycarbonyl, carbamoyl, *N*-C₁₋₆alkylcarbamoyl, *N*-(C₁₋₆alkyl)₂carbamoyl, C₂₋₆alkanoyl, amino, *N*-C₁₋₆alkylamino and *N,N*-(C₁₋₆alkyl)₂amino,

- 5 and any C₃₋₇cycloalkyl or heterocyclyl group in a R⁷⁰ group may be optionally substituted with one or two oxo or thioxo substituents,
and any of the R⁷⁰ groups defined hereinbefore which comprises a CH₂ group which is attached to 2 carbon atoms or a CH₃ group which is attached to a carbon atom may optionally bear on each said CH₂ or CH₃ group a substituent selected from hydroxy, amino, C₁₋₆alkoxy,
10 *N*-C₁₋₆alkylamino, *N,N*-(C₁₋₆alkyl)₂amino and heterocyclyl.

A preferred example of a substituent of formula (II) is a group where q is 0.

A particular example of a group R⁷⁰ in formula (II) is phenyl.

Another preferred substituent group for R⁵ is a group of formula (VI)



15

where R⁷¹ and R⁷² are independently selected from hydrogen or C₁₋₄alkyl, or R⁷¹ and R⁷² together form a bond, and R⁷³ is a group OR⁷⁴, NR⁷⁵R⁷⁶ where R⁷⁴, R⁷⁵ and R⁷⁶ are

- 20 independently selected from optionally substituted hydrocarbyl or optionally substituted heterocyclic groups, and R⁷⁵ and R⁷⁶ may additionally form together with the nitrogen atom to which they are attached, an aromatic or non-aromatic heterocyclic ring which may contain further heteroatoms.

- Suitable optional substituents for hydrocarbyl or heterocyclic groups R⁷⁴, R⁷⁵ and R⁷⁶
25 include functional groups as defined above. Heterocyclic groups R⁷⁴, R⁷⁵ and R⁷⁶ may further be substituted by hydrocarbyl groups.

In particular, R⁷¹ and R⁷² in sub-formula (VI) are hydrogen.

Particular examples of R⁷³ are groups OR⁷⁴ where R⁷⁴ is C₁₋₄alkyl.

Further examples of R^{75} are groups of formula $NR^{75}R^{76}$ where one of R^{75} or R^{76} is hydrogen and the other is optionally substituted C_{1-6} alkyl, optionally substituted aryl or optionally substituted heterocyclyl.

In particular, one of R^{75} or R^{76} is hydrogen and the other is C_{1-6} alkyl optionally substituted with trifluoromethyl, C_{1-3} alkoxy such as methoxy, cyano, thio C_{1-4} alkyl such as methylthio, or heterocyclyl optionally substituted with hydrocarbyl, such as indane, furan optionally substituted with C_{1-4} alkyl such as methyl.

In another embodiment, one of R^{75} or R^{76} is hydrogen and the other is an optionally substituted heterocyclic group such as pyridine, or a phenyl group optionally substituted with
10 for example one or more groups selected from halo, nitro, alkyl such as methyl, or alkoxy such as methoxy.

Suitable pharmaceutically acceptable salts of compounds of formula (I) include acid addition salts such as methanesulfonate, fumarate, hydrochloride, hydrobromide, citrate, maleate and salts formed with phosphoric and sulphuric acid. There may be more than one
15 cation or anion depending on the number of charged functions and the valency of the cations or anions. Where the compound of formula (I) includes an acid functionality, salts may be base salts such as an alkali metal salt for example sodium, an alkaline earth metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, *N*-methylpiperidine, *N*-ethylpiperidine, procaine, dibenzylamine, *N,N*-dibenzylethylamine or
20 amino acids for example lysine. A preferred pharmaceutically acceptable salt is a sodium salt.

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} alkyl esters such as
25 methyl or ethyl esters, C_{1-6} alkoxymethyl esters for example methoxymethyl, C_{1-6} alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{2-6} cycloalkoxy-carbonyloxy C_{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
30 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-dimethylpropionyloxymethoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and
5 phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

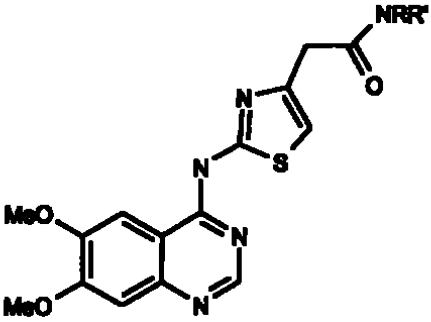
Suitable amides are derived from compounds of formula (I) which have a carboxy group which is derivatised into an amide such as a *N*-C₁₋₆alkyl and *N,N*-di-
10 (C₁₋₆alkyl)amide such as *N*-methyl, *N*-ethyl, *N*-propyl, *N,N*-dimethyl, *N*-ethyl-*N*-methyl or *N,N*-diethylamide.

Esters which are not *in vivo* hydrolysable may be useful as intermediates in the production of the compounds of formula (I).

Particular examples of compounds of formula (I) are set out in Tables 1 to 12 below.

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22

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Table 1

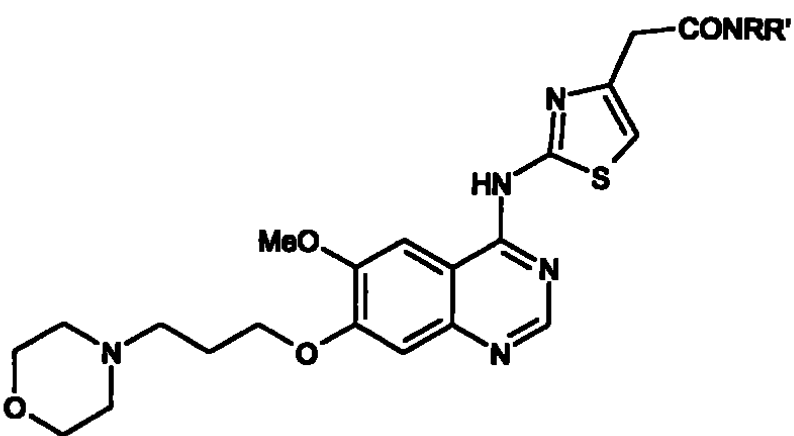
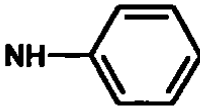
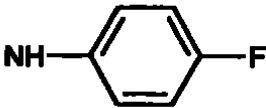
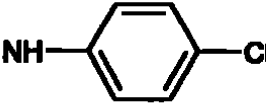
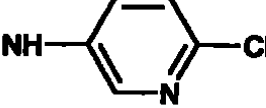
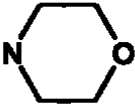
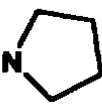
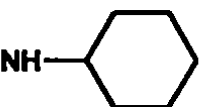


Compound No	NRR'	Compound No	NRR'
1		15	
2		16	
3		17	
4		18	
5		19	
6		20	
7		21	
8		22	
9		23	
10		24	
11		25	
12			
13			
14			

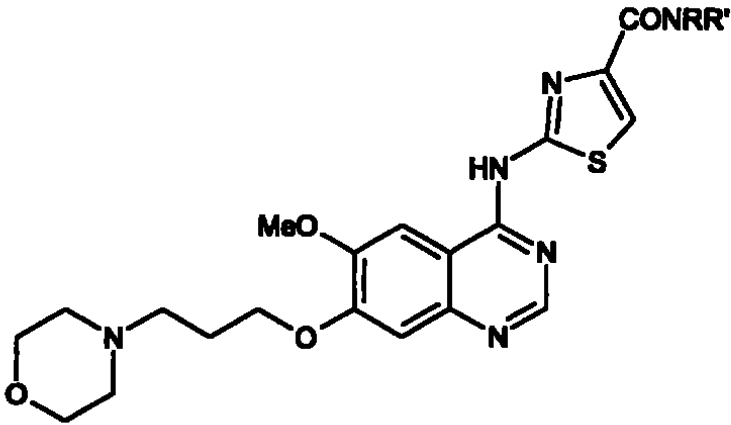
Table 1 (contd)

Compound No	NRR'	Compound No.	NRR'
26		39	
27		40	
28		41	
29		42	
30		43	
31		44	
32		45	
33		46	
34		47	
35		48	
36		49	
37		50	
38			

-17-
Table 2

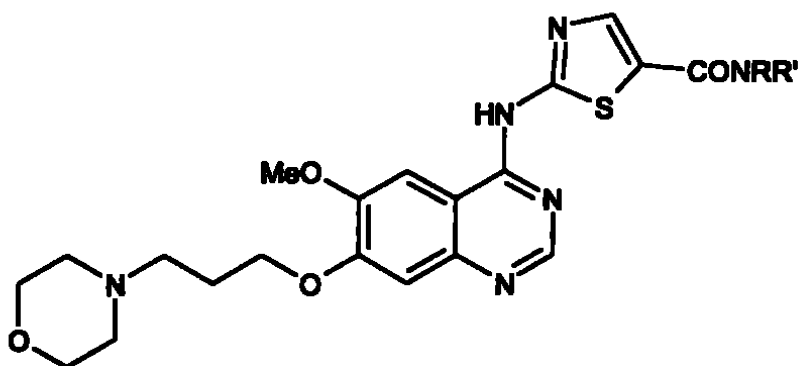
Compound No		
	NRR'	
51		
52		
53		
54		
55		
56		
57		
58		

-18-
Table 3



Compound No	NRR'
59	
60	
61	
62	
63	
64	
65	
66	

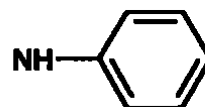
827 819
~~827 819~~



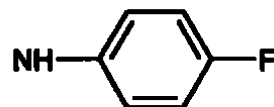
Compound No

NRR'

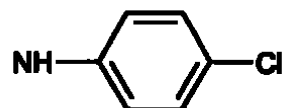
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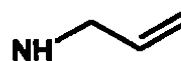
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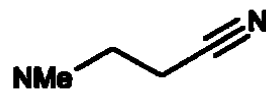
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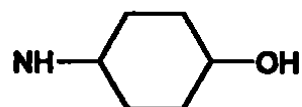
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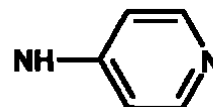
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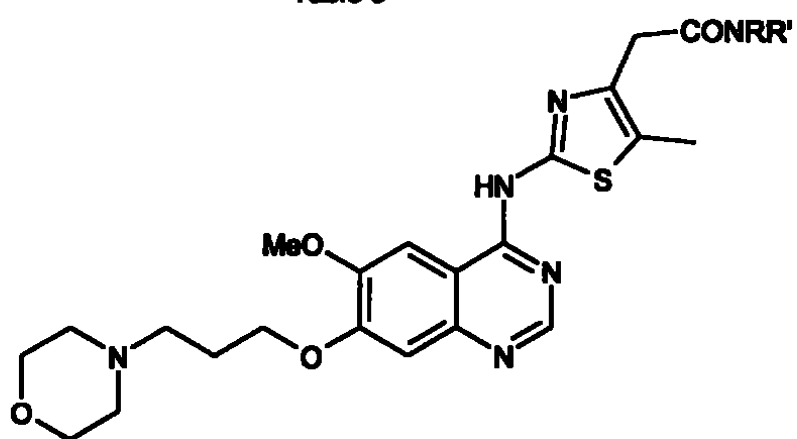
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73



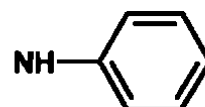
-20-
Table 5



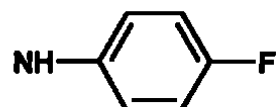
Compound No

NRR'

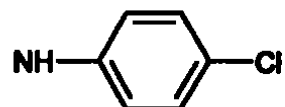
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75



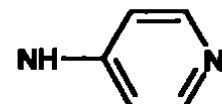
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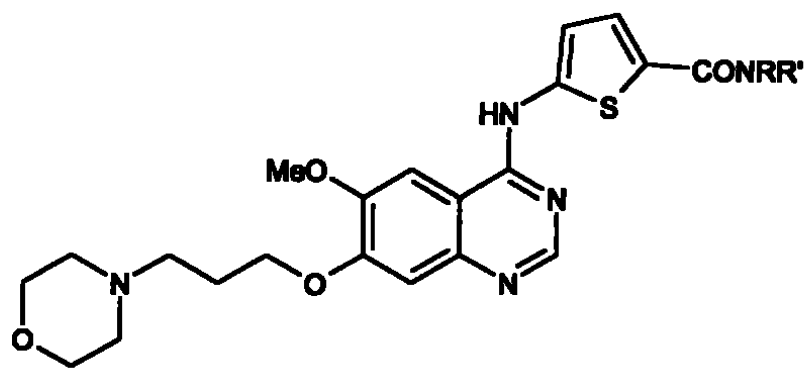
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78



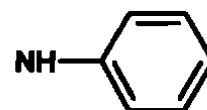
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Table 6



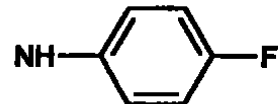
Compound No.

NRR'

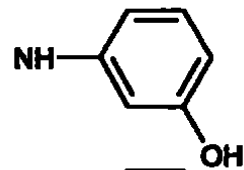
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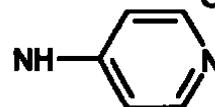
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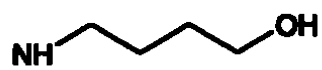
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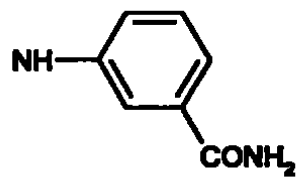
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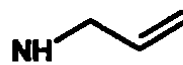
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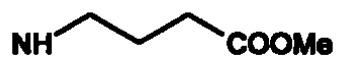
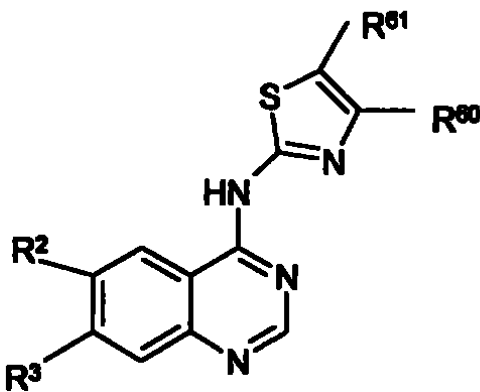


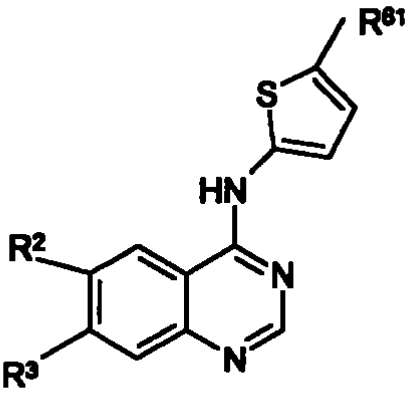
Table 7



No.	R ²	R ³	R ⁶⁰	R ⁶¹
200	OCH ₃	OCH ₃	CH ₂ COOCH ₂ CH ₃	H
201	OCH ₃	OCH ₃	CH ₂ COOH	H
202	OCH ₃	OCH ₃	CH ₃	COOCH ₂ CH ₃
203	OCH ₃	O(CH ₂) ₃ -N-morpholino	CH ₃	COOCH ₂ CH ₃
204	OCH ₃	O(CH ₂) ₃ -N-morpholino	CH ₃	COOH
205	OCH ₃	O(CH ₂) ₃ -N-morpholino	CH ₂ COOCH ₂ CH ₃	H
206	OCH ₃	O(CH ₂) ₃ -N-morpholino	COOCH ₂ CH ₃	H
207	OCH ₃	O(CH ₂) ₃ -N-morpholino	COOH	H
208	OCH ₃	O(CH ₂) ₃ -N-morpholino	H	COOCH ₂ CH ₃
209	OCH ₃	O(CH ₂) ₃ -N-morpholino	H	COOH
210	OCH ₃	O(CH ₂) ₃ -N-morpholino	CH ₂ COOCH ₂ CH ₃	CH ₃
211	OCH ₃	O(CH ₂) ₃ -N-morpholino	CH ₂ COOH	CH ₃

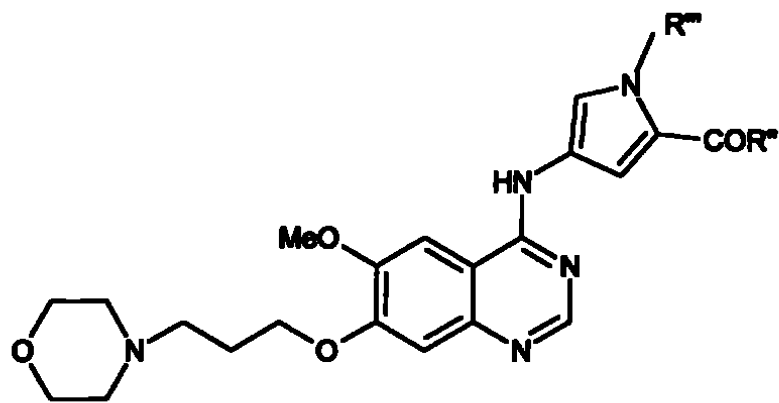
823 921
~~XXXX~~

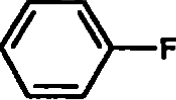
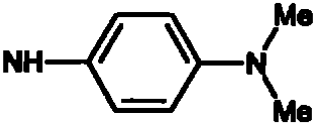
-23-
Table 8



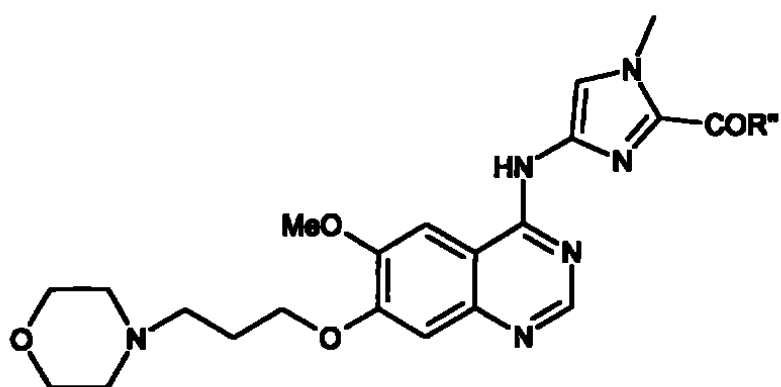
No.	R^2	R^3	R^{61}
212	OCH_3	$O(CH_2)_3-N\text{-morpholino}$	$COOH$
213	OCH_3	OCH_3	$COOCH_2CH_3$
214	OCH_3	OCH_3	$COOH$

-24-
Table 9



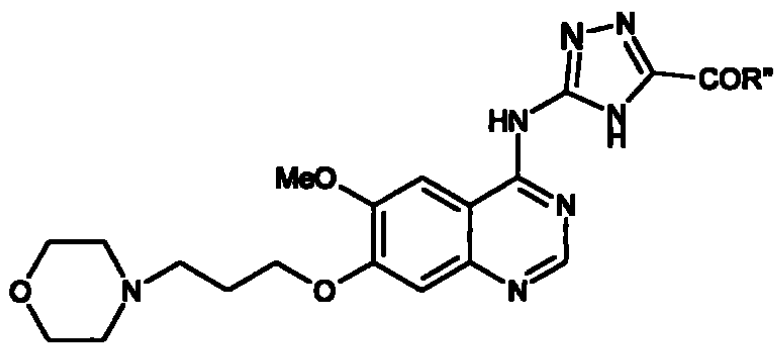
Compound No	R''	R''
250	CH ₃	OCH ₃
251	CH ₃	OH
252	CH ₃	NH- 
253	CH ₃	NH- 
254	CH ₃	NH- 
255	CH ₃	NH- 
256	H	OCH ₂ CH ₃
257	H	OH
258	H	NH- 
259	H	NH- 

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✓



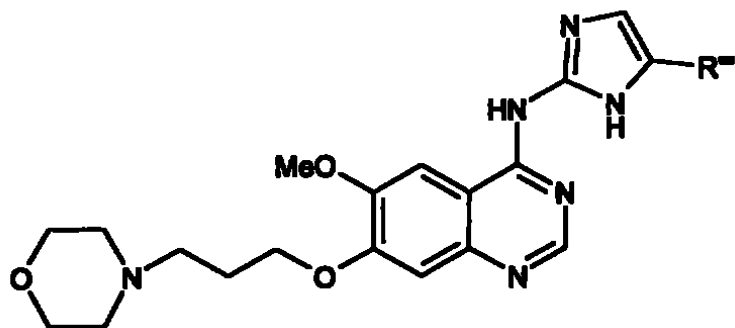
Compound No	R''
260	COOCH ₃
261	COOH
262	
263	
264	
265	
266	
267	

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Table 11



Compound No	R'
268	COOCH ₂ CH ₃
269	COOH
270	
271	
272	

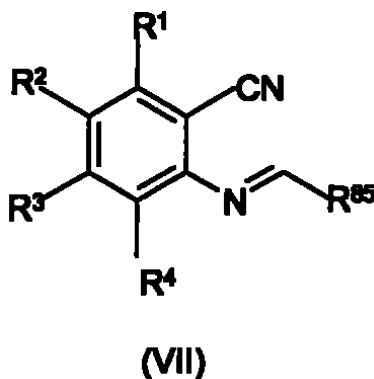
Table 12



Compound No.	R''
300	H
301	COOCH ₂ CH ₃

Other compounds of formula (I), in particular those in which R⁵ carries a carboxy or carboxyl ester substituent are described below in the Examples.

Compounds of formula (I) may be prepared by various methods which would be apparent from the literature. For example compounds of formula (I) where X is NH may be prepared by reacting a compound of formula (VII)



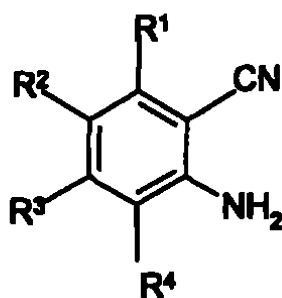
where R¹, R², R³, and R⁴ are as defined in relation to formula (I) and R⁶⁵ is a group NR⁶⁶R⁶⁷ where R⁶⁶ and R⁶⁷ are independently selected from alkyl such as methyl, with a compound of formula (VIII)



where R⁵ is a group R⁵ as defined in relation to formula (I) or a precursor group thereof; and thereafter if desired or necessary, converting a precursor group R⁵ to a group R⁵ and/or modifying substituents on the group R⁵. The reaction is suitably effected in an organic solvent such as an acetic acid at elevated temperatures, conveniently at the reflux temperature of the solvent.

Examples of reactions in which a precursor group R⁵ is converted to a group R⁵ and/or substituents on the group R⁵ are modified are standard chemical reactions, such as conversion of esters to acids, and thereafter, if required to the preferred amides. Examples of such reactions are provided hereinafter.

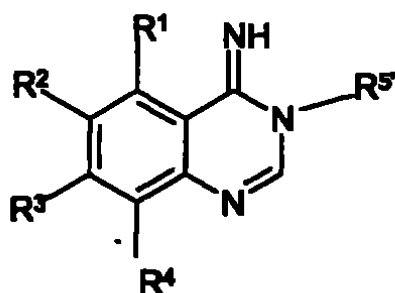
Compounds of formula (VII) are suitably prepared by reacting a compound of formula (IX)



(IX)

with an appropriate acetal such as N,N-dimethylformamide dimethyl acetal. The reaction is
 5 suitably effected in an organic solvent such as benzene, at elevated temperature, conveniently at the reflux temperature of the solvent.

Alternatively, compounds of formula (I) where X is NH may be prepared by rearranging a compound of formula (X)



(X)

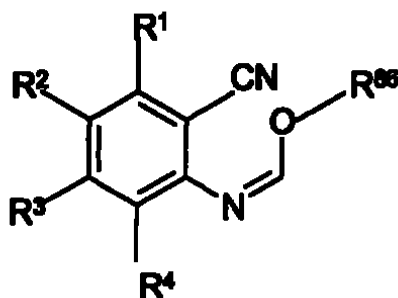
where R¹, R², R³ and R⁴ are as defined in relation to formula (I) and R⁵ is as defined in
 relation to formula (VIII) above, and thereafter if desired or necessary, converting a precursor
 15 group R⁵ to a group R⁵ and/or modifying substituents on the group R⁵, for example as described generally above.

The rearrangement reaction is suitably effected in an organic solvent such as an alkyl alcohol, in particular methanol, ethanol or cyclohexanol, acetic acid, or dimethylformamide, using a strong base such as sodium hydroxide, sodium acetate, sodium methylate, or
 20 dimethylamine. Elevated temperatures, for example of from 20°-120°C and preferably at about 75°C are employed.

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Compounds of formula (X) are suitably obtained by reacting a compound of formula (XI)



(XI)

where R^1 , R^2 , R^3 and R^4 are as defined in relation to formula (I) and R^6 is an alkyl group such as methyl; with a compound of formula (XII)

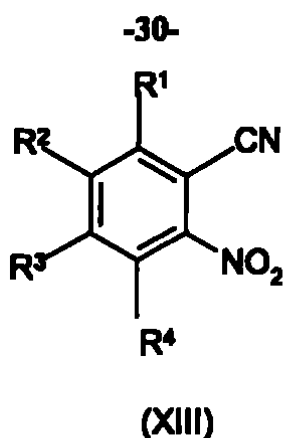


(XII)

where R^5 is as defined in relation to formula (VIII). The reaction is suitably effected in an organic solvent such as methylene chloride, in the presence of a salt such as pyridinium hydrochloride. Moderate temperatures for example of from 0°-50°C and conveniently ambient temperature are employed.

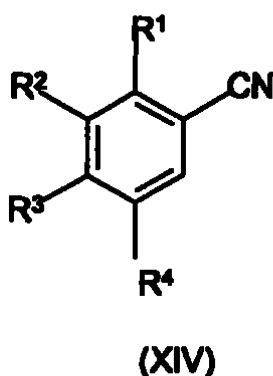
Compounds of formula (XI) are suitably prepared by reacting a compound of formula (IX) as defined above, with a trialkylorthoformate such as trimethylorthoformate. The reaction is suitably effected at elevated temperature, for example of from 50°C to 120°C, and preferably at about 100°C, in the presence of a catalytic amount of an acid such as p-toluene sulphonic acid.

Compounds of formula (IX) are either known compounds or they can be prepared by conventional methods. In particular, compounds of formula (IX) may be prepared by reduction of the corresponding nitro compound of formula (XIII)



where R^1 , R^2 , R^3 and R^4 are as defined in relation to formula (I). Suitable reaction conditions are illustrated hereinafter.

5 Compounds of formula (XIII) may be obtained by nitration of a compound of formula (XIV)



for example, using nitric acid as the nitrating agent. Again, suitable reaction conditions are
10 illustrated hereinafter.

The nitrile of formula (XIV) may be derived by reaction of the corresponding formamide with hydroxylamine as illustrated hereinafter.

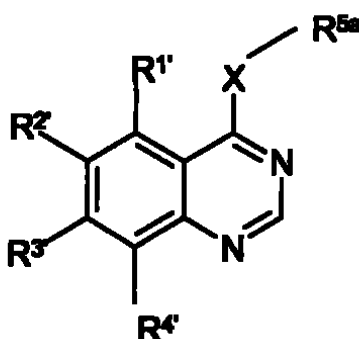
Compounds of formula (I) are inhibitors of aurora 2 kinase. As a result, these compounds can be used to treat disease mediated by these agents, in particular proliferative
15 disease.

According to a further aspect of the present invention there is provided a method for inhibiting aurora 2 kinase 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 an *in vivo* hydrolysable ester thereof.

20 Certain compounds of formula (I) are novel and these form a further aspect of the invention. Thus the invention further comprises a compound of formula (IA)

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(IA)

5

or a salt, ester or amide thereof;

where X is as defined in relation to formula (I);

R^{1'}, R^{2'}, R^{3'}, R^{4'} are equivalent to R¹, R², R³, R⁴ as defined in relation to formula (I) and R^{5a} is an optionally substituted 5-membered heteroaromatic ring, subject to the following provisos:

- 10 (i) that where R^{5a} is a pyrazole group, it carries a substituent of formula (k), (II) of (VI) above,
 (ii) that where X is NH and R^{5a} is a substituted pyrazolone or tetrazolyl group, at least one of R^{1'}, R^{2'}, R^{3'} and R^{4'} is other than hydrogen; or
 (iii) that where X is O and R^{5a} is 1-methyl-4-nitro-1H-imidazol-5-yl, at least one of R^{1'}, R^{2'}, R^{3'} and R^{4'} is other than hydrogen.

- 15 Preferably at least one of R^{1'}, R^{2'}, R^{3'} and R^{4'} is other than hydrogen.

Suitably R^{5a} is selected from the groups of sub-formulae (a)-(j) as set out above.

Preferably R^{5a} is pyrrole, imidazole, triazole, thiazole, thiophene, or thiadiazole, any of which may be optionally substituted.

In particular, R^{5a} is substituted by at least one group of formula (k), (II) of (VI) above.

- 20 Other preferred or particular groups and substituents in formula (IA) are as set out for the equivalent groups in formula (I) above.

According to a further aspect of the invention there is provided a compound of the formula (IA) as defined herein, or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, for use in a method of treatment of the human or animal body by
 25 therapy. In particular, the compounds are used in methods of treatment of proliferative disease such as cancer and in particular cancers such as colorectal or breast cancer where aurora 2 is upregulated.

The invention also provides a pharmaceutical composition comprising a compound of formula (IA) as defined herein, or a pharmaceutically acceptable salt, or an *in vivo* hydrolysable ester thereof, in combination with a pharmaceutically acceptable carrier.

Preferred or particular compounds of formula (IA) for use in the compositions of the invention are as described above in relation to preferred compounds of formula (I).

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert-diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal track, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose,

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methycellulose, hydroxypropylmethycellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxyethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example
5 heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or
10 condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

15 Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved
20 by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional
25 excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum
30 tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene

sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent,
5 preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable
10 solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Suppository formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients
15 include, for example, cocoa butter and polyethylene glycols.

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedure well known in the art.

20 Compositions for administration by insufflation may be in the form of a finely divided powder containing particles of average diameter of, for example, 30 μ or much less, the powder itself comprising either active ingredient alone or diluted with one or more physiologically acceptable carriers such as lactose. The powder for insufflation is then conveniently retained in a capsule containing, for example, 1 to 50mg of active ingredient for
25 use with a turbo-inhaler device, such as is used for insufflation of the known agent sodium cromoglycate.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile
30 fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

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For further information on Formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

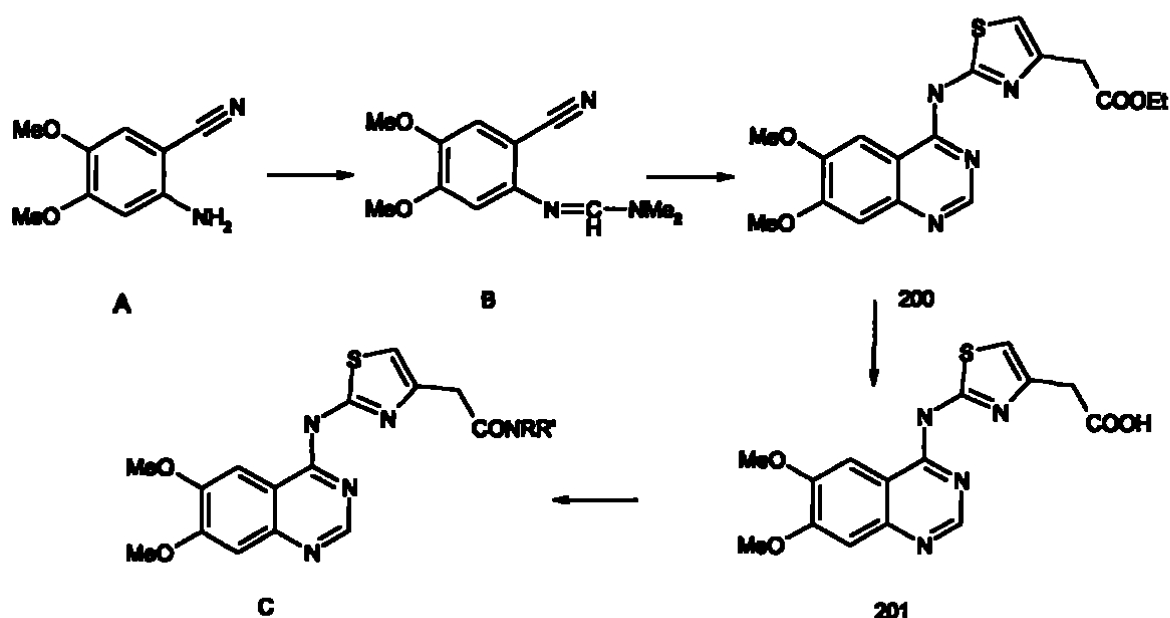
The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine. As mentioned above, compounds of the Formula I are useful in treating diseases or medical conditions which are due alone or in part to the effects of aurora 2 kinase.

In using a compound of the Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.5 mg to 75 mg per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.5 mg to 25 mg per kg body weight will be used. Oral administration is however preferred.

A further aspect of the invention comprises a compound of formula (I) as defined above, or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, for use in the preparation of a medicament for the treatment of proliferative disease. Preferred compounds of formula (I) for this purpose are as described above.

The following Examples illustrate the invention.

General Scheme 1**5 Compound B**

The amino nitrile A (534 mg, 3 mmol) in benzene (15 ml) was reacted with N,N-dimethylformamide dimethyl acetal (535 mg, 4.5 mmol) at 90°C, in a Dean Stark equipped flask. After 4.5 hours reflux, the solution was concentrated, and the residual oil triturated with ether to give the title compound as a solid (680 mg, 90 %).

10 ¹H NMR (CDCl₃) : 3.08 (s, 6H) ; 3.86 (s, 3H) ; 3.91 (s, 3H) ; 6.48 (s, 1H) ; 6.94 (s, 1H) ; 7.58 (s, 1H).

MS ES⁺ : 234 (M,H)⁺

Compound 200

15 A mixture of amidine B (1.4 g, 6 mmol), ethyl 2-amino-4-thiazoleacetate (1.4 g, 7.5 mmol) in acetic acid (14 ml) was heated at 130°C for 3 hours. The solvent was removed under vacuum, the residue was triturated in ethanol (5 ml) and a solution of NaHCO₃ (pH 8) for 10 minutes. The solid was recovered by filtration, washed with water, dissolved in CH₂Cl₂, and dried over MgSO₄. CH₂Cl₂ was evaporated, the residual oil treated with ether and pet. ether to give title
20 compound (1.8 g, 80 %).

¹H NMR (DMSO-d₆) : 1.2 (t, 3H) ; 3.74 (s, 2H) ; 3.95 (s, 6H) ; 4.1 (q, 2H) ; 7.02 (s, 1H) ; 7.26 (s, 1H) ; 8.14 (s, 1H) ; 8.68 (s, 1H).

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2**Compound 201**

Ester 200 (1.8 g, 4.8 mmol) was reacted with 2N NaOH (4.8 ml, 9.6 mmol) in ethanol (20 ml) at room temperature for 2 hours. The mixture was cooled to room temperature, acidified with EtOH, HCl (2N) to pH 3. Stirring was carried on for 15 minutes, and a yellow solid of title compound was recovered by filtration (1.7 g, 100 %).

¹HNMR (DMSO-d₆) : 3.71 (s, 2H) ; 3.96 (s, 3H) ; 3.97 (s, 3H) ; 7.11 (s, 1H) ; 7.28 (s, 1H) ; 8.3 (brs, 1H) ; 8.88 (s, 1H).

10 Synthesis of amide 5, general procedure

The acid 201 (86.5 mg, 0.25 mmol) in DMF (1 ml) was reacted with various amines (2.6 mmol) in presence of O-(7-azabenzotriazol-1-yl) N,N,N',N'-tetramethyluronium hexafluorophosphate (98 mg, 0.26 mmol), DIEA (33 mg, 0.26 mmol) at room temperature for 0.5 hour. A solution of NaHCO₃ (1 ml) and water (7 ml) was added to the mixture. The mixture was left overnight, and the precipitated solid was then recovered by filtration, washed with water and dried under vacuum in presence of P₂O₅, to give compounds of formula C as listed below.

Example 1

20 Using the reaction described in the General Scheme 1, starting with 4-aminomethyl pyridine (27 mg, 0.25 mmol) yielded Compound No. 1 in Table 1 (50 mg, 46 %).

¹HNMR (DMSO-d₆) : 3.64 (s, 2H) ; 3.95 (s, 3H) ; 3.96 (s, 3H) ; 4.32 (d, 2H) ; 6.98 (s, 1H) ; 7.26 (m, 3H) ; 8.15 (s, 1H) ; 8.49 (m, 3H) ; 8.68 (s, 1H).

Example 2

25 An analogous reaction to that described in the General Scheme 1, starting with morpholine (23 mg, 0.26 mmol) yielded Compound No 2 in Table 1 (70 mg, 67 %).

¹HNMR (DMSO-d₆, TFA) : 3.55 (br m, 8H) ; 3.88 (s, 2H) ; 3.97 (s, 3H) ; 4.0 (s, 3H) ; 7.15 (s, 1H) ; 7.27 (s, 1H) ; 7.92 (s, 1H) ; 9.07 (s, 1H).

30 Example 3

An analogous reaction to that described in the General Scheme 1, starting with 4-fluoroaniline (29 mg, 0.26 mmol) yielded the Compound No. 3 in Table 1 (75 mg, 68 %).

¹H NMR (DMSO-d₆) : 3.74 (s, 2H) ; 3.93 (s, 6H) ; 7.00 (s, 1H) ; 7.15 (t, 2H) ; 7.25 (s, 1H) ; 7.64 (m, 2H) ; 8.12 (s, 1H) ; 8.67 (s, 1H) ; 10.20 (s, 1H).

MS ES⁺ : 440 (M₁H)⁺

5 Example 4

An analogous reaction to that described in the General Scheme 1, starting with N,N-dimethyl-1,4-phenylenediamine (35 mg, 0.26 mmol) yielded Compound 4 in Table 1 (65 mg, 56 %).

¹H NMR (DMSO-d₆, TFA) : 3.2 (s, 6H) ; 3.9 (s, 2H) ; 3.97 (s, 3H) ; 4.0 (s, 3H) ; 7.27 (s, 1H) ; 7.3 (s, 1H) ; 7.65 (d, 2H) ; 7.8 (d, 2H) ; 7.99 (s, 1H).

10 MS ES⁺ : 465 (M₁H)⁺

Example 5

An analogous reaction to that described in the General Scheme 1, starting with 4-methoxyaniline (32 mg, 0.26 mmol) yielded Compound 5 in Table 1 (80 mg, 71 %).

15 ¹H NMR (DMSO-d₆) : 3.71 (s, 5H) ; 3.93 (s, 3H) ; 3.94 (s, 3H) ; 6.88 (d, 2H) ; 6.99 (s, 1H) ; 7.25 (s, 1H) ; 7.53 (d, 2H) ; 8.13 (s, 1H) ; 8.67 (s, 1H) ; 9.99 (s, 1H).

MS ES⁺ : 452 (M₁H)⁺

Example 6

20 An analogous reaction to that described in the General Scheme 1, starting with 5-methoxy-2-methylaniline (36 mg, 0.26 mmol) yielded Compound 6 in Table 1 (87 mg, 75 %).

¹H NMR (DMSO-d₆) : 2.13 (s, 3H) ; 3.69 (s, 3H) ; 3.81 (s, 2H) ; 3.96 (s, 6H) ; 6.65 (m, 1H) ; 7.05 (m, 1H) ; 7.09 (d, 1H) ; 7.21 (s, 1H) ; 7.26 (s, 1H) ; 8.13 (s, 1H) ; 8.68 (s, 1H) ; 9.3 (s, 1H).

25 MS ES⁺ : 466 (M₁H)⁺

Example 7

An analogous reaction to that described in the General Scheme 1, starting with aminoacetaldehyde dimethyl acetal (27 mg, 0.26 mmol) yielded Compound 7 in Table 1 (80
30 mg, 74 %).

¹H NMR (DMSO-d₆) : 3.2 (t, 2H) ; 3.29 (s, 3H) ; 3.31 (s, 3H) ; 3.55 (s, 2H) ; 3.94 (s, 6H) ; 4.37 (t, 1H) ; 6.92 (s, 1H) ; 7.26 (s, 1H) ; 8.02 (t, 1H) ; 8.14 (s, 1H) ; 8.67 (s, 1H).

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MS ES⁺ : 434 (M₁H)⁺

Example 8

An analogous reaction to that described in the General Scheme 1, starting with 3-

5 trifluoromethylaniline (42 mg, 0.26 mmol) yielded Compound 8 in Table 1 (72 mg, 59 %).

¹HNMR (DMSO-d₆) : 3.80 (s, 2H) ; 3.93 (s, 3H) ; 3.94 (s, 3H) ; 7.04 (s, 1H) ; 7.26 (s, 1H) ;
7.41 (d, 1H) ; 7.55 (t, 1H) ; 7.81 (d, 1H) ; 8.13 (s, 1H) ; 8.69 (s, 1H) ; 10.50 (s, 1H).

MS ES⁺ : 490 (M₁H)⁺

10 **Example 9**

An analogous reaction to that described in General Scheme 1, starting with N-

methylpiperazine (26 mg, 0.26 mmol) yielded Compound 9 in Table 1 (65 mg, 61 %).

¹HNMR (DMSO-d₆) : 2.73 and 2.77 (two t, 4H) ; 2.86 and 3.10 (two s, 3H) ; 3.56 and 3.74
(two t, 4H) ; 3.79 and 3.84 (two s, 2H) ; 3.95 (s, 6H) ; 6.95 (m, 1H) ; 7.26 (s, 1H) ; 8.14 (s,
15 1H) ; 8.68 (s, 1H).

MS ES⁺ : 429 (M₁H)⁺

Example 10

An analogous reaction to that described in General Scheme 1, starting with 2-

20 methoxyethylamine (20 mg, 0.26 mmol) yielded Compound 10 in Table 1 (68 mg, 67 %).

¹HNMR (DMSO-d₆) : 3.25 (s, 3H) ; 3.3 (m, 6H) ; 3.54 (s, 2H) ; 3.94 (s, 6H) ; 6.92 (s, 1H) ;
7.26 (s, 1H) ; 8.0 (t, 1H) ; 8.14 (s, 1H) ; 8.67 (s, 1H).

MS ES⁺ : 404 (M₁H)⁺

25 **Example 11**

An analogous reaction to that described in General Scheme 1, starting with 2-(2-aminoethyl)-

N-methylpyrrole (32 mg, 0.26 mmol) yielded Compound 11 in Table 1 (93 mg, 82 %).

¹HNMR (DMSO-d₆) : 3.3 (m, 4H) ; 3.5 (s, 2H) ; 3.94 (s, 6H) ; 5.78 (s, 1H) ; 5.84 (m, 1H) ;
6.58 (s, 1H) ; 6.89 (s, 1H) ; 7.24 (s, 1H) ; 8.01 (t, 1H) ; 8.13 (s, 1H) ; 8.66 (s, 1H).

30 MS ES⁺ : 453 (M₁H)⁺

Example 12

An analogous reaction to that described in the General Scheme 1, starting with 3-(methylamino)propionitrile (22 mg, 0.26 mmol) yielded Compound 12 in Table 1 (60 mg, 58 %).

5 ¹HNMR (DMSO-d₆) : 2.15 (s, 3H) ; 3.45 (m, 4H) ; 3.77 (s, 2H) ; 3.96 (s, 6H) ; 6.91 (s, 1H) ; 7.25 (s, 1H) ; 8.14 (s, 1H) ; 8.67 (s, 1H).

MS ES⁺ : 413 (M₁H)⁺

Example 13

10 An analogous reaction to that described in General Scheme 1, starting with 4-fluorobenzylamine (33 mg, 0.26 mmol) yielded Compound 13 in Table 1 (81 mg, 81 %).

¹HNMR (DMSO-d₆) : 3.59 (s, 2H) ; 3.95 (m, 6H) ; 4.27 (d, 2H) ; 6.94 (s, 1H) ; 7.15 (m, 2H) ; 7.26 (s, 1H) ; 7.31 (m, 2H) ; 7.95 (s, 1H) ; 8.14 (s, 1H) ; 8.41 (t, 1H) ; 8.67 (s, 1H).

MS ES⁺: 454 (M₁H)⁺

15 **Example 14**

An analogous reaction to that described in General Scheme 1, starting with 4-hydroxypiperidine (26 mg, 0.26 mmol) yielded Compound 14 in Table 1 (86 mg, 80 %).

¹HNMR (DMSO-d₆) : 1.21 (m, 2H) ; 1.65 (m, 2H) ; 3.02 (m, 1H) ; 3.16 (m, 1H) ; 3.65 (m, 1H) ; 3.78 (m, 3H) ; 4.71 (d, 1H) ; 6.91 (s, 1H) ; 7.26 (s, 1H) ; 8.14 (s, 1H) ; 9.67 (s, 1H).

20 MS ES⁺ : 430 (M₁H)⁺

Example 15

An analogous reaction to that described in General Scheme 1, starting with 3-aminoacetophenone (35 mg, 0.26 mmol) yielded Compound 15 in Table 1 (92 mg, 79 %).

25 ¹HNMR (DMSO-d₆) : 2.59 (s, 3H) ; 3.78 (s, 2H) ; 3.90 (s, 3H) ; 3.93 (s, 3H) ; 7.02 (s, 1H) ; 7.26 (s, 1H) ; 7.47 (t, 1H) ; 7.67 (d, 1H) ; 7.89 (d, 1H) ; 8.12 (s, 1H) ; 8.2 (s, 1H) ; 8.68 (s, 1H) ; 10.36 (s, 1H).

MS ES⁺ : 464 (M₁H)⁺.

30 **Example 16**

An analogous reaction to that described in General Scheme 1, starting with 3,5-difluoroaniline (34 mg, 0.26 mmol) yielded Compound 16 in Table 1 (71 mg, 64 %).

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¹HNMR (DMSO-d₆, TFA) : 3.90 (s, 2H) ; 3.93 (s, 3H) ; 3.97 (s, 3H) ; 6.89 (m, 1H) ; 7.27 (s, 1H) ; 7.29 (s, 1H) ; 7.35 (m, 2H) ; 7.96 (m, 1H) ; 9.10 (s, 1H).

MS ES⁺ : 458 (M₁H)⁺

5 Example 17

An analogous reaction to that described in General Scheme 1, starting with 3-cyanoaniline (31 mg, 0.26 mmol) yielded Compound 17 in Table 1(90 mg, 84 %).

MS ES⁺ : 447 (M₁H)⁺

10 Example 18

An analogous reaction to that described in General Scheme 1, starting with 2-fluoroaniline (29 mg, 0.26 mmol) yielded Compound 18 in Table 1(86 mg, 82 %).

MS ES⁺ : 440 (M₁H)⁺

Example 19

15 An analogous reaction to that described in General Scheme 1, starting with 3-(1-hydroxyethyl)aniline (36 mg, 0.26 mmol) yielded Compound 19 in Table 1(92 mg, 82 %).

MS ES⁺ : 466 (M₁H)⁺

Example 20

20 An analogous reaction to that described in General Scheme 1, starting with 2,3-difluoroaniline (34 mg, 0.26 mmol) yielded Compound 20 in Table 1(51 mg, 47 %).

¹HNMR (DMSO-d₆, TFA) : 3.98 (s, 3H) ; 4.01 (s, 3H) ; 4.03 (s, 2H) ; 7.19 (m, 2H) ; 7.27 (s, 1H) ; 7.29 (s, 1H) ; 7.73 (m, 1H) ; 7.99 (s, 1H) ; 9.11 (s, 1H).

MS ES⁺ : 458 (M₁H)⁺

25

Example 21

An analogous reaction to that described in General Scheme 1, starting with 2-methyl-4-fluoroaniline (33 mg, 0.26 mmol) yielded Compound 21 in Table 1(94 mg, 86 %).

MS ES⁺ : 454 (M₁H)⁺

30

Example 22

An analogous reaction to that described in General Scheme 1, starting with 2-fluoro-3-chloroaniline (38 mg, 0.26 mmol) yielded Compound 22 in Table 1(60 mg, 53 %).

¹HNMR (DMSO-d₆, TFA) : 3.95 (s, 3H) ; 3.98 (s, 3H) ; 4.01 (s, 2H) ; 7.20 (m, 1H) ; 7.24 (s, 1H) ; 7.26 (s, 1H) ; 7.31 (m, 1H) ; 7.88 (m, 1H) ; 7.96 (s, 1H) ; 9.08 (s, 1H).

MS ES⁺ : 474 (M₂H)⁺

Example 23

An analogous reaction to that described in General Scheme 1, starting with 2,5-difluoroaniline (34 mg, 0.26 mmol) yielded Compound 23 in Table 1(52 mg, 48 %).

¹HNMR (DMSO-d₆, TFA) : 3.97 (s, 3H) ; 4.00 (s, 2H) ; 4.01 (s, 3H) ; 6.97 (m, 1H) ; 7.26 (s, 1H) ; 7.29 (s, 1H) ; 7.33 (m, 1H) ; 7.94 (m, 1H) ; 7.98 (s, 1H) ; 9.11 (s, 1H).

MS ES⁺ : 458(M₂H)⁺

Example 24

An analogous reaction to that described in General Scheme 1, starting with 3-aminobenzamide (36 mg, 0.26 mmol) yielded Compound 24 in Table 1(94 mg, 84 %).

MS ES⁺ : 465 (M₂H)⁺

Example 25

An analogous reaction to that described in General Scheme 1, starting with 4-aminophenol (29 mg, 0.26 mmol) yielded Compound 25 in Table 1(89 mg, 84 %).

¹HNMR (DMSO-d₆, TFA) : 3.81 (s, 2H) ; 3.97 (s, 3H) ; 4.00 (s, 3H) ; 6.71 (d, 2H) ; 7.23 (s, 1H) ; 7.27 (s, 1H) ; 7.40 (d, 2H) ; 7.95 (s, 1H) ; 9.09 (s, 1H).

MS ES⁺ : 438 (M₂H)⁺

Example 26

An analogous reaction to that described in General Scheme 1, starting with 2-fluoro-5-methylaniline (33 mg, 0.26 mmol) yielded Compound 26 in Table 1(88 mg, 81 %).

MS ES⁺ : 454 (M₂H)⁺

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2**Example 27**

An analogous reaction to that described in General Scheme 1, starting with 2-bromo-4-fluoroaniline (50 mg, 0.26 mmol) yielded Compound 27 in Table 1 (68 mg, 55 %).

¹H NMR (DMSO-d₆, TFA) : 3.89 (s, 2H) ; 3.94 (s, 3H) ; 3.97 (s, 3H) ; 7.21 (m, 1H) ; 7.25 (s, 1H) ; 7.6 (s, 1H) ; 7.61 (m, 1H) ; 7.92 (m, 1H) ; 7.95 (s, 1H) ; 9.07 (s, 1H).

MS ES⁺ : 518, 520 (M₂H)⁺

Example 28

An analogous reaction to that described in General Scheme 1, starting with 3,4-difluoroaniline (34 mg, 0.26 mmol) yielded Compound 28 in Table 1 (81 mg, 74 %).

MS ES⁺ : 458 (M₂H)⁺

Example 29

An analogous reaction to that described in General Scheme 1, starting with isonipecotamide (34 mg, 0.26 mmol) yielded Compound 29 in Table 1 (96 mg, 88 %).

MS ES⁺ : 457 (M₂H)⁺

Example 30

An analogous reaction to that described in General Scheme 1, starting with 4-trifluoromethoxyaniline (47 mg, 0.26 mmol) yielded Compound 30 in Table 1 (105 mg, 87 %).

MS ES⁺ : 506 (M₂H)⁺

Example 31

An analogous reaction to that described in General Scheme 1, starting with 5-amino-2-methoxypyridine (33 mg, 0.26 mmol) yielded Compound 31 in Table 1 (86 mg, 79 %).

MS ES⁺ : 453 (M₂H)⁺

Example 32

An analogous reaction to that described in General Scheme 1, starting with 2,4-difluoroaniline (34 mg, 0.26 mmol) yielded Compound 32 in Table 1 (81 mg, 74 %).

MS ES⁺ : 458 (M₂H)⁺

Example 33

An analogous reaction to that described in General Scheme 1, starting with 4-aminoresorcinol hydrochloride (43 mg, 0.26 mmol) yielded Compound 33 in Table 1 (84 mg, 77 %).

MS ES⁺ : 454 (M₂H)⁺

5

Example 34

An analogous reaction to that described in General Scheme 1, starting with 3-aminopyridine (25 mg, 0.26 mmol) yielded Compound 34 in Table 1 (101 mg, 100 %).

MS ES⁺ : 423 (M₂H)⁺

10

Example 35

An analogous reaction to that described in General Scheme 1, starting with 4-chloroaniline (34 mg, 0.26 mmol) yielded Compound 35 in Table 1 (109 mg, 100 %).

MS ES⁺ : 456, 458 (M₂H)⁺.

15

Example 36

An analogous reaction to that described in General Scheme 1, starting with pyrrolidine (19 mg, 0.26 mmol) yielded Compound 36 in Table 1 (33 mg, 35 %).

20 MS ES⁺ : 400 (M₂H)⁺

Example 37

An analogous reaction to that described in General Scheme 1, starting with 3-methoxyaniline (33 mg, 0.26 mmol) yielded Compound 37 in Table 1 (94 mg, 87 %).

25 ¹H NMR (DMSO-d₆, TFA) : 3.72 (s, 3H) ; 3.87 (s, 2H) ; 3.96 (s, 3H) ; 4.0 (s, 3H) ; 6.64 (m, 1H) ; 7.14 (d, 1H) ; 7.21 (d, 1H) ; 7.22 (s, 1H) ; 7.24 (s, 1H) ; 7.27 (s, 1H) ; 7.95 (s, 1H) ; 9.09 (s, 1H).

MS ES⁺ : 452 (M₂H)⁺

Example 38

30 An analogous reaction to that described in General Scheme 1, starting with 3-hydroxy-4-methoxyaniline (37 mg, 0.26 mmol) yielded Compound 38 in Table 1 (95 mg, 85 %).

MS ES⁺ : 468 (M₂H)⁺

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Example 39

An analogous reaction to that described in General Scheme 1, starting with 3-nitroaniline (36 mg, 0.26 mmol) yielded Compound 39 in Table 1 (87 mg, 78 %).

MS ES⁺ : 467 (M,H)⁺

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Example 40

An analogous reaction to that described in General Scheme 1, starting with 1-methyl-3-nitroaniline (40 mg, 0.26 mmol) yielded Compound 40 in Table 1 (50 mg, 44 %).

MS ES⁺ : 481 (M,H)⁺

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Example 41

An analogous reaction to that described in General Scheme 1, starting with 2-anilinoethanol (36 mg, 0.26 mmol) yielded Compound 41 in Table 1 (45 mg, 41 %).

MS ES⁺ : 466 (M,H)⁺

15 **Example 42**

An analogous reaction to that described in General Scheme 1, starting with 4-trifluoromethylaniline (43 mg, 0.26 mmol) yielded Compound 42 in Table 1 (86 mg, 73 %).

MS ES⁺ : 490 (M,H)⁺

20 **Example 43**

An analogous reaction to that described in General Scheme 1, starting with 3-amino-6-chloropyridine (33 mg, 0.26 mmol) yielded Compound 43 in Table 1 (90 mg, 82 %).

¹H NMR (DMSO-d₆, TFA) : 3.92 (s, 2H) ; 3.96 (s, 3H) ; 4.0 (s, 3H) ; 7.27 (s, 1H) ; 7.28 (s, 1H) ; 7.46 (d, 1H) ; 7.98 (s, 1H) ; 8.1 (d, 1H) ; 8.65 (d, 1H) ; 9.1 (s, 1H).

25 MS ES⁺ : 457, 459 (M,H)⁺**Example 44**

An analogous reaction to that described in General Scheme 1, starting with 2-methoxy-5-chloroaniline (42 mg, 0.26 mmol) yielded Compound 44 in Table 1 (90 mg, 77 %).

30 MS ES⁺ : 486, 488 (M,H)⁺

Example 45

An analogous reaction to that described in General Scheme 1, starting with 2-methylaminoethanol (20 mg, 0.26 mmol) yielded Compound 45 in Table 1 (83 mg, 86 %).

MS ES⁺ : 404 (M₂H)⁺

5

Example 46

An analogous reaction to that described in General Scheme 1, starting with 4-aminopyridine (25 mg, 0.26 mmol) yielded Compound 46 in Table 1 (101 mg, 100 %).

MS ES⁺ : 423 (M₂H)⁺

10 **Example 47**

An analogous reaction to that described in General Scheme 1, starting with 3-methyl-4-bromoaniline (49 mg, 0.26 mmol) yielded Compound 47 in Table 1 (120 mg, 97 %).

MS ES⁺ : 516, 517 (M₂H)⁺

15 **Example 48**

An analogous reaction to that described in General Scheme 1, starting with 2-chloro-5-methoxyaniline (42 mg, 0.26 mmol) yielded Compound 48 in Table 1 (65 mg, 56 %).

¹HNMR (DMSO-d₆, TFA) : 3.73 (s, 2H) ; 3.98 (m, 9H) ; 6.78 (m, 1H) ; 7.28 (s, 2H) ; 7.39 (d, 1H) ; 7.50 (d, 1H) ; 7.98 (s, 1H) ; 9.10 (s, 1H);

20 MS ES⁺ : 486, 488 (M₂H)⁺**Example 49**

An analogous reaction to that described in General Scheme 1, starting with 4-aminotoluene (28 mg, 0.26 mmol) yielded Compound 49 in Table 1 (89 mg, 85 %).

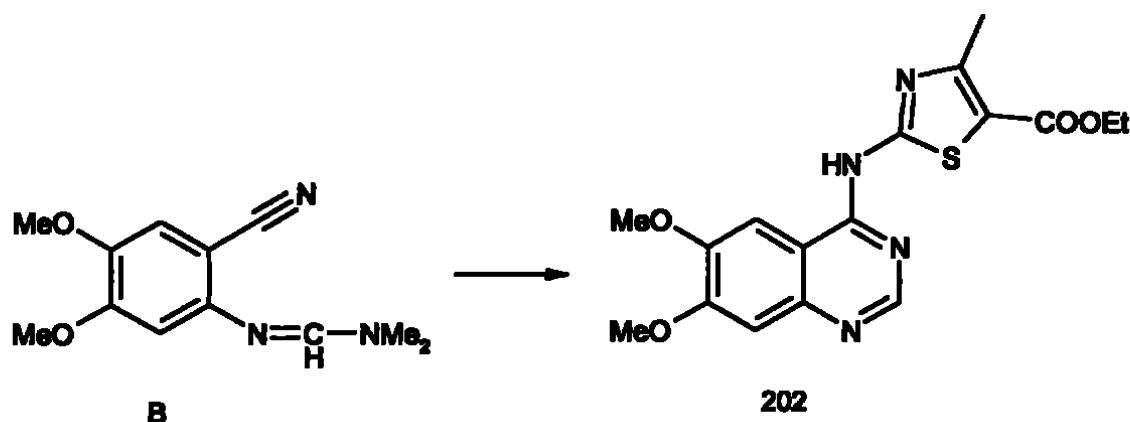
25 MS ES⁺ : 436 (M₂H)⁺**Example 50**

An analogous reaction to that described in General Scheme 1, starting with R(-)-2-pyrrolidinemethanol (27 mg, 0.26 mmol) yielded Compound 50 in Table 1 (81 mg, 78 %).

30 MS ES⁺ : 430 (M₂H)⁺

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Example 50A**Preparation of Compound 202**

5 Amidine B (117 mg, 0.5 mmol) in acetic acid (12 ml) was reacted with ethyl-2-amino-4-methylthiazol-5-carboxylate (112 mg, 0.6 mmol) at 130°C for 3 hours. The solvent was evaporated, the residue was taken up into ethanol, and stirred for 10 minutes with a solution of NaHCO₃. The solid was recovered by filtration, washed with water, ether and dried under vacuum, to give title compound as a yellow solid (157 mg, 84 %).

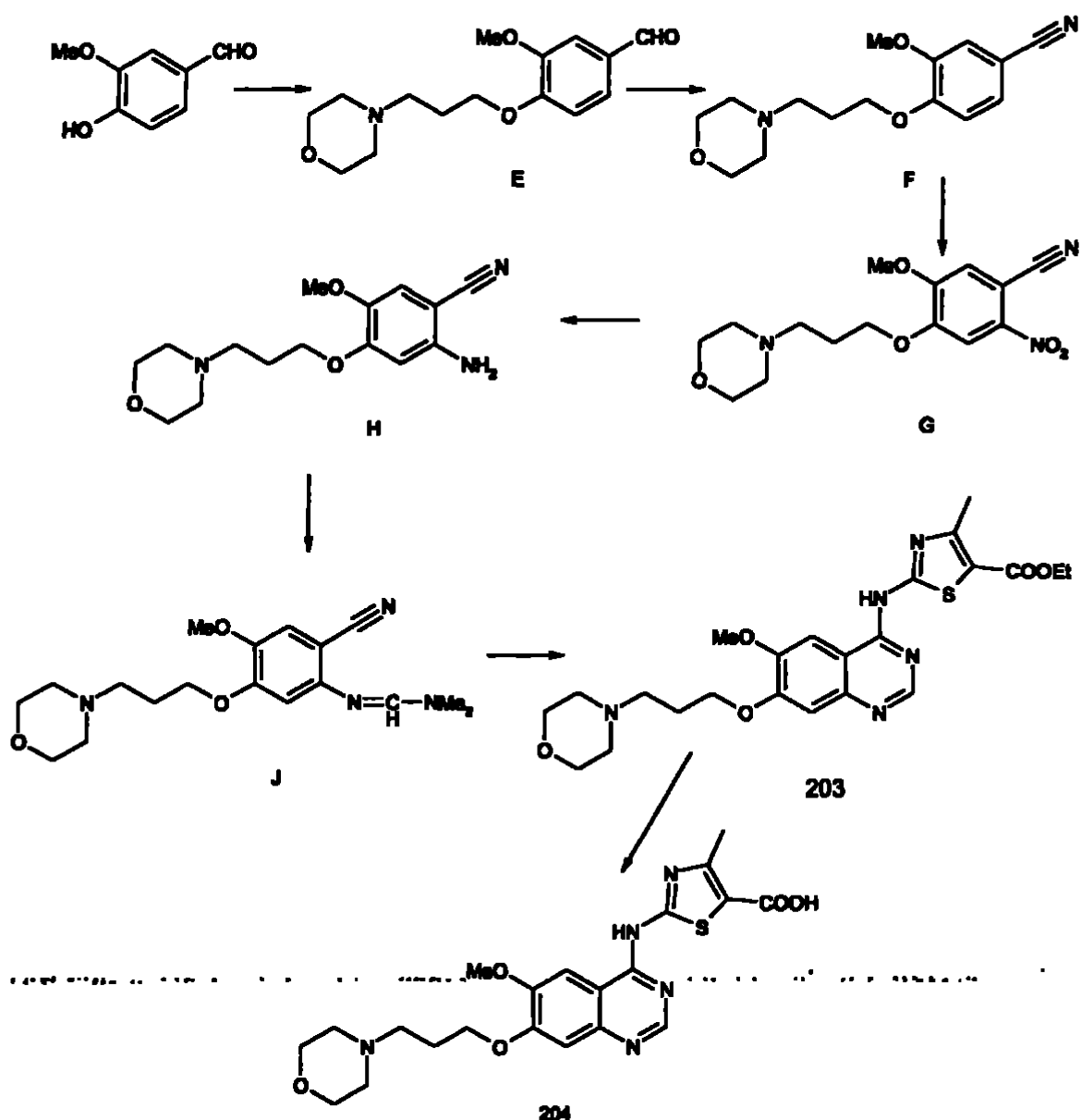
10 ¹HNMR (DMSO-d₆) : 1.31 (t, 3H) ; 2.6 (s, 3H) ; 3.96 (s, 6H) ; 4.27 (q, 2H) ; 7.28 (s, 1H) ; 8.11 (s, 1H) ; 8.77 (s, 1H).

MS ES⁺ : 375 (M₁H)⁺

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General Scheme 2

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Compound E

Vanilline (30.4 g, 0.2 mol) was solubilized in DMF (200 ml) in presence of K_2CO_3 at 50°C. N-(3-chloropropyl)morpholine was slowly added over 30 minutes to this mixture, which was heated over night at 80°C. Formed KCl was removed by filtration, the solvent was

10 evaporated, and the residual orange oil dissolved in AcOEt, washed with water 2x, dried over $MgSO_4$, filtered and concentrated. The residual oil crystallises to give title compound as a white solid (45.6 g, 82 %).

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¹HNMR (DMSO-d₆, TFA) : 2.22 (m, 2H) ; 3.13 (t, 2H) ; 3.32 (t, 2H) ; 3.52 (d, 2H) ; 3.67 (t, 2H) ; 3.84 (s, 3H) ; 4.02 (d, 2H) ; 4.18 (t, 2H) ; 7.20 (d, 1H) ; 7.43 (d, 1H) ; 7.58 (d, 1H) ; 9.90 (s, 1H).

MS ES⁺ : 280 (M_rH)⁺

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Compound E

The aldehyde E (5.6 g, 20 mmol) was added to a solution of sodium acetate (3.3 g, 40 mmol) and hydroxylamine hydrochloride (2.8 g, 40 mmol) in acetic acid (25 ml). The mixture was refluxed for 18 hours, cooled, diluted with water and extracted with methylene chloride, dried

10 over MgSO₄, filtered, concentrated, to give title compound (5.1 g, 93 %).

¹HNMR (DMSO-d₆, TFA) : 2.19 (m, 2H) ; 3.12 (t, 2H) ; 3.29 (t, 2H) ; 3.50 (d, 2H) ; 3.67 (t, 2H) ; 3.81 (s, 3H) ; 4.01 (d, 2H) ; 4.15 (t, 2H) ; 7.12 (d, 1H) ; 7.39 (s, 1H) ; 7.41 (d, 1H).

MS ES⁺ : 277 (M_rH)⁺

15 Compound G

The nitrile F (37.2 g, 135 mmol) in acetic acid (100 ml) was added to a solution of nitric acid (d = 1.42) 180 ml, at such a rate to maintain the temperature below 30°C. The mixture was stirred at room temperature over night. A solution of potassium hydroxide (10N, 370 ml) was then added slowly to the solution at 0° leading to a final pH of 11-12. The reaction was

20 extracted with CH₂Cl₂, the organic phases were dried over MgSO₄, filtered, evaporated to give a yellow solid which was washed with ether, dried to give title compound (22 g, 50 %).

¹HNMR (DMSO-d₆, TFA) : 2.2 (m, 2H) ; 3.13 (t, 2H) ; 3.3 (t, 2H) ; 3.53 (d, 2H) ; 3.67 (t, 2H) ; 3.99 (s, 3H) ; 4.01 (d, 2H) ; 4.31 (t, 2H) ; 7.74 (s, 1H) ; 7.90 (s, 1H).

25 Compound H

Compound G (21 g, 65 mmol) in solution in CH₂Cl₂ (250 ml), was reacted with sodium hydrosulfite (92 g, 458 mmol) in solution in water (250 ml) in presence of tetrabutyl ammonium chloride (12.7 g, 45.8 mmol) at room temperature, over night. Sodium hydroxide (2N) was then added, and the reaction mixture was extracted with CH₂Cl₂, the organic phase

30 was washed with water, dried over MgSO₄, filtered, evaporated. The residue was purified by silica gel chromatography, eluent : AcOEt / CH₂Cl₂ : 50/50 followed by MeOH / AcOEt / CH₂Cl₂ 5/45/50 to 20/30/50 to give title compound (12.5 g, 66 %).

¹HNMR (DMSO-d₆, TFA) : 2.2 (m, 2H) ; 3.13 (t, 2H) ; 3.31 (t, 2H) ; 3.53 (d, 2H) ; 3.68 (t, 2H) ; 3.71 (s, 3H) ; 4.05 (m, 4H) ; 6.56 (s, 1H) ; 7.02 (s, 1H).

MS ES⁺ : 292(M₁H)⁺

5 Compound I

The amino nitrile H (2.91 g, 10 mmol) in solution in toluene (50 ml) was reacted with N,N-dimethylformamide dimethyl acetal (1.79 g, 15 mmol), at 105°C for 5 hours, in a Dean Stark equipped flask. The solvent was evaporated, the residue triturated with ether to give title compound (3.4 g, 98 %).

10 ¹HNMR (DMSO-d₆) : 1.87 (m, 2H) ; 2.36 (m, 6H) ; 2.95 (s, 3H) ; 3.04 (s, 3H) ; 3.56 (t, 4H) ; 3.72 (s, 3H) ; 4.06 (t, 2H) ; 6.72 (s, 1H) ; 7.07 (s, 1H) ; 7.89 (s, 1H).

MS ES⁺ : 347 (M₁H)⁺

Compound 203

15 Amidine J (173 mg, 0.5 mmol) was dissolved in AcOH (1.7 ml) in presence of ethyl-2-amino-4-methyl thiazole-5-carboxylate (112 mg, 0.6 mmol) and heated at 130°C for 3 hours. The solvent was removed by evaporation, and the residual solid was stirred in ethanol and a diluted solution of NaHCO₃ for 10 minutes. The solid was washed with water, dried over P₂O₅ under vacuum, to give a yellow powder of title compound (170 mg, 70 %).

20 ¹HNMR (DMSO-d₆, TFA) : 1.32 (t, 3H) ; 2.30 (m, 2H) ; 2.68 (s, 3H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.99 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (m, 4H) ; 7.38 (s, 1H) ; 8.01 (s, 1H) ; 9.26 (s, 1H).

MS ES⁺ : 488 (M₁H)⁺

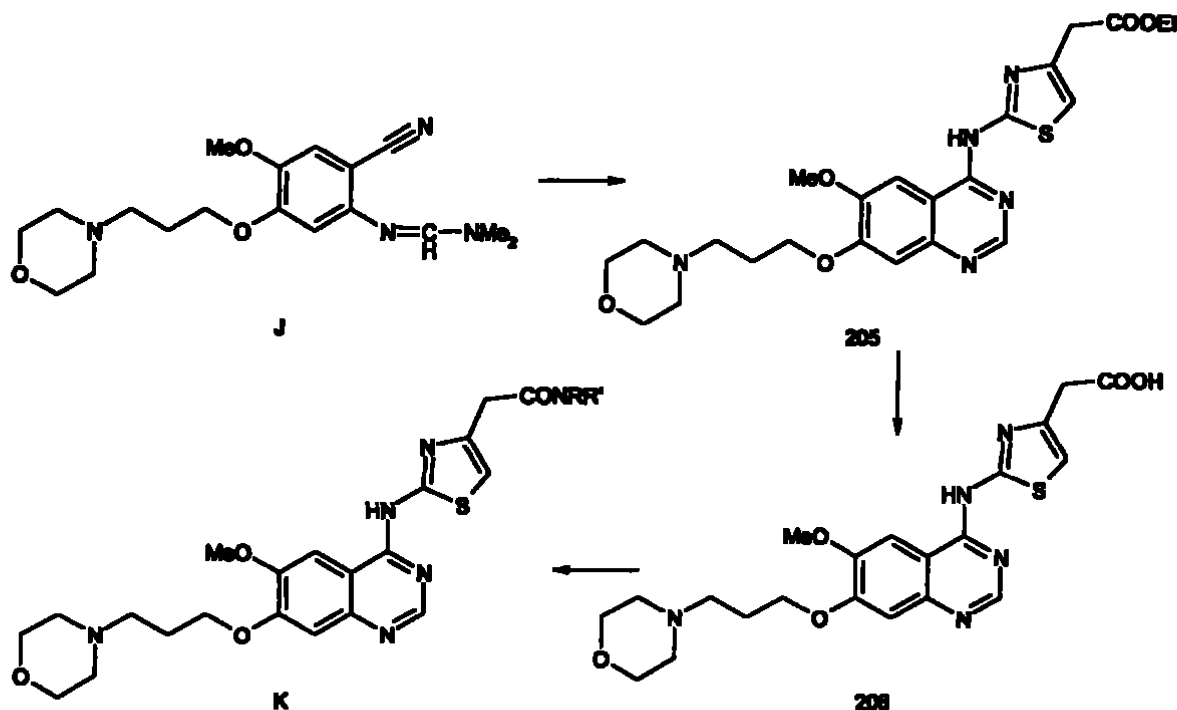
Compound 204

25 The ester 203 (122 mg, 0.25 mmol) was suspended in ethanol (5 ml) and reacted with sodium hydroxide (10N, 0.5 ml) at 80°C for 1 hour. The reaction mixture was cooled, acidified (pH 3.5), the yellow precipitate was filtered, washed with water, dried under vacuum, to give title compound (100 mg, 87 %).

30 ¹HNMR (DMSO-d₆, TFA) : 2.32 (m, 2H) ; 2.62 (s, 3H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.57 (d, 2H) ; 3.71 (t, 2H) ; 3.99 (s, 3H) ; 4.03 (d, 2H) ; 4.33 (t, 2H) ; 7.35 (s, 1H) ; 7.98 (s, 1H) ; 9.23 (s, 1H).

MS ES⁺ : 460 (M₁H)⁺

General Scheme 3

**Compound 205**

- 5 Amidine J (2.08 g, 6 mmol) was reacted with ethyl 2-amino-4-thiazolacetate (1.34 g, 7.2 mmol) in acetic acid (2 ml) at 130°C for 4 hours, under argon. The solvent was evaporated, the residual oil was triturated in ether / petr. ether, and the solid filtered. This solid was suspended in water at pH 9 (NaHCO₃) and extracted with CH₂Cl₂, dried, evaporated, to give title compound (2 g, 68 %).
- 10 ¹HNMR (DMSO-d₆, TFA) : 2.3 (m, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 3.87 (s, 2H) ; 4.0 (s, 3H) ; 4.04 (d, 2H) ; 4.15 (q, 2H) ; 4.31 (t, 2H) ; 7.28 (s, 1H) ; 7.34 (s, 1H) ; 8.06 (s, 1H) ; 9.15 (s, 1H).
- MS ES⁺ : 488 (M₀H)⁺

15 **Compound 206**

Ester 205 (2 g, 4.1 mmol) was suspended in ethanol (20 ml). 2N sodium hydroxide (4.1 ml, 8.2 mmol) was added to the suspension which was stirred for 3 hours at room temperature. HCl 2N was added to the solution, the yellow precipitate was filtered, washed with water, ethanol, ether and dried under vacuum, to give title compound (1.98 g, 99 %).

¹HNMR (DMSO-d₆, TFA) : 2.31 (m, 2H) ; 3.16 (t, 2H) ; 3.55 (d, 2H) ; 3.71 (t, 2H) ; 3.79 (s, 2H) ; 4.0 (s, 3H) ; 4.03 (d, 2H) ; 4.31 (t, 2H) ; 7.25 (s, 1H) ; 7.34 (s, 1H) ; 8.01 (s, 1H) ; 9.12 (s, 1H).

MS ES⁺ : 460 (M₁H)⁺

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Synthesis of amides K, general procedure

The acid 206 (83 mg, 0.17 mmol) in DMF (0.8 ml) was reacted with amine (0.17 mmol) in presence of O-(7-azabenzotriazol-1-yl) N,N,N',N'-tetramethyluronium hexafluorophosphate (78 mg, 0.204 mmol), DIEA (52 mg, 0.4 mmol), for 6 hours at room temperature. The reaction mixture was then treated with a solution of NaHCO₃ (6 ml) with stirring for 2 hours, washed with water, cooled to 5°C, and the solid filtered, triturated with ether, dried under vacuum over P₂O₅ to give title compounds.

Example 51

15 An analogous reaction to that described in General Scheme 3, starting with aniline (19 mg, 0.2 mmol) yielded Compound 51 in Table 2 (73 mg, 81 %).

¹HNMR (DMSO-d₆, TFA) : 2.29 (m, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.88 (s, 2H) ; 3.98 (s, 3H) ; 4.03 (d, 2H) ; 4.3 (t, 2H) ; 7.09 (t, 1H) ; 7.27 (s, 1H) ; 7.33 (m, 3H) ; 7.63 (d, 2H) ; 7.99 (s, 1H) ; 9.12 (s, 1H).

20 MS ES⁺ : 535 (M₁H)⁺.

Example 52

An analogous reaction to that described in General Scheme 3, starting with 4-fluoroaniline (23 mg, 0.2 mmol) yielded Compound 52 in Table 2 (79 mg, 84 %).

25 ¹HNMR (DMSO-d₆-TFA) : 2.29 (m, 2H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.67 (t, 2H) ; 3.87 (s, 2H) ; 3.98 (s, 3H) ; 4.02 (d, 2H) ; 4.3 (t, 2H) ; 7.17 (t, 2H) ; 7.27 (s, 1H) ; 7.32 (s, 1H) ; 7.63 (m, 2H) ; 7.99 (s, 1H) ; 9.11 (s, 1H).

MS ES⁺ : 553 (M₁H)⁺.

30 Example 53

An analogous reaction to that described in General Scheme 3, starting with 4-dimethylaminoaniline (28 mg, 0.2 mmol) yielded Compound 53 in Table 2 (52 mg, 53 %).

¹HNMR (DMSO-d₆-TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.19 (s, 6H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.91 (s, 2H) ; 3.98 (s, 3H) ; 4.03 (d, 2H) ; 4.30 (t, 2H) ; 7.28 (s, 1H) ; 7.33 (s, 1H) ; 7.64 (d, 1H) ; 7.77 (d, 1H) ; 8.01 (s, 1H) ; 9.12 (s, 1H).

MS ES⁺ : 578 (M₂H)⁺

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Example 54

An analogous reaction to that described in General Scheme 3, starting with 4-chloroaniline (26 mg, 0.2 mmol) yielded Compound 54 in Table 2(72 mg, 75 %).

¹HNMR (DMSO-d₆, TFA) : 2.31 (m, 2H) ; 3.14 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.89 (s, 2H) ; 3.98 (s, 3H) ; 4.03 (d, 2H) ; 4.3 (t, 2H) ; 7.27 (s, 1H) ; 7.32 (s, 1H) ; 7.38 (d, 1H) ; 7.65 (d, 1H) ; 8.0 (s, 1H) ; 9.12 (s, 1H).

MS ES⁺ : 567, 569 (M⁺H).

Example 55

15 An analogous reaction to that described in General Scheme 3, starting with 3-amino-6-chloropyridine (26 mg, 0.2 mmol) yielded Compound 55 in Table 2(80 mg, 83 %).

¹HNMR (DMSO-d₆, TFA) : 2.28 (m, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.93 (s, 2H) ; 3.98 (s, 3H) ; 4.04 (d, 2H) ; 4.3 (t, 2H) ; 7.29 (s, 1H) ; 7.33 (s, 1H) ; 7.49 (d, 1H) ; 8.01 (s, 1H) ; 8.09 (d, 1H) ; 8.66 (d, 1H) ; 9.13 (s, 1H).

20 MS ES⁺ : 570, 572 (M₂H)⁺.

Example 56

An analogous reaction to that described in General Scheme 3, starting with morpholine (18 mg, 0.2 mmol) yielded Compound 56 in Table 2(14 mg, 16 %).

25 ¹HNMR (DMSO-d₆, TFA) : 2.3 (m, 2H) ; 3.17 (t, 2H) ; 3.37 (t, 2H) ; 3.6 (m, 12H) ; 3.9 (s, 2H) ; 3.99 (s, 3H) ; 4.03 (d, 2H) ; 4.3 (t, 2H) ; 7.17 (s, 1H) ; 7.3 (s, 1H) ; 7.95 (s, 1H) ; 9.09 (s, 1H).

MS ES⁺ : 529 (M₂H)⁺

30 Example 57

An analogous reaction to that described in General Scheme 3, starting with pyrrolidine (14 mg, 0.2 mmol) yielded Compound 57 in Table 2(73 mg, 84 %).

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was extracted with CH_2Cl_2 , dried, and purified by silica gel chromatography, eluent CH_2Cl_2 / MeOH 98/2 $\rightarrow$ 90/10, to give title compound (0.738 g, 52 %).

$^1\text{H NMR}$ ($\text{DMSO}-d_6$, TFA) : 1.34 (t, 3H) ; 2.28 (m, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 4.03 (s, 3H) ; 4.04 (d, 2H) ; 4.34 (m, 4H) ; 7.45 (s, 1H) ; 8.33 (s, 1H) ; 8.44 (s, 1H) ; 9.26 (s, 1H).
MS ES^+ : 474 (M_nH)⁺

Compound 207

Ester 206 (946 mg, 2 mmol) in suspension in ethanol (20 ml) was treated with sodium hydroxide (6N, 4 ml) at 75°C for 45 minutes. The reaction mixture was then cooled to room temperature, acidified (pH 3) with 6N HCl. The precipitate was filtered, washed with ethanol, triturated with ether, dried under vacuum, to give title compound (795 mg, 80 %).

$^1\text{H NMR}$ ($\text{DMSO}-d_6$, TFA) : 2.34 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.76 (t, 2H) ; 4.03 (m, 5H) ; 4.35 (t, 2H) ; 7.48 (s, 1H) ; 8.26 (s, 1H) ; 8.41 (s, 1H) ; 9.29 (s, 1H).

Synthesis of amides of general structure M, general procedure

The acid 207 (79 mg, 0.16 mmol) in DMF (1 ml) was reacted with amine (0.19 mmol) in presence of O-(7-azabenzotriazol-1-yl) N,N,N',N'-tetramethyluronium hexafluorophosphate (73 mg, 0.19 mmol), DIEA (52 mg, 0.4 mmol), for 1 hour at room temperature. The reaction mixture was then treated with a solution of NaHCO_3 (5 ml) with stirring for 0.5 hour, and the solid filtered, dried under vacuum over P_2O_5 . For the compounds which did not precipitate, the solution was concentrated to dryness, the residues were washed with methylene chloride / methanol, filtered. Alumine was added to the methylene chloride / methanol solution and the solvent evaporated. Purification of the compounds was carried out by chromatography over alumine, eluent CH_2Cl_2 ; CH_2Cl_2 / MeOH : 95/5, to give title compounds.

Example 59:

An analogous reaction to that described in General Scheme 4, starting with aniline (18 mg, 0.19 mmol) yielded Compound 59 in Table 3 (50 mg, 60 %).

$^1\text{H NMR}$ ($\text{DMSO}-d_6$, TFA) : 2.3 (m, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.03 (d, 2H) ; 4.05 (s, 3H) ; 4.34 (t, 2H) ; 7.14 (t, 1H) ; 7.39 (t, 2H) ; 7.45 (s, 1H) ; 7.8 (d, 2H) ; 8.29 (s, 1H) ; 8.41 (s, 1H) ; 9.29 (s, 1H).

MS ES⁺ : 521 (M₂H)⁺.

Example 60

An analogous reaction to that described in General Scheme 4, starting with 4-fluoroaniline (21 mg, 0.19 mmol) yielded Compound 60 in Table 3(70 mg, 82 %).

5 ¹HNMR (DMSO-d₆, TFA) : 2.3 (m, 2H) ; 3.16 (t, 2H) ; 3.33 (t, 2H) ; 3.56 (d, 2H) ; 3.68 (t, 2H) ; 4.03 (d, 2H) ; 4.04 (s, 3H) ; 4.35 (t, 2H) ; 7.22 (t, 2H) ; 7.45 (s, 1H) ; 7.83 (m, 2H) ; 8.28 (s, 1H) ; 8.4 (s, 1H) ; 9.27 (s, 1H).

MS ES⁺ : 539 (M₂H)⁺

10 **Example 61**

An analogous reaction to that described in General Scheme 4, starting with 4-chloroaniline (24 mg, 0.19 mmol) yielded Compound 61 in Table 3(70 mg, 79 %).

¹HNMR (DMSO-d₆, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.68 (t, 2H) ; 4.04 (m, 5H) ; 4.35 (t, 2H) ; 7.45 (m, 3H) ; 7.84 (d, 2H) ; 8.29 (s, 1H) ; 8.4 (s, 1H) ; 9.27 (s, 1H).

MS ES⁺ : 555, 557 (M₂H)⁺

Example 62

An analogous reaction to that described in General Scheme 4, starting with cyclohexylamine (19 mg, 0.19 mmol) yielded Compound 62 in Table 3(60 mg, 72 %).

¹HNMR (DMSO-d₆, TFA) : 1.32 (m, 5H) ; 1.62 (m, 1H) ; 1.73 (m, 2H) ; 1.87 (m, 2H) ; 2.33 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.75 (m, 1H) ; 4.03 (s, 3H) ; 4.05 (d, 2H) ; 4.33 (t, 2H) ; 7.42 (s, 1H) ; 8.07 (s, 1H) ; 8.32 (s, 1H) ; 9.24 (s, 1H).

MS ES⁺ : 527 (M₂H)⁺

25

Example 63

An analogous reaction to that described in General Scheme 4, starting with 3-(methylamino)-propionitrile (16 mg, 0.19 mmol) yielded Compound 63 in Table 3(40 mg, 49 %).

30 ¹HNMR (DMSO-d₆, TFA) : 2.3 (m, 2H) ; 2.88 (s, 3H) ; 3.14 (m, 4H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.71 (t, 2H) ; 3.75 (m, 2H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 7.44 (s, 1H) ; 7.85 (s, 1H) ; 8.37 (s, 1H) ; 9.27 (s, 1H).

MS ES⁺ : 512 (M₂H)⁺

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PZ**Example 64**

An analogous reaction to that described in General Scheme 4, starting with 4-hydroxypiperidine (19 mg, 0.19 mmol) yielded Compound 64 in Table 3 (45 mg, 54 %).

¹H NMR (DMSO-d₆, TFA) : 1.36 (m, 2H) ; 1.78 (m, 2H) ; 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.29 (m, 2H) ; 3.37 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.77 (m, 2H) ; 3.84 (m, 1H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 7.42 (s, 1H) ; 7.75 (s, 1H) ; 8.35 (s, 1H) ; 9.27 (s, 1H).

MS ES⁺ : 529 (M₁H)⁺.

Example 65 :

10 An analogous reaction to that described in General Scheme 4, starting with 4-aminopyridine (18 mg, 0.19 mmol) yielded Compound 65 in Table 3 (35 mg, 42 %).

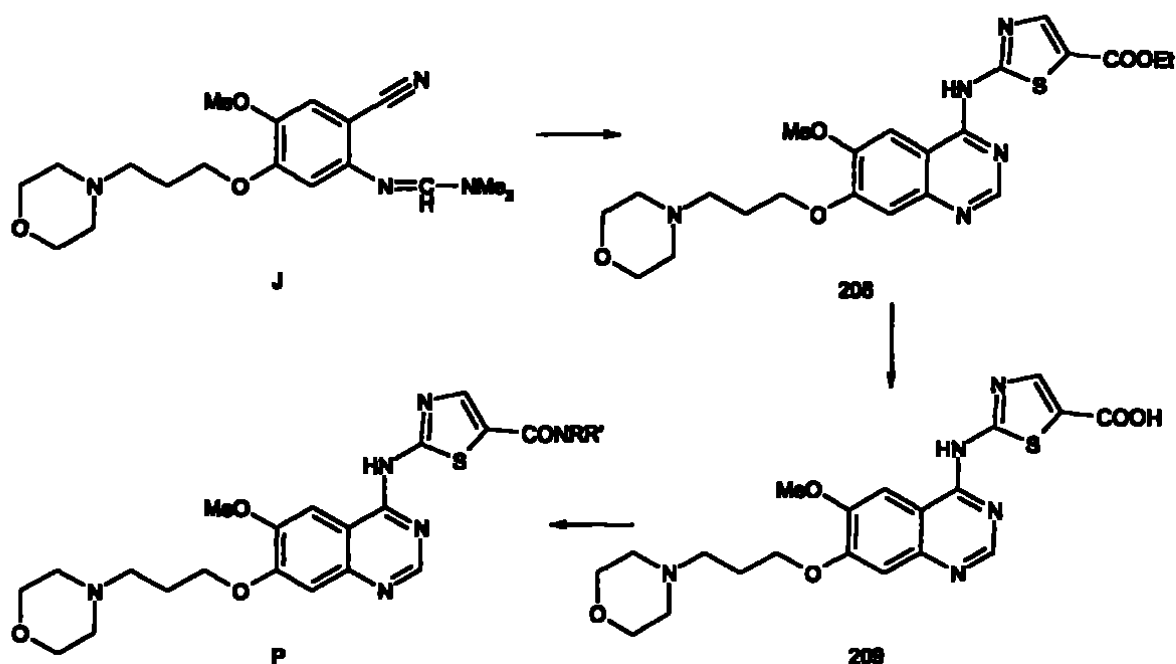
¹H NMR (DMSO-d₆, TFA) : 2.29 (m, 2H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 4.03 (m, 5H) ; 4.34 (t, 2H) ; 7.48 (s, 1H) ; 8.41 (d, 2H) ; 8.43 (s, 1H) ; 8.52 (s, 1H) ; 8.81 (d, 2H) ; 9.24 (s, 1H).

15 MS ES⁺ : 522 (M₁H)⁺

Example 66

An analogous reaction to that described in General Scheme 4, starting with 2-chloroaniline (24 mg, 0.19 mmol) yielded Compound 66 in Table 3 (25 mg, 28 %).

20 ¹H NMR (DMSO-d₆, TFA) : 2.3 (m, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.04 (d, 2H) ; 4.05 (s, 3H) ; 4.35 (t, 2H) ; 7.24 (t, 1H) ; 7.42 (t, 1H) ; 7.47 (s, 1H) ; 7.6 (d, 1H) (M₁H)⁺.

General Scheme 5Compound 208

The amidine **J** (1.52 g, 4.4 mmol) in AcOH (15 ml) was reacted with ethyl 2-amino-5-thiazolcarboxylate (757 mg, 4.4 mmol) at 130°C under argon for 3 hours. The solvent was evaporated, the residual oil was dissolved in methylene chloride and purified by silica gel chromatography, eluent CH₂Cl₂, CH₂Cl₂ / MeOH : 95/5, to give title compound as a yellow solid (1.44 g, 70 %).

¹HNMR (DMSO-d₆, TFA) : 1.33 (t, 3H) ; 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.36 (t, 2H) ; 3.53 (d, 2H) ; 3.68 (t, 2H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.35 (m, 4H) ; 7.41 (s, 1H) ; 8.14 (s, 1H) ; 8.44 (s, 1H) ; 9.3 (s, 1H).

MS ES⁺ : 474 (M₀H)⁺

Compound 209

Ester **208** (1.6 g, 3.4 mmol) in suspension in ethanol (32 ml) was reacted with sodium hydroxide (6N, 6 ml) at 75°C for 1 hour. The cooled solution was acidified with HCl (6N) to pH 4. The solid was filtered, washed with EtOH, ether, dried, to give a yellow solid (1.65 g, 86 %).

¹HNMR (DMSO-d₆, TFA) : 2.28 (m, 2H) ; 3.12 (t, 2H) ; 3.32 (t, 2H) ; 3.51 (d, 2H) ; 3.66 (t, 2H) ; 3.97 (s, 3H) ; 3.99 (d, 2H) ; 4.31 (t, 2H) ; 7.37 (s, 1H) ; 8.06 (s, 1H) ; 8.32 (s, 1H) ; 9.24 (s, 1H).

MS ES⁺ : 446 (M₀H)⁺

Synthesis of amides of general structure P, general procedure

The acid 209 (95 mg, 0.17 mmol) in DMF, 1 ml was reacted with amine (0.2 mmol) in presence of O-(7-azabenzotriazol-1-yl) N,N,N',N'-tetramethyluronium hexafluorophosphate (91 mg, 0.24 mmol), DIEA (110 mg, 0.85 mmol) for 14 hours at room temperature and 5 hours at 50°C. The reaction mixture was then treated with a solution of NaHCO₃ (1 ml) with stirring for 0.5 hour, and concentrated. The residue was washed with methylene chloride / methanol (1/1, 25 ml). Alumine was added to the organic phase, which was then evaporated. Purification of the compound was carried out by chromatography over alumine, eluent CH₂Cl₂, CH₂Cl₂ / MeOH / 95/5, to give title compounds.

10

Example 67

An analogous reaction to that described in General Scheme 5, starting with aniline (19 mg, 0.2 mmol) yielded Compound 67 in Table 4 (30 mg, 34 %).

¹HNMR (DMSO-d₆, TFA) : 2.31 (m, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 7.14 (t, 1H) ; 7.39 (m, 3H) ; 7.73 (d, 2H) ; 8.05 (s, 1H) ; 8.61 (s, 1H) ; 9.28 (s, 1H).

MS ES⁺ : 521 (M₁H)⁺

Example 68

20 An analogous reaction to that described in General Scheme 5, starting with 4-fluoroaniline (23 mg, 0.2 mmol) yielded Compound 68 in Table 4 (58 mg, 64 %).

¹HNMR (DMSO-d₆, TFA) : 2.31 (m, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (t, 2H) ; 7.20 (t, 1H) ; 7.38 (s, 1H) ; 7.73 (m, 1H) ; 8.05 (s, 1H) ; 8.57 (s, 1H) ; 9.28 (s, 1H).

25 MS ES⁺ : 539 (M₁H)⁺

Example 69 :

An analogous reaction to that described in General Scheme 5, starting with 4-chloroaniline (26 mg, 0.2 mmol) yielded Compound 69 in Table 4 (32 mg, 34 %).

30 ¹HNMR (DMSO-d₆, TFA) : 2.32 (m, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.33 (t, 2H) ; 7.39 (s, 1H) ; 7.44 (d, 2H) ; 7.76 (d, 2H) . 8.06 (s, 1H) ; 8.6 (s, 1H) ; 9.29 (s, 1H).

MS ES⁺ : 555, 557 (M₁H)⁺

Example 70

An analogous reaction to that described in General Scheme 5, starting with allylamine (12 mg, 0.2 mmol) yielded Compound 70 in Table 4 (32 mg, 39 %).

¹HNMR (DMSO-d₆, TFA) : 2.3 (m, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.7 (t, 2H) ; 3.92 (d, 2H) ; 4.0 (s, 3H) ; 4.03 (d, 2H) ; 4.33 (t, 2H) ; 5.16 (d, 1H) ; 5.25 (d, 1H) ; 5.9 (m, 1H) ; 7.38 (s, 1H) ; 8.02 (s, 1H) ; 8.36 (s, 1H) ; 9.24 (s, 1H).

MS ES⁺ : 485 (M₁H)⁺

Example 71

10 An analogous reaction to that described in General Scheme 5, starting with 3-(methylamino)-propionitrile (17 mg, 0.2 mmol) yielded Compound 71 in Table 4 (32 mg, 39 %).

¹HNMR (DMSO-d₆, TFA) : 2.3 (m, 2H) ; 2.89 (m, 3H) ; 3.15 (t, 2H) ; 3.34 (m, 4H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.8 (m, 2H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.33 (t, 2H) ; 7.38 (s, 1H) ; 8.07 (s, 1H) ; 8.22 (s, 1H) ; 9.25 (s, 1H).

15 MS ES⁺ : 512 (M₁H)⁺.

Example 72

An analogous reaction to that described in General Scheme 5, starting with 4-hydroxypiperidine (20 mg, 0.2 mmol) yielded Compound 72 in Table 4 (12 mg, 13 %).

20 ¹HNMR (DMSO-d₆, TFA) : 1.45 (m, 2H) ; 1.82 (m, 2H) ; 2.31 (m, 2H) ; 3.15 (m, 4H) ; 3.35 (t, 2H) ; 3.4 (m, 2H) ; 3.54 (d, 2H) ; 3.7 (t, 2H) ; 3.79 (m, 1H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (t, 2H) ; 7.38 (s, 1H) ; 8.06 (s, 1H) ; 8.09 (s, 1H) ; 9.23 (s, 1H).

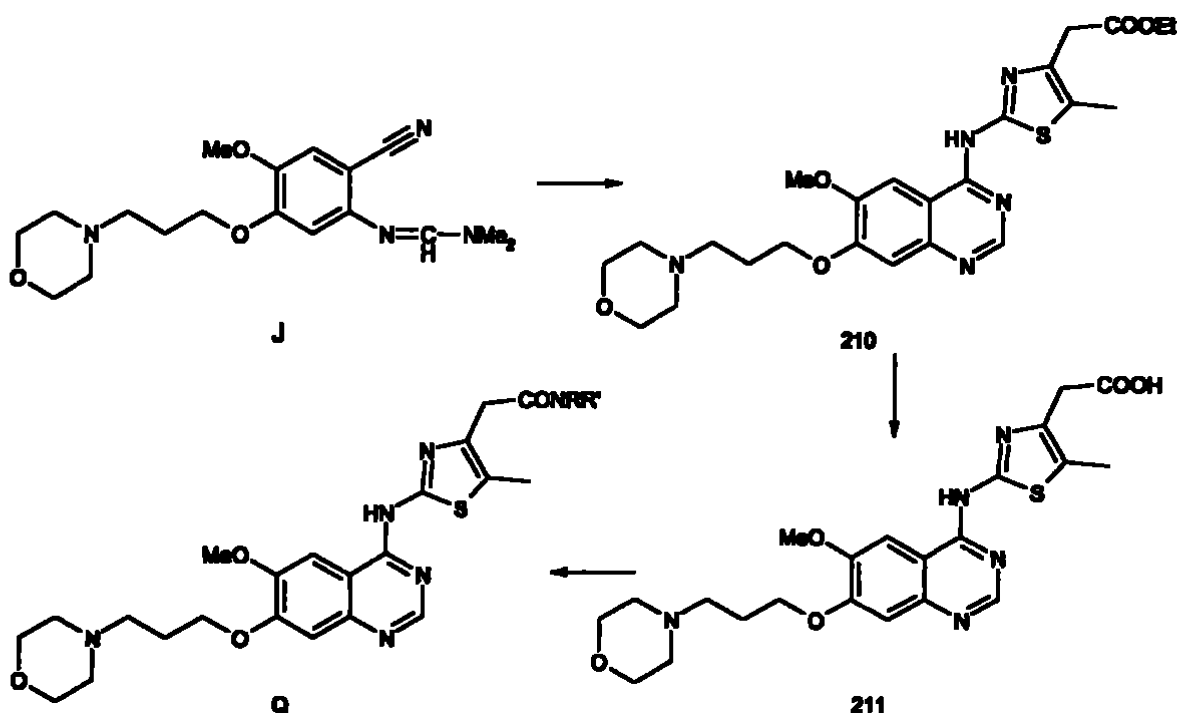
MS ES⁺ : 529 (M₁H)⁺

Example 73

25 An analogous reaction to that described in General Scheme 5, starting with 4-aminopyridine (19 mg, 0.2 mmol) yielded Compound 73 in Table 4 (50 mg, 57 %).

¹HNMR (DMSO-d₆, TFA) : 2.29 (m, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.7 (t, 2H) ; 4.02 (s, 3H) ; 4.03 (d, 2H) ; 4.34 (t, 2H) ; 7.46 (s, 1H) ; 8.15 (s, 1H) ; 8.27 (d, 2H) ; 8.78 (s, 1H) ; 8.8 (d, 2H) ; 9.31 (s, 1H).

30 MS ES⁺ : 522 (M₁H)⁺

General Scheme 6Compound 210

- 5 Amidine J (450 mg, 1.3 mmol) was reacted with methyl 2-amino-5-methyl-4-thiazolacetate (242 mg, 1.3 mmol) in acetic acid (5 ml) at 130°C for 3 hours, under argon. The solvent was evaporated, ethylacetate and water were added to the residual oil, the pH adjusted to 9 with a saturated solution of sodium bicarbonate and the mixture extracted with ethylacetate. The organic phase was washed with a saturated solution of sodium chloride, dried over
- 10 magnesium sulphate, filtered, concentrated. The residual oil was purified by silica gel chromatography, eluent CH_2Cl_2 / MeOH : 98/2 to 95/5 to give title compound (380 mg, 60 %).

$^1\text{H NMR}$ ($\text{DMSO}-d_6$, TFA) : 2.3 (m, 2H) ; 2.35 (s, 3H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.68 (s, 3H) ; 3.83 (s, 2H) ; 3.98 (s, 3H) ; 4.03 (d, 2H) ; 4.29 (t, 2H) ; 7.31 (s, 1H) ; 7.96 (s, 1H) ; 9.06 (s, 1H).

15

MS ES^+ : 488 (M_nH^+)

Compound 211

- Ester 210 (360 mg, 0.74 mmol) in ethanol (10 ml) was reacted with sodium hydroxide (6N, 1 ml) at room temperature for 1 hour. HCl (6N) was then added to the solution cooled to 0°C,
- 20 and the pH adjusted to 3-4. The solid was recovered by filtration, washed with ethanol, ether, dried under vacuum, to give title compound as a dihydrochloride (550 mg, 83 %).

¹HNMR (DMSO-d₆, TFA) : 2.34 (m, 5H) ; 3.13 (t, 2H) ; 3.32 (t, 2H) ; 3.52 (d, 2H) ; 3.74 (s, 2H) ; 3.78 (t, 2H) ; 3.98 (s, 3H) ; 4.01 (d, 2H) ; 4.31 (t, 2H) ; 7.37 (s, 1H) ; 7.91 (s, 1H) ; 9.03 (s, 1H).

MS ES⁺ : 474 (M,H)⁺

5

Synthesis of amides of general structure Q, general procedure

The acid 211 (87 mg, 0.13 mmol) in DMF (1 ml) was reacted with amine (0.169 mmol) in presence of O-(7-azabenzotriazol-1-yl) N,N,N',N'-tetramethyluronium hexafluorophosphate (69 mg, 0.182 mmol), diisopropylethylamine (84 mg, 0.65 mmol) over night, at room temperature. The reaction mixture was diluted with water (5 ml) and a concentrated solution of sodium bicarbonate (1 ml). The solid was filtered, washed with water, ethanol, ether, and dried under vacuum, to give title compounds. For the compounds which did not precipitate, the solution was concentrated to dryness, the residues were washed with methylene chloride, methanol, filtered. Alumine was added to the methylene chloride / methanol solution, and the solvent was evaporated. Purification of the compounds was carried out by chromatography over alumine, eluent CH₂Cl₂ / MeOH : 98/2 to 95/5, to give title compounds.

Example 74

An analogous reaction to that described in General Scheme 6, starting with aniline (16 mg, 0.17 mmol) yielded Compound 74 in Table 5 (50 mg, 70 %).

¹HNMR (DMSO-d₆, TFA) : 2.28 (m, 2H) ; 2.37 (s, 3H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.56 (d, 2H) ; 3.68 (t, 2H) ; 3.84 (s, 2H) ; 3.96 (s, 3H) ; 4.03 (d, 2H) ; 4.28 (t, 2H) ; 7.07 (t, 1H) ; 7.29 (s, 1H) ; 7.3 (t, 2H) ; 7.61 (d, 2H) ; 7.89 (s, 1H) ; 9.02 (s, 1H).

MS ES⁺ : 549 (M,H)⁺

25

Example 75

An analogous reaction to that described in General Scheme 6, starting with 4-fluoroaniline (19 mg, 0.17 mmol) yielded Compound 75 in Table 5 (50 mg, 67 %).

¹HNMR (DMSO-d₆, TFA) : 2.3 (m, 2H) ; 2.38 (s, 3H) ; 3.16 (t, 2H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.84 (s, 2H) ; 3.97 (s, 3H) ; 4.03 (d, 2H) ; 4.29 (t, 2H) ; 7.16 (t, 2H) ; 7.29 (s, 1H) ; 7.64 (m, 2H) ; 7.9 (s, 1H) ; 9.03 (s, 1H).

MS ES⁺ : 567 (M,H)⁺

30

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X**Example 76**

An analogous reaction to that described in General Scheme 6, starting with 4-chloroaniline (22 mg, 0.17 mmol) yielded Compound 76 in Table 5 (45 mg, 59 %).

¹HNMR (DMSO-d₆, TFA) : 2.28 (m, 2H) ; 2.37 (s, 3H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.85 (s, 2H) ; 3.97 (s, 3H) ; 4.03 (d, 2H) ; 4.29 (t, 2H) ; 7.29 (s, 1H) ; 7.37 (d, 2H) ; 7.65 (d, 2H) ; 7.9 (s, 1H) ; 9.03 (s, 1H).

MS ES⁺ : 583 (M₂H)⁺

Example 77

10 An analogous reaction to that described in General Scheme 6, starting with 4-hydroxypiperidine (17 mg, 0.17 mmol) yielded Compound 77 in Table 5 (45 mg, 62 %).

¹HNMR (DMSO-d₆, TFA) : 1.42 (m, 2H) ; 1.82 (m, 2H) ; 2.31 (m, 5H) ; 3.08 (m, 1H) ; 3.16 (t, 2H) ; 3.27 (m, 1H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.78 (m, 2H) ; 3.83 (s, 2H) ; 3.92 (m, 1H) ; 3.97 (s, 3H) ; 4.03 (d, 2H) ; 4.29 (t, 2H) ; 7.28 (s, 1H) ; 7.85 (s, 1H) ; 9.0 (s, 1H).

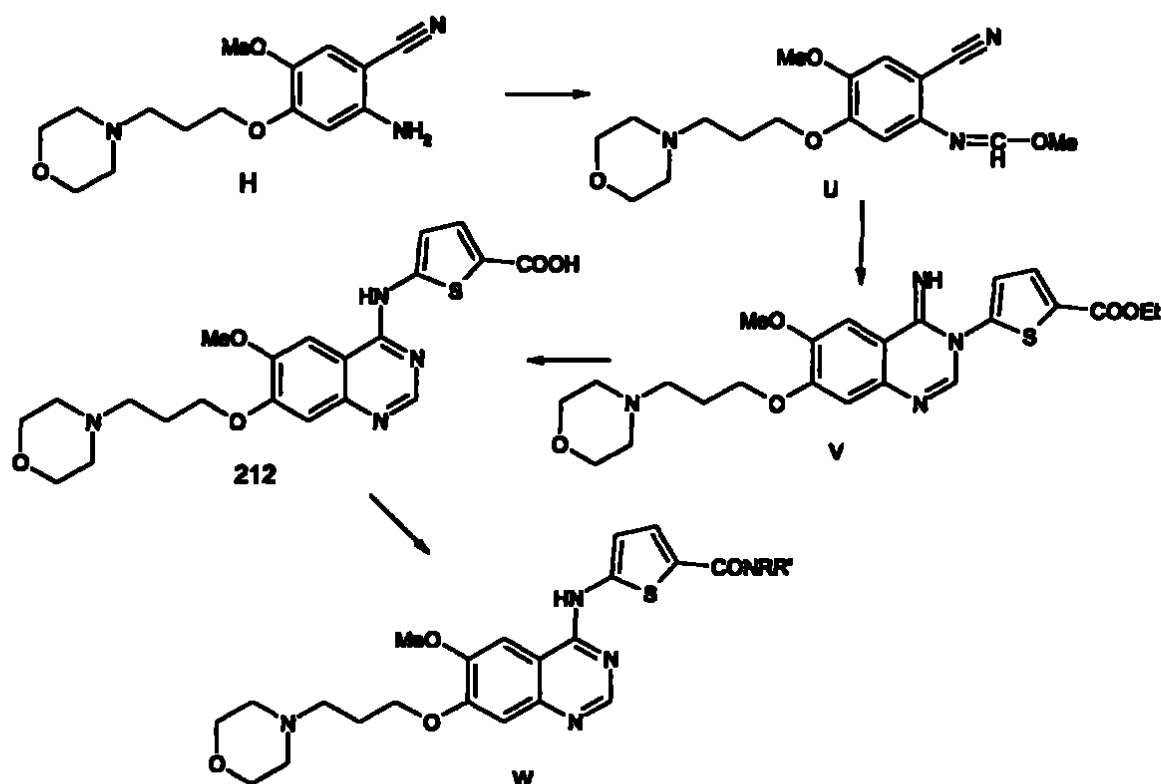
MS ES⁺ : 557 (M₂H)⁺.

Example 78

20 An analogous reaction to that described in General Scheme 6, starting with 4-aminopyridine (16 mg, 0.17 mmol) yielded Compound 78 in Table 5 (35 mg, 49 %).

¹HNMR (DMSO-d₆, TFA) : 2.29 (m, 2H) ; 2.39 (s, 3H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.96 (s, 3H) ; 4.02 (d, 2H) ; 4.04 (s, 2H) ; 4.29 (t, 2H) ; 7.33 (s, 1H) ; 7.92 (s, 1H) ; 8.1 (d, 2H) ; 8.76 (d, 2H) ; 9.06 (s, 1H).

MS ES⁺ : 550 (M₂H)⁺.

General Scheme 7

5

Compound U

The amino nitrile H (2.91 g, 10 mmol) was reacted with trimethylorthoformate (10 ml) in presence of p-toluene-sulfonic acid (38 mg, 2 mmol) at 80°C for 6 hours. The solvent was evaporated, the residue crystallised from ether to give title compound (3.01 g, 90.4 %).

10 ¹HNMR (DMSO-d₆) : 1.9 (t, 2H) ; 2.4 (m, 6H) ; 3.58 (t, 4H) ; 3.78 (s, 3H) ; 3.85 (s, 3H) ; 4.08 (t, 2H) ; 6.88 (s, 1H) ; 7.28 (s, 1H) ; 8.2 (s, 1H).

MS ES⁺ : 334 (M,H)⁺

Compound V

15 Imidate U (0.25 g, 0.75 mmol) in CH₂Cl₂ (5 ml) was reacted with ethyl 2-amino-5-thiophenecarboxylate (0.13 g, 0.79 mmol) in presence of pyridinium hydrochloride (0.09 g, 0.75 mmol), at room temperature over night. Ethyl acetate was then added, and the solid was recovered by filtration, washed with ethyl acetate, dried under vacuum, to give product (0.23 g, 65 %).

¹HNMR (DMSO-d₆, TFA) : 1.33 (t, 3H) ; 2.28 (m, 2H) ; 3.12 (t, 2H) ; 3.32 (t, 2H) ; 3.53 (d, 2H) ; 3.73 (t, 2H) ; 3.96 (s, 3H) ; 4.02 (d, 2H) ; 4.37 (m, 4H) ; 7.45 (s, 1H) ; 7.67 (d, 1H) ; 7.95 (d, 1H) ; 8.12 (s, 1H) ; 8.52 (s, 1H).

MS ES⁺ : 473 (M₁H)⁺

5

Compound 212

Ester V (1.1 g, 2.3 mmol) in methanol (20 ml) was treated with sodium hydroxide (2N, 20 ml) at 75°C for 4 hours, and at room temperature over night. Methanol was evaporated, and the remaining aqueous solution was kept for 24 hours at 5°C. The solid was filtered, washed with
10 water, MeOH / CH₂Cl₂ : 1/1, dried under vacuum to give title compound (0.9 g, 87 %).

¹HNMR (DMSO-d₆, TFA) : 2.31 (m, 2H) ; 3.14 (t, 2H) ; 3.33 (t, 2H) ; 3.53 (d, 2H) ; 3.76 (t, 2H) ; 4.01 (d, 2H) ; 4.07 (s, 3H) ; 4.33 (t, 2H) ; 7.44 (s, 1H) ; 7.54 (d, 1H) ; 7.68 (d, 1H) ; 8.54 (s, 1H) ; 9.22 (s, 1H).

MS ES⁺ : 445 (M₁H)⁺

15

Synthesis of amides of general structure W. general procedure

Acid 212 (80 mg, 0.18 mmol) in DMF (1.5 ml) was reacted with amine (0.216 mmol) in presence of O-(7-azabenzotriazol-1-yl) N,N,N',N'-tetramethyluronium hexafluorophosphate (80 mg, 0.21 mmol), DIEA (80 µl, 0.46 mmol), for 3 hours at room temperature. The reaction
20 mixture was then treated with a solution of NaHCO₃ (2 ml) with stirring for 0.5 hour, the solid filtered, washed with water, ether, dried under vacuum over P₂O₅, to give title compound.

Example 79

An analogous reaction to that described in General Scheme 7, starting with aniline (17 µl, 0.186 mmol) yielded Compound 79 in Table 6 (80 mg, 86 %).
25

¹HNMR (DMSO-d₆, TFA) : 2.32 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.53 (d, 2H) ; 3.69 (t, 2H) ; 4.01 (d, 2H) ; 4.03 (s, 3H) ; 4.3 (t, 2H) ; 7.7 (t, 1H) ; 7.32 (m, 4H) ; 7.73 (d, 2H) ; 7.98 (d, 1H) ; 8.18 (s, 1H) ; 9.22 (s, 1H).

MS ES⁺ : 520 (M₁H)⁺

30

Example 80

An analogous reaction to that described in General Scheme 7, starting with 4-fluoroaniline (24 mg, 0.216 mmol) yielded Compound 80 in Table 6 (62 mg, 64 %).

¹HNMR (DMSO-d₆, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 4.05 (m, 5H) ; 4.33 (t, 2H) ; 7.21 (t, 2H) ; 7.33 (d, 1H) ; 7.4 (s, 1H) ; 7.77 (m, 2H) ; 7.98 (d, 1H) ; 8.2 (s, 1H) ; 9.25 (s, 1H).

MS ES⁺ : 538 (M₀H)⁺.

Example 81

10 An analogous reaction to that described in General Scheme 7, starting with 3-aminophenol (24 mg, 0.216 mmol) yielded Compound 81 in Table 6 (60 mg, 66 %).

¹HNMR (DMSO-d₆, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.7 (t, 2H) ; 4.04 (d, 2H) ; 4.06 (s, 3H) ; 4.33 (t, 2H) ; 6.53 (m, 1H) ; 7.13 (m, 2H) ; 7.3 (d, 1H) ; 7.36 (d, 1H) ; 7.4 (s, 1H) ; 7.96 (s, 1H) ; 8.0 (d, 1H) ; 8.26 (s, 1H) ; 9.25 (s, 1H).

15 MS ES⁺ : 536 (M₀H)⁺.

Example 82

An analogous reaction to that described in General Scheme 7, starting with 4-aminopyridine (20 mg, 0.216 mmol) yielded Compound 82 in Table 6 (16 mg, 19 %).

20 ¹HNMR (DMSO-d₆, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 4.03 (d, 2H) ; 4.05 (s, 3H) ; 4.32 (t, 2H) ; 7.01 (d, 1H) ; 7.03 (s, 1H) ; 8.18 (d, 1H) ; 8.22 (s, 1H) ; 8.3 (d, 2H) ; 8.76 (d, 2H) ; 9.3 (s, 1H).

MS ES⁺ : 521 (M₀H)⁺.

Example 83

25 An analogous reaction to that described in General Scheme 7, starting with 4-amino-1-butanol (19 mg, 0.216 mmol) yielded Compound 83 in Table 6 (22 mg, 28 %).

¹HNMR (DMSO-d₆, TFA) : 1.46 (m, 2H) ; 1.58 (m, 2H) ; 2.3 (m, 2H) ; 3.16 (t, 2H) ; 3.26 (t, 2H) ; 3.36 (t, 2H) ; 3.44 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.04 (m, 5H) ; 4.32 (t, 2H) ; 7.26 (d, 1H) ; 7.39 (s, 1H) ; 7.7 (d, 1H) ; 8.19 (s, 1H) ; 9.21 (s, 1H).

30 MS ES⁺ : 516 (M₀H)⁺.

YHS
843**Example 84**

An analogous reaction to that described in General Scheme 7, starting with 3-aminobenzamide (29 mg, 0.216 mmol) yielded Compound 84 in Table 6 (60 mg, 77 %).

¹HNMR (DMSO-d₆, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.67 (t, 2H) ; 4.03 (d, 2H) ; 4.05 (s, 3H) ; 4.32 (t, 2H) ; 7.34 (d, 1H) ; 7.39 (s, 1H) ; 7.42 (t, 1H) ; 7.62 (d, 1H) ; 7.96 (d, 1H) ; 8.05 (d, 1H) ; 8.21 (m, 2H) ; 9.27 (s, 1H).

MS ES⁺ : 563 (M,H)⁺.

Example 85

10 An analogous reaction to that described in General Scheme 7, starting with allylamine (12 mg, 0.216 mmol) yielded title Compound 85 in Table 6 (20 mg., 43 %).

¹HNMR (DMSO-d₆, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.91 (d, 2H) ; 4.04 (m, 5H) ; 4.32 (t, 2H) ; 5.12 (d, 1H) ; 5.2 (d, 1H) ; 5.91 (m, 1H) ; 7.26 (d, 1H) ; 7.38 (s, 1H) ; 7.75 (d, 1H) ; 8.19 (s, 1H) ; 9.22 (s, 1H).

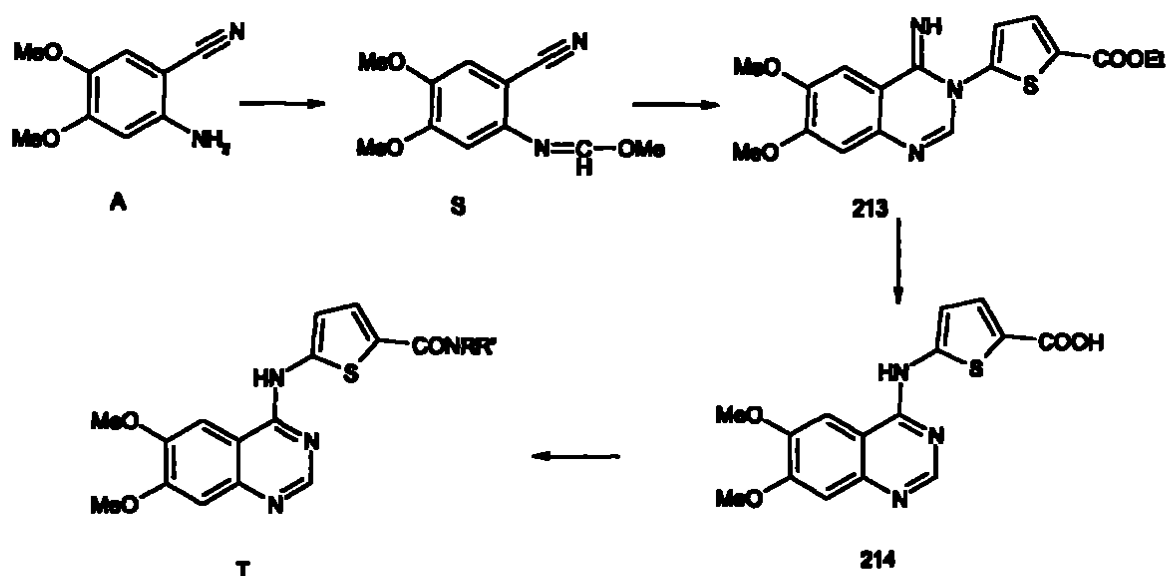
15 MS ES⁺ : 484 (M,H)⁺.

Example 86

An analogous reaction to that described in General Scheme 7, starting with Methyl-4-aminobutyrate (25 mg, 0.216 mmol) yielded Compound 86 in Table 6 (18 mg, 23 %).

20 ¹HNMR : 1.8 (t, 2H) ; 2.3 (m, 2H) ; 2.39 (t, 2H) ; 3.16 (t, 2H) ; 3.28 (t, 2H) ; 3.35 (t, 2H) ; 3.56 (d, 2H) ; 3.6 (s, 3H) ; 3.67 (t, 2H) ; 4.04 (m, 5H) ; 4.32 (t, 2H) ; 7.26 (d, 1H) ; 7.38 (s, 1H) ; 7.69 (d, 1H) ; 8.19 (s, 1H) ; 9.22 (s, 1H).

MS ES⁺ : 544 (M,H)⁺.

General Scheme 8**Compound S**

- 5 Aminonitrile A (1.78 g, 10 mmol) was treated with trimethylorthoformate (10 ml) and a catalytic amount of p-toluene sulfonic acid at 100°C for 1 hour. The mixture was cooled to room temperature, ethyl acetate was added, and the insoluble solid removed by filtration, the solvent was then evaporated, the residue triturated with ether to give title compound as a yellow solid (1.56 g, 71 %).

10 ¹HNMR (DMSO-d₆): 3.77 (s, 3H) ; 3.83 (s, 3H) ; 3.84 (s, 3H) ; 6.87 (s, 1H) ; 7.26 (s, 1H) ; 8.19 (s, 1H).

MS ES⁺ : 221 (M₂H)⁺.

Compound 213

- 15 Imidate S (0.165 g, 0.75 mmol) was reacted with ethyl 2-amino-5-thiophenecarboxylate (0.13 g, 0.79 mmol) in methylene chloride (4 ml) in presence of pyridinium hydrochloride (88 mg, 0.75 mmol) at room temperature for 4 hours. The solvent was evaporated, and the residue was purified by silica gel chromatography, eluent : AcOEt / CH₂Cl₂, 1/1 ; followed by MeOH / AcOEt / CH₂Cl₂, 1/4/5, to give title compound (0.135 g, 50 %).

20 ¹HNMR (DMSO-d₆, TFA) : 1.33 (t, 3H) ; 3.95 (s, 3H) ; 4.03 (s, 3H) ; 4.38 (q, 2H) ; 7.43 (s, 1H) ; 7.67 (d, 1H) ; 7.95 (d, 1H) ; 8.05 (s, 1H) ; 8.52 (s, 1H).

MS ES⁺ : 360 (M₂H)⁺

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Compound 214

The ester 213 (72 mg, 0.2 mmol) in methanol (2 ml) was treated with sodium hydroxide (2N, 2 ml) at 75°C for 1.5 hour. The reaction mixture was cooled to room temperature, and the pH adjusted to 3 by addition of HCl 2N. The solid was recovered by filtration, washed with

5 water, dried under vacuum in presence of P_2O_5 , to give title compound (83 mg, 100 %).

$^1\text{HNMR}$ ($\text{DMSO}-d_6$, TFA) : 4.02 (s, 3H) ; 4.04 (s, 3H) ; 7.38 (s, 1H) ; 7.42 (d, 1H) ; 7.68 (d, 1H) ; 8.35 (s, 1H) ; 9.21 (s, 1H).

MS ES^+ : 332 (M_nH) $^+$.

10 Example 87**Synthesis of compound of General formula T where $\text{NRR}' = \text{NHPH}$ (Compound 87)**

Quinazoline 214 (45 mg, 0.108 mmol) in DMF (1 ml) was reacted with aniline (12 μl , 0.13 mmol) in presence of O-(7-azabenzotriazol-1-yl) N,N,N',N'-tetramethyluronium hexafluorophosphate (50 mg, 0.13 mmol), DIEA (75 μl , 0.43 mmol) for 1.5 hour at room
15 temperature. A saturated solution of sodium bicarbonate (2 ml) was added to the mixture which was stirred for 0.5 hour. The solid was filtered, washed with water, and purified by chromatography over alumine, eluent AcOEt / CH_2Cl_2 : 1/1 to MeOH / AcOEt / CH_2Cl_2 : 1/4/5, to give title compound (15 mg, 34 %).

$^1\text{HNMR}$ ($\text{DMSO}-d_6$) : 3.97 (s, 3H) ; 4.01 (s, 3H) ; 7.05 (d, 1H) ; 7.09 (t, 1H) ; 7.29 (s, 1H) ;
20 7.36 (t, 2H) ; 7.74 (d, 2H) ; 7.91 (d, 1H) ; 7.92 (s, 1H) ; 8.72 (s, 1H).

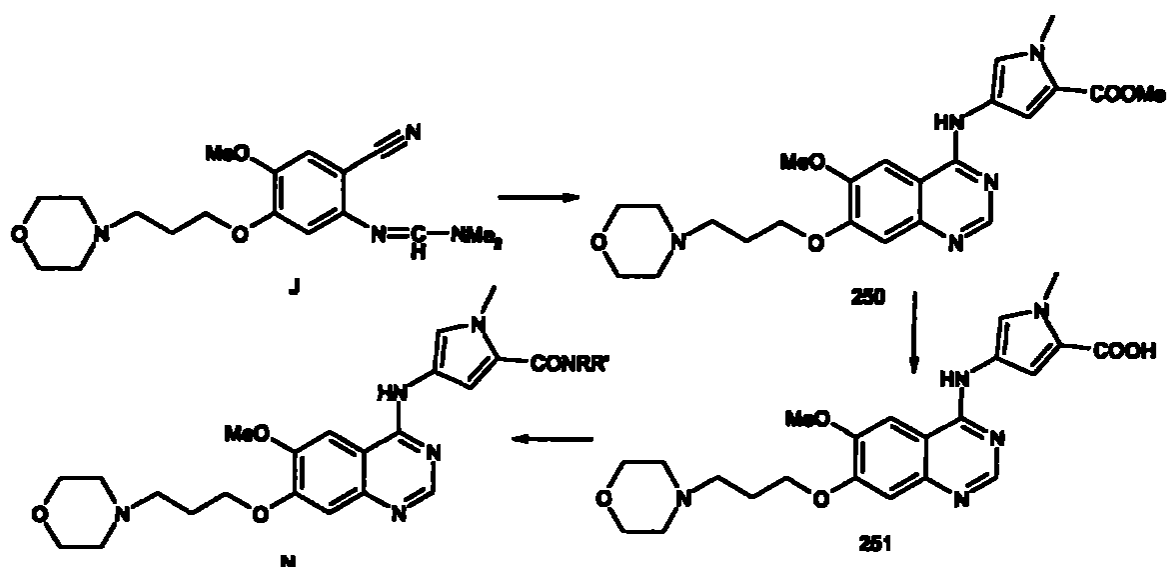
MS ES^+ : 406 (M_nH) $^+$

Example 88**Synthesis of Compound 88 of General formula T where NRR' is $\text{NHPH}(4\text{-F})$**

25 An analogous reaction to that described in the Example 87, starting with quinazoline 213 (60 mg, 0.14 mmol), 4-fluoroaniline (17 μl , 0.17 mmol) yielded title compound (15 mg, 24 %).

$^1\text{HNMR}$ ($\text{DMSO}-d_6$, TFA) : 4.04 (s, 3H) ; 4.06 (s, 3H) ; 7.18 (t, 2H) ; 7.32 (d, 1H) ; 7.35 (s, 1H) ; 7.75 (t, 2H) ; 7.98 (d, 1H) ; 8.17 (s, 1H) ; 9.23 (s, 1H).

MS ES^+ : 425 (M_nH) $^+$.

General Scheme 9Example 89: Preparation of Compound 250 in Table 9

- 5 Amidine J (1.04 g, 3 mmol) in acetic acid (10 ml) was reacted with methyl 4-amino-1-methyl-2-pyrrolicarboxylate hydrochloride (686 mg, 3.6 mmol) and dimethylamine in methanol (1.25 M 2.9 ml, 3.6 mmol) at 130°C for 5.5 hours. The solvent was evaporated, water and an aqueous solution of sodium bicarbonate were added to the residue, the precipitate was filtered, dried under vacuum over P₂O₅. The solid was redissolved in a large
- 10 volume of tetrahydrofuran, methylene chloride, methanol, the solution was concentrated, the solid filtered, washed with ether, dried, to give title compound (1.18 g, 86 %).
- ¹HNMR (DMSO-d₆, TFA) : 2.31 (m, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.8 (s, 3H) ; 3.95 (s, 3H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.29 (t, 2H) ; 7.26 (d, 1H) ; 7.32 (s, 1H) ; 7.69 (d, 1H) ; 8.06 (s, 1H) ; 8.94 (s, 1H).
- 15 MS ES⁺ : 456 [M₂H]⁺

Example 90: Preparation of Compound 251 in Table 9

- Ester 250 (1.34 g, 3 mmol) was treated with sodium hydroxide (6N, 3 ml) in ethanol (25 ml) at 75° for 2 hours. The solution was then cooled to room temperature, acidified to pH 3 with
- 20 HCl (6N), the precipitate was recovered by filtration, washed with ethanol, ether, dried under vacuum to give title compound (636 mg, 42 %).

¹H NMR (DMSO-d₆, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.72 (t, 2H) ; 4.02 (m, 5H) ; 4.3 (t, 2H) ; 7.19 (s, 1H) ; 7.32 (s, 1H) ; 7.62 (s, 1H) ; 8.17 (s, 1H) ; 8.93 (s, 1H).

MS ES⁺ : 428 [M,H]⁺

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Example 91: Synthesis of amides N. general procedure

Acid 251 (79 mg, 0.15 mmol) in DMF (1 ml) was reacted with O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (62 mg, 0.165 mmol), the appropriate amine (1.65 mmol) and DIEA (68 mg, 0.525 mmol) at room temperature for 1.5 hour. The reaction mixture was then diluted with water (4 ml) and an aqueous solution of sodium bicarbonate (1 ml). The solid was recovered by filtration, redissolved in tetrahydrofuran, methylene chloride, and concentrated, the precipitated solid was recovered, washed with ether, dried under vacuum, to give title compound.

15 **Example 92: Preparation of Compound 252 in Table 9**

Compound of example 1 was obtained by reaction of the N-hydroxybenzotriazol ester of 3 (56 mg, 0.1 mmol) with aniline (11 mg, 0.12 mmol) in DMF (1 ml) at 105°C for 3 hours. Water was added to the cooled reaction mixture, which was extracted with ethylacetate, the organic phase was washed with water, dried over-MgSO₄, filtered and concentrated to give title compound (12 mg, 23 %). The N-hydroxybenzotriazol ester was obtained as described in the general procedure of Example 91.

¹H NMR (DMSO-d₆, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.97 (s, 3H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.29 (t, 2H) ; 7.08 (t, 1H) ; 7.33 (m, 3H) ; 7.4 (s, 1H) ; 7.63 (s, 1H) ; 7.74 (d, 2H) ; 8.1 (s, 1H) ; 8.93 (s, 1H).

25 MS ES⁺ : 517 [M,H]⁺

Example 93: Preparation of Compound 253 in Table 9

An analogous reaction to that described in Example 92, but starting with 4-fluoroaniline (22 mg, 0.195 mmol) yielded title compound (40 mg, 57 %).

30 ¹H NMR (DMSO-d₆, TFA) : 2.3 (m, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.72 (t, 2H) ; 3.97 (s, 3H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.3 (t, 2H) ; 7.18 (t, 2H) ; 7.34 (s, 1H) ; 7.4 (d, 1H) ; 7.63 (d, 1H) ; 7.76 (m, 1H) ; 8.11 (s, 1H) ; 8.94 (s, 1H).

MS ES⁺ : 535 [M₂H]⁺

Example 94: Preparation of Compound 254 in Table 9

An analogous reaction to that described in Example 92, but starting with cyclohexylamine (16 mg, 0.17 mmol) yielded title compound (60 mg, 76 %).

¹HNMR (DMSO-d₆, TFA) : 1.14 (m, 1H) ; 1.3 (m, 4H) ; 1.62 (m, 1H) ; 1.8 (m, 4H) ; 2.29 (m, 2H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (m, 3H) ; 3.9 (s, 3H) ; 4.0 (s, 3H) ; 4.03 (d, 2H) ; 4.28 (t, 2H) ; 7.14 (d, 1H) ; 7.31 (s, 1H) ; 7.49 (d, 1H) ; 8.07 (s, 1H) ; 8.9 (s, 1H).

MS ES⁺ : 523 [M₂H]⁺

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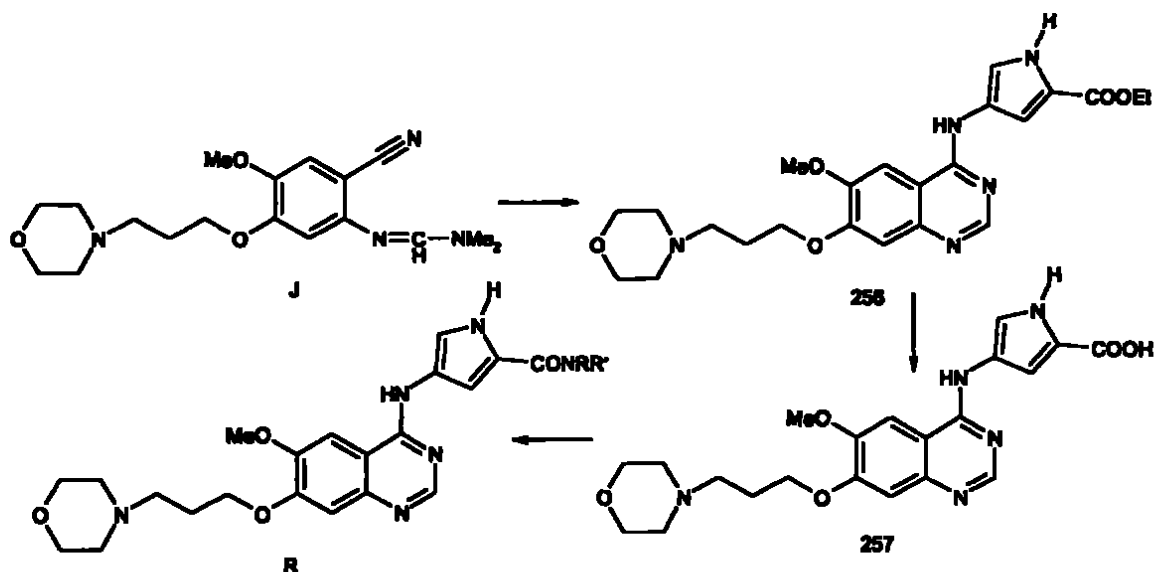
Example 95: Preparation of Compound 255 in Table 9

An analogous reaction to that described in the Example 92, but starting with N,N-dimethyl-1,4-phenylenediamine (23 mg, 0.17 mmol) yielded title compound (61 mg, 73 %).

¹HNMR (DMSO-d₆, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.21 (s, 6H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.97 (s, 3H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.29 (t, 2H) ; 7.35 (s, 1H) ; 7.45 (d, 1H) ; 7.66 (m, 3H) ; 7.93 (d, 2H) ; 8.1 (s, 1H) ; 8.93 (s, 1H).

MS ES⁺ : 560 [M₂H]⁺

General Scheme 10.



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Example 96: Preparation of Compound 256 in Table 9

Amidine J (1.38 g, 4 mmol) in acetic acid (14 ml) was reacted with ethyl 4-amino-2-pyrrolecarboxylate (0.702 g, 4.56 mmol) at 130°C for 5 hours. The solution was concentrated,

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the solid recovered by filtration and washed with ether. This solid was then treated with a diluted solution of sodium bicarbonate, filtered, washed with water and dried under vacuum over P_2O_5 to give title compound (1.34 g, 73 %).

^1H NMR (DMSO- d_6) : 1.3 (t, 3H) ; 1.95 (t, 2H) ; 2.38 (m, 4H) ; 2.44 (t, 2H) ; 3.58 (m, 4H) ;
5 3.94 (s, 3H) ; 4.16 (d, 2H) ; 4.23 (q, 2H) ; 7.05 (d, 1H) ; 7.14 (s, 1H) ; 7.59 (d, 1H) ; 7.75 (s, 1H) ; 8.46 (s, 1H) ; 9.53 (s, 1H) ; 11.72 (s, 1H).

MS ES⁺ : 456 [M₂H]⁺

Example 96: Preparation of Compound 257 in Table 9

10 Ester 256 (1.34 g, 3 mmol) in ethanol (25 ml) was treated with sodium hydroxide (6N, 3 ml) at 75°C for 2 hours. The solution was cooled, and acidified with hydrochloric acid (6N) to pH 3. The precipitate was filtered, washed with ethanol, ether, dried under vacuum over P_2O_5 , to give title compound (0.63 g, 42 %).

^1H NMR (DMSO- d_6 , TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.72 (t,
15 2H) ; 4.02 (s, 3H) ; 4.03 (d, 2H) ; 4.3 (t, 2H) ; 7.19 (d, 1H) ; 7.32 (s, 1H) ; 7.62 (d, 1H) ; 8.17 (s, 1H) ; 8.93 (s, 1H).

MS ES⁺ : 428 [M₂H]⁺

Example 97: Preparation of Compound 258 in Table 9

20 Acid 256 (75 mg, 0.15 mmol) in DMF (0.7 ml) was reacted with O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (68 mg, 0.18 mmol), aniline (17 mg, 0.18 mmol) and DIEA (62 mg, 0.48 mmol) at room temperature over night. The reaction mixture was then diluted with a saturated solution of sodium bicarbonate (5 ml), and stirred for 1 hour. The solid was filtered, washed with water, dried under vacuum over P_2O_5 , to give
25 title compound (30 mg, 40 %).

^1H NMR (DMSO- d_6 , TFA) : 2.3 (m, 2H) ; 3.16 (t, 2H) ; 3.37 (t, 2H) ; 3.54 (d, 2H) ; 3.69 (t, 2H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.31 (t, 2H) ; 7.08 (t, 1H) ; 7.35 (m, 3H) ; 7.46 (d, 1H) ; 7.56 (d, 1H) ; 7.77 (d, 1H) ; 8.1 (s, 1H) ; 8.93 (s, 1H).

MS ES⁺ : 503 [M₂H]⁺

30 Example 98: Preparation of Compound 259 in Table 9

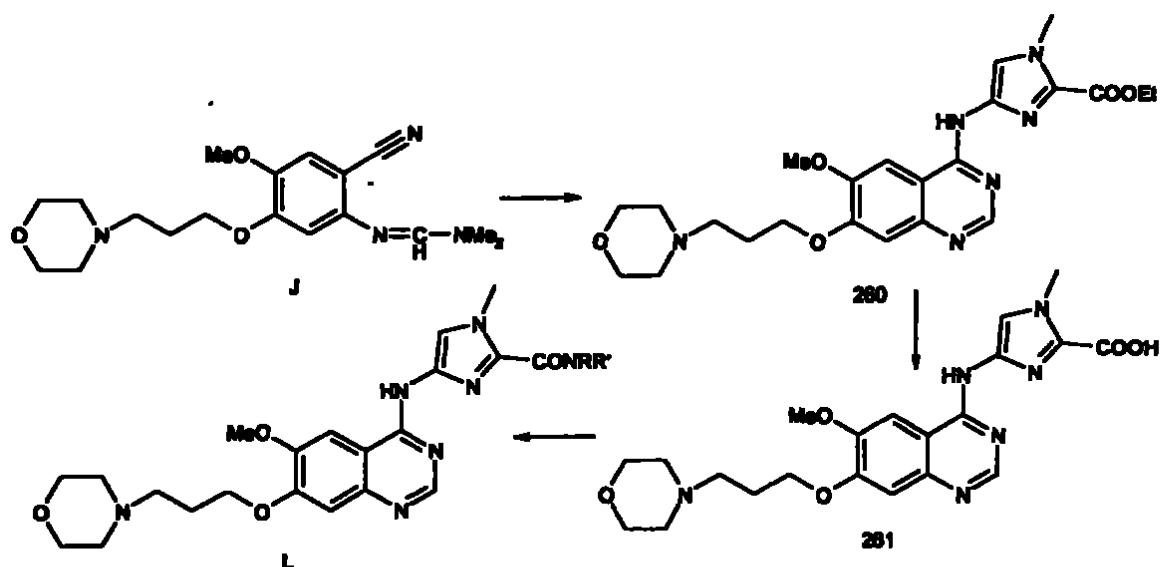
An analogous reaction to that described for the Example 97, but starting with cyclohexylamine (18 mg, 0.18 mmol) yielded title compound (30 mg, 39 %).

¹HNMR (DMSO-d₆, TFA) : 1.13 (m, 1H) ; 1.3 (m, 4H) ; 1.63 (m, 1H) ; 1.8 (m, 4H) ; 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.76 (m, 1H) ; 4.0 (s, 1H) ; 4.03 (d, 2H) ; 4.3 (t, 2H) ; 7.2 (d, 1H) ; 7.3 (s, 1H) ; 7.43 (d, 1H) ; 8.0 (s, 1H) ; 8.9 (s, 1H).

MS ES⁺ : 509 [M₄H]⁺

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General Scheme 11



Example 99: Preparation of Compound 260 in Table 10

- 10 Amidine J (1.04 g, 3 mmol) in acetic acid (10 ml) was reacted with ethyl 4-amino-1-methyl-2-imidazolecarboxylate hydrochloric acid (0.74 g, 3.6 mmol) in presence of dimethylamine / MeOH (1.25N, 2.9 ml, 3.6 mmol) at 130°C for 3 hours. The solvent was evaporated, the residue triturated with ether and filtered. The solid was suspended in water, the pH adjusted to 9 with an aqueous solution of sodium bicarbonate, the suspension was filtered, washed with
- 15 water, dried under vacuum over P₂O₅, to give title compound (1.1 g, 78 %).

¹HNMR (DMSO-d₆) : 1.32 (t, 3H) ; 1.96 (m, 2H) ; 2.37 (m, 4H) ; 2.44 (t, 2H) ; 3.58 (m, 4H) ; 3.94 (s, 3H) ; 4.0 (s, 3H) ; 4.17 (t, 2H) ; 4.28 (q, 2H) ; 7.16 (s, 1H) ; 7.99 (s, 1H) ; 8.07 (s, 1H) ; 8.53 (s, 1H) ; 10.55 (s, 1H).

Example 100: Preparation of Compound 261 in Table 10

- 20 Ester 260 (1.1 g, 2.34 mmol) in ethanol (23 ml) was reacted with sodium hydroxyde (6N, 2.3 ml) at 80°C for 2.5 hours. The mixture was cooled, and acidified with hydrochloric acid (6N) to pH 3. The suspension was recovered by centrifugation, washed with ethanol, ether, dried under vacuum over P₂O₅, to give title compound (930 mg, 73 %).

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847

¹HNMR (DMSO-d₆, TFA) : 2.31 (m, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.76 (t, 2H) ; 4.01 (s, 3H) ; 4.05 (m, 5H) ; 4.32 (t, 2H) ; 7.41 (s, 1H) ; 8.03 (s, 1H) ; 8.38 (s, 1H) ; 9.0 (s, 1H).

MS ES⁺ : 443 [M₂H]⁺

5

Example 101: Preparation of Compounds of General Structure I

Acid 261 (88 mg, 0.16 mmol) in DMF (1 ml) was reacted with O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluroniumhexafluorophosphate (73 mg, 0.19 mmol), the appropriate amine (0.18 mmol) and DIEA (82 mg, 0.4 mmol) at room temperature for 3 hours. The

10 solution was then diluted with a saturated solution of sodium bicarbonate (4 ml) and stirred at room temperature for 3 hours. The precipitate was filtered, washed with water, dried under vacuum over P₂O₅, to give title compound.

Example 102: Preparation of Compound 262 in Table 10

15 An analogous reaction to that described in Example 101, but starting with aniline (17 mg, 0.18 mmol) yielded title compound (37 mg, 44 %).

¹HNMR (DMSO-d₆, TFA) : 2.3 (m, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.02 (m, 5H) ; 4.06 (s, 3H) ; 4.31 (t, 2H) ; 7.13 (t, 1H) ; 7.38 (m, 3H) ; 7.78 (d, 2H) ; 7.99 (s, 1H) ; 8.27 (s, 1H) ; 9.01 (s, 1H). -- --

20 MS ES⁺ : 518 [M₂H]⁺

Example 103: Preparation of Compound 263 in Table 10

An analogous reaction to that described in Example 101, but starting with 4-fluoroaniline (20 mg, 0.18 mmol) yielded title compound (84 mg, 97 %).

25 ¹HNMR (DMSO-d₆, TFA) : 2.3 (m, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.1 (s, 3H) ; 4.31 (t, 2H) ; 7.21 (t, 2H) ; 7.39 (s, 1H) ; 7.82 (m, 2H) ; 7.98 (s, 1H) ; 8.32 (s, 1H) ; 9.01 (s, 1H).

MS ES⁺ : 536 [M₂H]⁺

30 **Example 104: Preparation of Compound 264 in Table 10**

An analogous reaction to that described in Example 101, but starting with N,N-dimethyl-1,4-phenylenediamine (24 mg, 0.18 mmol) yielded title compound (80 mg, 88 %).

¹HNMR (DMSO-d₆, TFA) : 2.3 (m, 2H) ; 3.17 (t, 2H) ; 3.21 (s, 6H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.02 (m, 5H) ; 4.1 (s, 3H) ; 4.31 (t, 2H) ; 7.4 (s, 1H) ; 7.66 (d, 2H) ; 7.98 (d, 2H) ; 8.01 (s, 1H) ; 8.32 (s, 1H) ; 9.01 (s, 1H).

MS ES⁺ : 561 [M₂H]⁺

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Example 105: Preparation of Compound 265 in Table 10

An analogous reaction to that described in Example 101, but starting with 4-chloroaniline (23 mg, 0.18 mmol) yielded title compound (55 mg, 62 %).

¹HNMR (DMSO-d₆, TFA) : 2.3 (m, 2H) ; 3.17 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.1 (s, 3H) ; 4.32 (t, 2H) ; 7.39 (s, 1H) ; 7.43 (d, 2H) ; 7.84 (d, 2H) ; 7.99 (s, 1H) ; 8.32 (s, 1H) ; 9.01 (s, 1H).

MS ES⁺ : 552, 554 [M₂H]⁺

Example 106: Preparation of Compound 266 in Table 10

15 An analogous reaction to that described in Example 101, but starting with pyrrolidine (13 mg, 0.18 mmol) yielded title compound (50 mg, 62 %).

¹HNMR (DMSO-d₆, TFA) : 1.85 (m, 4H) ; 2.28 (m, 2H) ; 3.15 (t, 2H) ; 3.32 (t, 2H) ; 3.5 (m, 4H) ; 3.66 (t, 2H) ; 3.89 (m, 5H) ; 3.98 (m, 5H) ; 4.27 (t, 2H) ; 7.33 (s, 1H) ; 7.85 (s, 1H) ; 8.29 (s, 1H) ; 8.96 (s, 1H).

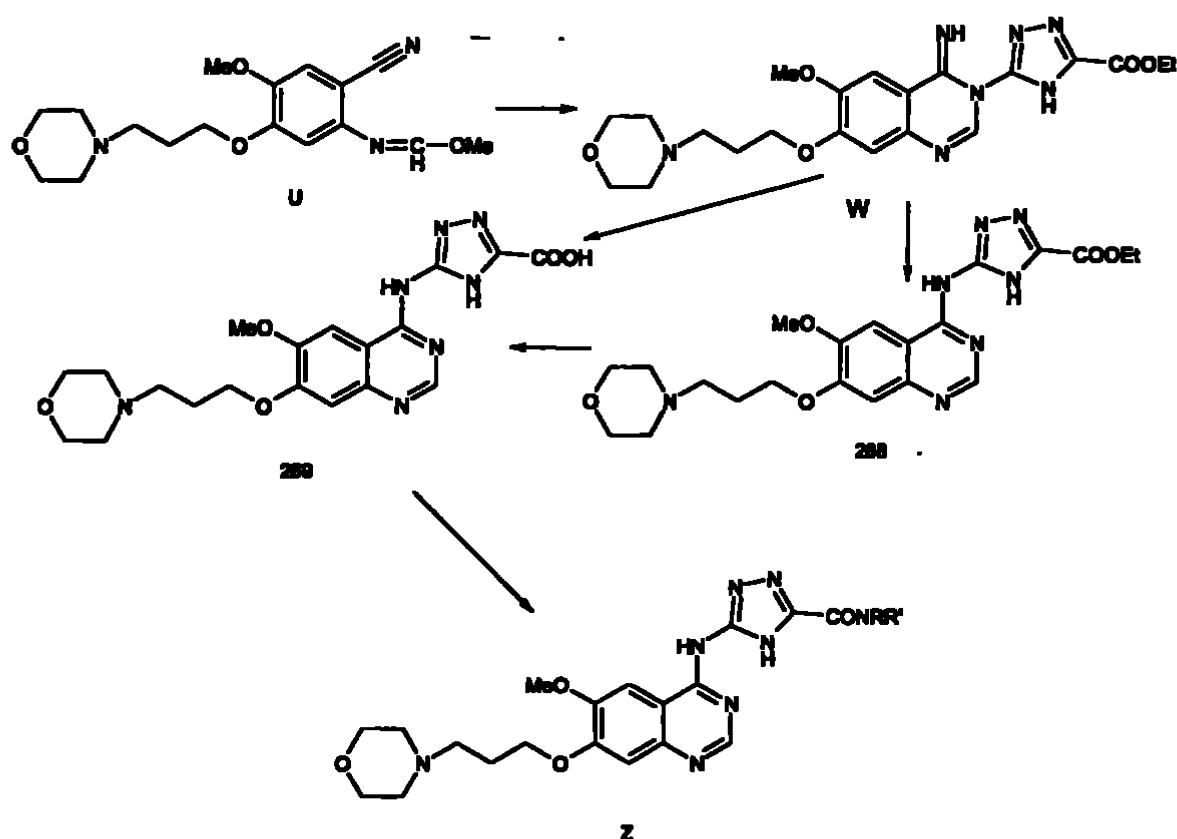
20 MS ES⁺ : 496 [M₂H]⁺

Example 107: Preparation of Compound 267 in Table 10

An analogous reaction to that described in Example 101, but starting with cyclohexylamine (18 mg, 0.18 mmol) yielded title compound (54 mg, 64 %).

25 ¹HNMR (DMSO-d₆, TFA) : 1.19 (m, 1H) ; 1.35 (m, 4H) ; 1.61 (m, 1H) ; 1.71 (m, 2H) ; 1.85 (m, 2H) ; 2.31 (m, 2H) ; 3.16 (t, 2H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.69 (t, 2H) ; 3.75 (m, 1H) ; 4.01 (s, 3H) ; 4.04 (m, 5H) ; 4.3 (t, 2H) ; 7.37 (s, 1H) ; 7.9 (s, 1H) ; 8.29 (s, 1H) ; 8.99 (s, 1H).

MS ES⁺ : 524 [M₂H]⁺

General Scheme 12**Example 108:****5 Step (a) Preparation of Intermediates of General formula W**

Imidate U (2 g, 6 mmol) in dimethylformamide (40 ml) was reacted with ethyl 5-amino-4H-1,2,4-triazole-3-carboxylate hydrochloric acid (1.16 g, 6 mmol) in presence of sodium hydride (60 %, 504 mg, 12.6 mmol) at 110°C for 7 hours, under argon. The mixture was then cooled to room temperature, and acetic acid (1.03 ml, 18 mmol) was added, the solvent was
 10 evaporated under vacuum, the residue purified by silica gel chromatography, eluent : CH₂Cl₂ / MeOH, 90/10 to give title compound (1.07 g, 39 %).

¹H NMR (DMSO-d₆, TFA) : 1.39 (t, 3H) ; 2.28 (m, 2H) ; 3.15 (t, 2H) ; 3.32 (t, 2H) ; 3.56 (d, 2H) ; 3.68 (t, 2H) ; 3.98 (s, 3H) ; 4.05 (d, 2H) ; 4.37 (t, 2H) ; 4.52 (q, 2H) ; 7.49 (s, 1H) ; 8.12 (s, 1H) ; 8.71 (s, 1H).

15 MS ES⁺ : 458 [M₁H]⁺

Step (b) : Preparation of Compound 268 in Table 11

Triazole ester W (80 mg, 0.17 mmol) in dimethylformamide (3 ml) was treated with dimethylamine acetate (0.52 mmol) at 70°C for 20 minutes. The mixture was cooled, the

solvent evaporated, and the residue purified by silica gel chromatography, eluent CH_2Cl_2 / MeOH / NH_3 , 90/10/1 to give title product (60 mg, 75 %).

^1H NMR ($\text{DMSO}-d_6$, TFA) : 1.34 (t, 3H) ; 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 4.0 (s, 3H) ; 4.04 (d, 2H) ; 4.36 (m, 4H) ; 7.48 (s, 1H) ; 8.26 (s, 1H) ; 9.01 (s, 1H).

MS ES^+ : 458 $[\text{M}_n\text{H}]^+$

Example 109: Preparation of Compound 269 in Table 11

Triazole ester 268 (900 mg, 1.97 mmol) in methanol (20 ml), was treated with sodium hydroxide (2N, 20 ml) at 80°C for 1.5 hour. The mixture was cooled, and acidified to pH 2.5 with hydrochloric acid (6N), the solid was recovered by filtration dried under vacuum over P_2O_5 to give title compound (843 mg, 100 %).

^1H NMR ($\text{DMSO}-d_6$, TFA) : 2.37 (m, 2H) ; 3.12 (t, 2H) ; 3.3 (t, 2H) ; 3.5 (d, 2H) ; 3.87 (t, 2H) ; 3.97 (d, 2H) ; 4.01 (s, 3H) ; 4.35 (t, 2H) ; 7.63 (s, 1H) ; 8.32 (s, 1H) ; 8.97 (s, 1H).

MS ES^+ : 430 $[\text{M}_n\text{H}]^+$.

Example 110: Preparation of Compound 270 in Table 11

Acid 269 (120 mg, 0.28 mmol) in DMF (2 ml) was reacted with aniline (0.025 ml, 0.28 mmol) in presence of O-(7-azabenzotriazol-1-yl) N,N,N',N'-tetramethyluronium hexafluorophosphate (106 mg, 0.28 mmol) and DIEA (0.12 ml, 0.7 mmol) at room temperature for 4 hours. The solvent was evaporated, the residue dissolved in methylene chloride / methanol, and treated with a methanolic solution of dimethylamine (2M, 1 ml) at room temperature over night. The solvent was evaporated, and the residue purified by flash silica gel chromatography, eluent CH_2Cl_2 / MeOH , 90/10 to give title compound (12 mg, 9 %).

^1H NMR ($\text{DMSO}-d_6$, TFA) : 2.3 (m, 2H) ; 3.18 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.33 (t, 2H) ; 7.16 (t, 1H) ; 7.39 (t, 2H) ; 7.45 (s, 1H) ; 7.83 (d, 2H) ; 8.2 (s, 1H) ; 8.95 (s, 1H).

MS ES^+ : 505 $[\text{M}_n\text{H}]^+$

851 849
5/8

-79-

Example 111: Preparation of Compound 271 in Table 11

An analogous reaction to that described in Example 110, but starting with 4-fluoroaniline (0.13 ml, 1.4 mmol) yielded title compound (44 mg, 18 %).

¹H NMR (DMSO-d₆, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 4.0 (s, 3H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 7.23 (t, 2H) ; 7.44 (s, 1H) ; 7.86 (m, 1H) ; 8.18 (s, 1H) ; 8.93 (s, 1H).

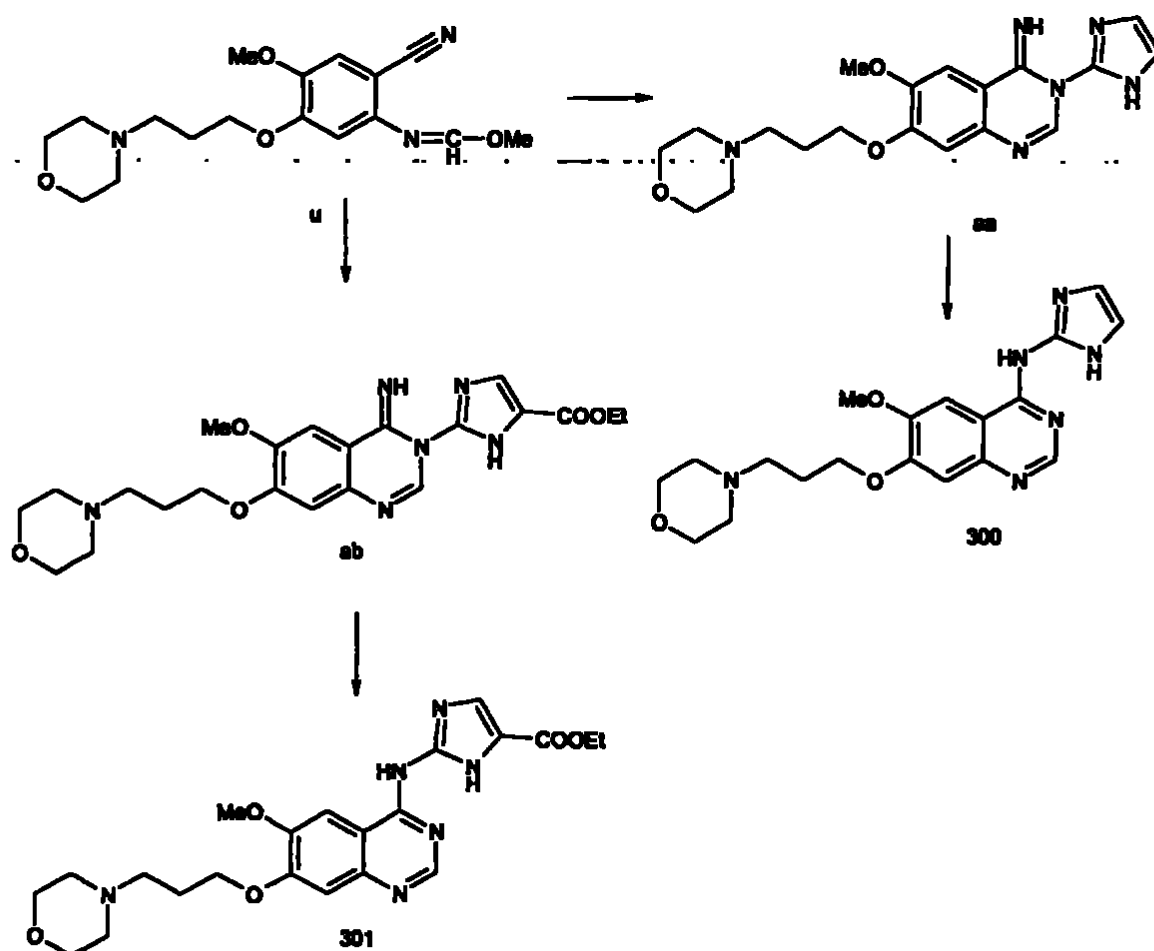
MS ES⁺ : 523 [M₄H]⁺

Example 112: Preparation of Compound 272 in Table 11

10 An analogous reaction to that described in Example 110 but starting with allylamine (0.13 ml, 1.75 mmol) yielded the title compound (26 mg, 10 %).

¹H NMR (DMSO-d₆, TFA) : 2.3 (m, 2H) ; 3.16 (t, 2H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.94 (d, 2H) ; 3.99 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (t, 2H) ; 5.13 (d, 1H) ; 5.18 (d, 1H) ; 5.92 (m, 1H) ; 7.41 (s, 1H) ; 8.17 (s, 1H) ; 8.91 (s, 1H).

15 MS ES⁺ : 469 [M₄H]⁺

General Scheme 13

Example 113: Preparation of Compound 300 in Table 12**Step 1: Preparation of Compound aa**

Imidate u, (200 mg, 0.6 mmol) in DMF (4 ml) was condensed with 2-aminoimidazole, sulfate (160 mg, 0.6 mmol) in presence of sodium hydride (60 %, 50 mg, 1.26 mmol) at 90°C for 2
5 hours. The mixture was cooled, acetic acid (0.01 ml, 1.8 mmol) was added, the solvent was evaporated, and the residue purified by silica gel chromatography, eluent CH₂Cl₂ / MeOH, 90/10 to give title compound (112 mg, 48 %).

¹HNMR (DMSO-d₆, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.33 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.97 (s, 3H) ; 4.03 (d, 2H) ; 4.36 (t, 2H) ; 7.41 (s, 2H) ; 7.47 (s, 1H) ; 8.13 (s, 1H) ; 8.66
10 (s, 1H).

MS ES⁺ : 385 [M₂H]⁺

Step 2: Preparation of Compound 300

Imidazole aa (105 mg, 0.273 mmol) in DMF (2 ml) was heated at 80°C for 0.3 hour in
15 presence of dimethylamine acetate (0.819 mmol), the solvent was evaporated, and the residue was purified by silica gel chromatography, eluent CH₂Cl₂ / MeOH sat. NH₃, 90/10 to give title compound (78 mg, 74 %).

¹HNMR (DMSO) : 1.96 (m, 2H) ; 2.39 (m, 4H) ; 2.46 (t, 2H) ; 3.6 (m, 4H) ; 3.9 (s, 3H) ; 4.18 (t, 2H) ; 6.9 (s, 2H) ; 7.14 (s, 1H) ; 7.84 (s, 1H) ; 8.39 (s, 1H).

20 MS ES⁺ : 385 [M₂H]⁺

Example 114: Preparation of Compound 301 in Table 12**Step 1: Preparation of Compound ah**

Imidate u (250 mg, 0.751 mmol) in DMF (4 ml) was reacted with ethyl 2-aminoimidazole-4-
25 carboxylate (117 mg, 0.751 mmol) in presence of sodium hydride (60 %, 30 mg, 0.826 mmol) at 100° C for 3 hours. The mixture was cooled, acetic acid (0.13 ml, 2.25 mmol) was added, the solvent was evaporated, and the residue purified by silica gel chromatography to give title compound (125 mg, 36 %).

¹HNMR (DMSO-d₆, TFA) : 1.32 (t, 3H) ; 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.98 (s, 3H) ; 4.03 (d, 2H) ; 4.33 (q, 2H) ; 4.37 (t, 2H) ; 7.49 (s, 1H) ; 8.11 (s, 1H) ; 8.2 (s, 1H) ; 8.65 (s, 1H).

MS ES⁺ : 457 [M₂H]⁺

Step 2: Preparation of Compound 301 in Table 12

Imidazole 3 (122 mg, 0.268 mmol) in DMF (2 ml) was heated at 80°C for 0.3 hour in presence of dimethylamine acetate (0.802 mmol). The solvent was evaporated, and the residue
5 was purified by silica gel chromatography, eluent CH₂Cl₂ / MeOH sat. NH₃ 95/5 to 90/10 to give title compound (105 mg, 86 %).

¹HNMR (DMSO-d₆, TFA) : 1.32 (t, 3H) ; 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.94 (s, 3H) ; 4.03 (d, 2H) ; 4.27 (t, 2H) ; 4.33 (q, 2H) ; 7.27 (s, 1H) ; 7.84 (s, 1H) ; 7.92 (s, 1H) ; 8.76 (s, 1H).

10 MS ES⁺ : 457 [M₂H]⁺

Biological Data

The compounds of the invention inhibit the serine/threonine kinase activity of the aurora2 kinase and thus inhibit the cell cycle and cell proliferation. These properties may be assessed,
15 for example, using one or more of the procedures set out below:

(a) In Vitro aurora2 kinase inhibition test

This assay determines the ability of a test compound to inhibit serine/threonine kinase activity. DNA encoding aurora2 may be obtained by total gene synthesis or by cloning. This
20 DNA may then be expressed in a suitable expression system to obtain polypeptide with serine/threonine kinase activity. In the case of aurora2, the coding sequence was isolated from cDNA by polymerase chain reaction (PCR) and cloned into the BamH1 and Not1 restriction endonuclease sites of the baculovirus expression vector pFastBac HTc (GibcoBRL/Life technologies). The 5' PCR primer contained a recognition sequence for the restriction
25 endonuclease BamH1 5' to the aurora2 coding sequence. This allowed the insertion of the aurora2 gene in frame with the 6 histidine residues, spacer region and rTEV protease cleavage site encoded by the pFastBac HTc vector. The 3' PCR primer replaced the aurora2 stop codon with additional coding sequence followed by a stop codon and a recognition sequence for the restriction endonuclease Not1 . This additional coding sequence (5' TAC CCA TAC GAT
30 GTT CCA GAT TAC GCT TCT TAA 3') encoded for the polypeptide sequence YPYDVPDYAS. This sequence, derived from the influenza hemagglutinin protein, is frequently used as a tag epitope sequence that can be identified using specific monoclonal

antibodies. The recombinant pFastBac vector therefore encoded for an N-terminally 6 his tagged, C terminally influenza hemagglutinin epitope tagged aurora2 protein. Details of the methods for the assembly of recombinant DNA molecules can be found in standard texts, for example Sambrook et al. 1989, *Molecular Cloning - A Laboratory Manual*, 2nd Edition, Cold Spring Harbor Laboratory press and Ausubel et al. 1999, *Current Protocols in Molecular Biology*, John Wiley and Sons Inc.

Production of recombinant virus can be performed following manufacturer's protocol from GibcoBRL. Briefly, the pFastBac-1 vector carrying the aurora2 gene was transformed into *E. coli* DH10Bac cells containing the baculovirus genome (bacmid DNA) and via a transposition event in the cells, a region of the pFastBac vector containing gentamycin resistance gene and the aurora2 gene including the baculovirus polyhedrin promoter was transposed directly into the bacmid DNA. By selection on gentamycin, kanamycin, tetracycline and X-gal, resultant white colonies should contain recombinant bacmid DNA encoding aurora2. Bacmid DNA was extracted from a small scale culture of several BH10Bac white colonies and transfected into *Spodoptera frugiperda* Sf21 cells grown in TC100 medium (GibcoBRL) containing 10% serum using CellFECTIN reagent (GibcoBRL) following manufacturer's instructions. Virus particles were harvested by collecting cell culture medium 72 hrs post transfection. 0.5 mls of medium was used to infect 100 ml suspension culture of Sf21s containing 1×10^7 cells/ml. Cell culture medium was harvested 48 hrs post infection and virus titre determined using a standard plaque assay procedure. Virus stocks were used to infect Sf9 and "High 5" cells at a multiplicity of infection (MOI) of 3 to ascertain expression of recombinant aurora2 protein.

For the large scale expression of aurora2 kinase activity, Sf21 insect cells were grown at 28°C in TC100 medium supplemented with 10% foetal calf serum (Viralex) and 0.2% F68 Pluronic (Sigma) on a Wheaton roller rig at 3 r.p.m. When the cell density reached 1.2×10^6 cells ml⁻¹ they were infected with plaque-pure aurora2 recombinant virus at a multiplicity of infection of 1 and harvested 48 hours later. All subsequent purification steps were performed at 4°C. Frozen insect cell pellets containing a total of 2.0×10^8 cells were thawed and diluted with lysis buffer (25 mM HEPES (N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulphonic acid]) pH7.4 at 4°C, 100 mM KCl, 25 mM NaF, 1 mM Na₂VO₄, 1 mM PMSF (phenylmethylsulphonyl fluoride), 2 mM 2-mercaptoethanol, 2 mM imidazole, 1 µg/ml aprotinin, 1 µg/ml pepstatin, 1 µg/ml leupeptin), using 1.0 ml per 3×10^7 cells. Lysis was achieved using a dounce homogeniser, following which the lysate was centrifuged at 41,000g

for 35 minutes. Aspirated supernatant was pumped onto a 5 mm diameter chromatography column containing 500 μ l Ni NTA (nitrilo-tri-acetic acid) agarose (Qiagen, product no. 30250) which had been equilibrated in lysis buffer. A baseline level of UV absorbance for the eluent was reached after washing the column with 12 ml of lysis buffer followed by 7 ml of wash buffer (25 mM HEPES pH7.4 at 4°C, 100 mM KCl, 20 mM imidazole, 2 mM 2-mercaptoethanol). Bound aurora2 protein was eluted from the column using elution buffer (25 mM HEPES pH7.4 at 4°C, 100 mM KCl, 400 mM imidazole, 2 mM 2-mercaptoethanol). An elution fraction (2.5 ml) corresponding to the peak in UV absorbance was collected. The elution fraction, containing active aurora2 kinase, was dialysed exhaustively against dialysis buffer (25 mM HEPES pH7.4 at 4°C, 45% glycerol (v/v), 100 mM KCl, 0.25% Nonidet P40 (v/v), 1 mM dithiothreitol).

Each new batch of aurora2 enzyme was titrated in the assay by dilution with enzyme diluent (25mM Tris-HCl pH7.5, 12.5mM KCl, 0.6mM DTT). For a typical batch, stock enzyme is diluted 1 in 666 with enzyme diluent & 20 μ l of dilute enzyme is used for each assay well. Test compounds (at 10mM in dimethylsulphoxide (DMSO)) were diluted with water & 10 μ l of diluted compound was transferred to wells in the assay plates. "Total" & "blank" control wells contained 2.5% DMSO instead of compound. Twenty microlitres of freshly diluted enzyme was added to all wells, apart from "blank" wells. Twenty microlitres of enzyme diluent was added to "blank" wells. Twenty microlitres of reaction mix (25mM Tris-HCl, 78.4mM KCl, 2.5mM NaF, 0.6mM dithiothreitol, 6.25mM MnCl₂, 6.25mM ATP, 7.5 μ M peptide substrate [biotin-LRRWSLGLRRWSLGLRRWSLGLRRWSLGL]) containing 0.2 μ Ci [γ ³²P]ATP (Amersham Pharmacia, specific activity $\geq$ 2500Ci/mmol) was then added to all test wells to start the reaction. The plates were incubated at room temperature for 60 minutes. To stop the reaction 100 μ l 20% v/v orthophosphoric acid was added to all wells. The peptide substrate was captured on positively-charged nitrocellulose P30 filtermat (Whatman) using a 96-well plate harvester (TomTek) & then assayed for incorporation of ³²P with a Beta plate counter. "Blank" (no enzyme) and "total" (no compound) control values were used to determine the dilution range of test compound which gave 50% inhibition of enzyme activity. In this test, compound 52 in Table 2 gave 50% inhibition of enzyme activity at a concentration of 0.167 μ M, and Compound 253 in Table 9 gave 50% inhibition of enzyme activity at 0.089 μ M.

(a) In Vitro cell proliferation assay

This assay determines the ability of a test compound to inhibit the growth of adherent mammalian cell lines, for example the human tumour cell line MCF7.

MCF-7 (ATCC HTB-22) or other adherent cells were typically seeded at 1×10^3 cells per well (excluding the peripheral wells) in DMEM (Sigma Aldrich) without phenol red, plus 10% foetal calf serum, 1% L-glutamine and 1% penicillin/streptomycin in 96 well tissue culture treated clear plates (Costar). The following day (day 1), the media was removed from a no treatment control plate and the plate stored at -80°C . The remaining plates were dosed with compound (diluted from 10mM stock in DMSO using DMEM (without phenol red, 10% FCS, 1% L-glutamine, 1% penicillin/streptomycin). Untreated control wells were included on each plate. After 3 days in the presence / absence of compound (day 4) the media was removed and the plates stored at -80°C . Twenty four hours later the plates were thawed at room temperature and cell density determined using the CyQUANT cell proliferation assay kit (c-7026/c-7027 Molecular Probes Inc.) according to manufacturers directions. Briefly, 200 μl of a cell lysis / dye mixture (10 μl of 20X cell lysis buffer B, 190 μl of sterile water, 0.25 μl of CYQUANT GR dye) was added to each well and the plates incubated at room temperature for 5 minutes in the dark. The fluorescence of the wells was then measured using a fluorescence microplate reader (gain 70, 2 reads per well, 1 cycle with excitation 485nm and emission 530nm using a CytoFluor plate reader (PerSeptive Biosystems Inc.)). The values from day 1 and day 4 (compound treated) together with the values from the untreated cells were used to determine the dilution range of a test compound that gave 50% inhibition of cell proliferation. Compound 52 in Table 2 was effective in this test at $0.616\mu\text{M}$ and Compound 253 in Table 8 was effective at $5.9\mu\text{M}$.

These values could also be used to calculate the dilution range of a test compound at which the cell density dropped below the day 1 control value. This indicates the cytotoxicity of the compound.

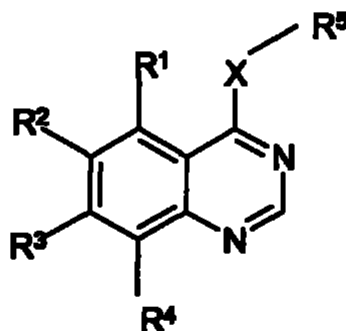
(a) In Vitro cell cycle analysis assay

This assay determines the ability of a test compound to arrest cells in specific phases of the cell cycle. Many different mammalian cell lines could be used in this assay and MCF7 cells are included here as an example. MCF-7 cells were seeded at 3×10^5 cells per T25 flask (Costar) in 5 ml DMEM (no phenol red 10% FCS, 1% L-glutamine 1% penicillin /

streptomycin). Flasks were then incubated overnight in a humidified 37°C incubator with 5% CO₂. The following day 1ml of DMEM (no phenol red 10% FCS, 1% L-glutamine 1% penicillin / streptomycin) carrying the appropriate concentration of test compound solubilised in DMSO was added to the flask . A no compound control treatments was also included (0.5% DMSO). The cells were then incubated for a defined time (usually 24 hours) with compound. After this time the media was aspirated from the cells and they were washed with 5ml of prewarmed (37°C) sterile PBSA, then detached from the flask by brief incubation with trypsin and followed by resuspension in 10ml of 1% Bovine Serum Albumin (BSA, Sigma-Aldrich Co.) in sterile PBSA. The samples were then centrifuged at 2200rpm for 10 min. The supernatant was aspirated and the cell pellet was resuspended in 200µl of 0.1% (w/v) Tris sodium citrate, 0.0564% (w/v) NaCl, 0.03% (v/v) Nonidet NP40, [pH 7.6]. Propidium Iodide (Sigma Aldrich Co.) was added to 40µg/ml and RNAase A (Sigma Aldrich Co.) to 100µg/ml. The cells were then incubated at 37°C for 30 minutes. The samples were centrifuged at 2200rpm for 10 min, the supernatant removed and the remaining pellet (nuclei) resuspended in 200µl of sterile PBSA. Each sample was then syringed 10 times using 21 gauge needle. The samples were then transferred to LPS tubes and DNA content per cell analysed by Fluorescence activated cell sorting (FACS) using a FACScan flow cytometer (Becton Dickinson). Typically 25000 events were counted and recorded using CellQuest v1.1 software (Verity Software). Cell cycle distribution of the population was calculated using Modfit software (Verity Software) and expressed as percentage of cells in G0/G1, S and G2/M phases of the cell cycle.

Treating MCF7 cells with 1µM Compound 52 in Table 2 for 24 hours produced the following changes in cell cycle distribution:

Treatment	% Cells in G2/M
DMSO (control)	9.27%
10µM Compound 52	>50%

855 853
Z**CLAIMS****1. The use of a compound of formula (I)**

5

(I)

or a salt, ester or amide thereof;

10 where X is O, or S, S(O) or S(O)₂ or NR⁶ where R⁶ is hydrogen or C₁₋₆alkyl;R⁵ is an optionally substituted 5-membered heteroaromatic ring,R¹, R², R³, R⁴ are independently selected from, halo, cyano, nitro, trifluoromethyl, C₁₋₃alkyl, -NR⁷R⁸ (wherein R⁷ and R⁸, which may be the same or different, each represents hydrogen or C₁₋₃alkyl), or -X¹R⁹ (wherein X¹ represents a direct bond, -O-, -CH₂-, -OCO-, carbonyl, -S-, -15 SO-, -SO₂-, -NR¹⁰CO-, -CONR¹¹-, -SO₂NR¹²-, -NR¹³SO₂- or -NR¹⁴- (wherein R¹⁰, R¹¹, R¹², R¹³ and R¹⁴ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl), and R⁹ is selected from one of the following groups:1) hydrogen or C₁₋₃alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro or amino,20 2) C₁₋₃alkylX²COR¹⁵ (wherein X² represents -O- or -NR¹⁶- (in which R¹⁵ represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹⁶ represents C₁₋₃alkyl, -NR¹⁷R¹⁸ or -OR¹⁹ (wherein R¹⁷, R¹⁸ and R¹⁹ which may be the same or different each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl));25 3) C₁₋₃alkylX³R²⁰ (wherein X³ represents -O-, -S-, -SO-, -SO₂-, -OCO-, -NR²¹CO-, -CONR²²-, -SO₂NR²³-, -NR²⁴SO₂- or -NR²⁵- (wherein R²¹, R²², R²³, R²⁴ and R²⁵ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁰ represents hydrogen, C₁₋₃alkyl, cyclopentyl, cyclohexyl or a 5-6-membered saturated heterocyclic group with 1-2

heteroatoms, selected independently from O, S and N, which C₁₋₃alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C₁₋₄alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl and C₁₋₄alkoxy);

- 5 4) C₁₋₃alkylX⁴C₁₋₃alkylX⁵R²⁶ (wherein X⁴ and X⁵ which may be the same or different are each -O-, -S-, -SO-, -SO₂-, -NR²⁷CO-, -CONR²⁸-, -SO₂NR²⁹-, -NR³⁰SO₂- or -NR³¹- (wherein R²⁷, R²⁸, R²⁹, R³⁰ and R³¹ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁶ represents hydrogen or C₁₋₃alkyl);
- 5) R³² (wherein R³² is a 5-6-membered saturated heterocyclic group (linked via carbon or
10 nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl and C₁₋₄alkylsulphonyl(C₁₋₄alkyl));
- 6) C₁₋₃alkylR³² (wherein R³² is as defined hereinbefore);
- 7) C₂₋₃alkenylR³² (wherein R³² is as defined hereinbefore);
- 15 8) C₂₋₃alkynylR³² (wherein R³² is as defined hereinbefore);
- 9) R³³ (wherein R³³ represents a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-3 heteroatoms selected from O, N and S, which pyridone, phenyl or aromatic heterocyclic group may carry up to 5 substituents on an available carbon atom selected from hydroxy, halogeno, amino, C₁₋₄alkyl, C₁₋₄alkoxy,
20 C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy, carboxy, trifluoromethyl, cyano, -CONR³⁴R³⁵ and -NR³⁶COR³⁷ (wherein R³⁴, R³⁵, R³⁶ and R³⁷, which may be the same or different, each represents hydrogen, C₁₋₄alkyl or C₁₋₃alkoxyC₂₋₃alkyl));
- 10) C₁₋₃alkylR³³ (wherein R³³ is as defined hereinbefore);
- 11) C₂₋₃alkenylR³³ (wherein R³³ is as defined hereinbefore);
- 25 12) C₂₋₃alkynylR³³ (wherein R³³ is as defined hereinbefore);
- 13) C₁₋₃alkylX⁶R³³ (wherein X⁶ represents -O-, -S-, -SO-, -SO₂-, -NR³⁸CO-, -CONR³⁹-, -SO₂NR⁴⁰-, -NR⁴¹SO₂- or -NR⁴²- (wherein R³⁸, R³⁹, R⁴⁰, R⁴¹ and R⁴² each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R³³ is as defined hereinbefore);
- 14) C₂₋₃alkenylX⁷R³³ (wherein X⁷ represents -O-, -S-, -SO-, -SO₂-, -NR⁴³CO-, -CONR⁴⁴-, -SO₂NR⁴⁵-, -NR⁴⁶SO₂- or -NR⁴⁷- (wherein R⁴³, R⁴⁴, R⁴⁵, R⁴⁶ and R⁴⁷ each independently
30 represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R³³ is as defined hereinbefore);

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15) $C_{2,3}\text{alkynyl}X^8R^{33}$ (wherein X^8 represents $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^{48}CO-$, $-CONR^{49}-$, $-SO_2NR^{50}-$, $-NR^{51}SO_2-$ or $-NR^{52}-$ (wherein R^{48} , R^{49} , R^{50} , R^{51} and R^{52} each independently represents hydrogen, $C_{1,3}\text{alkyl}$ or $C_{1,3}\text{alkoxy}C_{2,3}\text{alkyl}$) and R^{33} is as defined hereinbefore);

16) $C_{1,3}\text{alkyl}X^9C_{1,3}\text{alkyl}R^{33}$ (wherein X^9 represents $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^{53}CO-$, $-CONR^{54}-$

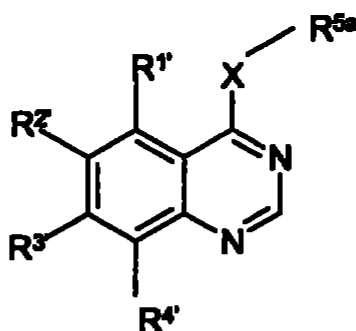
5 , $-SO_2NR^{55}-$, $-NR^{56}SO_2-$ or $-NR^{57}-$ (wherein R^{53} , R^{54} , R^{55} , R^{56} and R^{57} each independently represents hydrogen, $C_{1,3}\text{alkyl}$ or $C_{1,3}\text{alkoxy}C_{2,3}\text{alkyl}$) and R^{33} is as defined hereinbefore); and

17) $C_{1,3}\text{alkyl}X^9C_{1,3}\text{alkyl}R^{32}$ (wherein X^9 and R^{32} are as defined hereinbefore);

in the preparation of a medicament for use in the inhibition of aurora 2 kinase.

10 2. A method for inhibiting aurora 2 kinase 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), as defined in claim 1 or a pharmaceutically acceptable salt, or an *in vivo* hydrolysable ester thereof.

15 3. A compound of formula (IA)



(IA)

20

or a salt, ester or amide thereof;

where X is as defined in relation to formula (I);

$R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$ are equivalent to R^1 , R^2 , R^3 , R^4 as defined in relation to formula (I) and R^{5a} is an optionally substituted 5-membered heteroaromatic ring, subject to the following provisos:

25 (i) that where R^{5a} is a pyrazole group, it carries a substituent of formula (k), (II) of (VI) above,

(ii) that where X is NH and R^{4a} is a substituted pyrazolone or tetrazolyl group, at least one of R^{1'}, R^{2'}, R^{3'} and R^{4'} is other than hydrogen; or

(iii) that where X is O and R^{4a} is 1-methyl-4-nitro-1H-imidazol-5-yl, at least one of R^{1'}, R^{2'}, R^{3'} and R^{4'} is other than hydrogen.

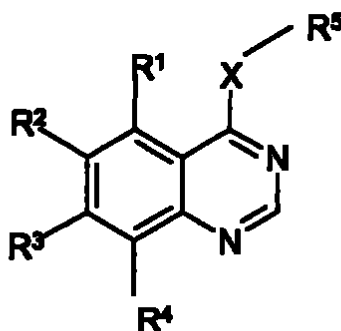
5

4. A compound according to claim 3, for use in a method of treatment of the human or animal body by therapy.

10 5. A pharmaceutical composition comprising a compound according to claim 3, in combination with a pharmaceutically acceptable carrier.

ABSTRACT**TITLE: CHEMICAL COMPOUNDS**

5 The use of a compound of formula (I)



(I)

10 or a salt, ester or amide thereof;

where X is O, or S, S(O) or S(O)₂ or NR⁶ where R⁶ is hydrogen or C₁₋₆alkyl,;

R⁵ is an optionally substituted 5-membered heteroaromatic ring,

R¹, R², R³, R⁴ are independently selected from various specified moieties, in the preparation of

15 a medicament for use in the inhibition of aurora 2 kinase.

Certain compounds are novel and these, together with pharmaceutical compositions containing them are also described and claimed.



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2020
Bogotá, D.C.,

Doctor:
Ramiro Castro Duque
Apoderado
Astrazeneca AB

Oficio N°
06397

ASUNTO:	Radicación N°	02-116483
	Solicitud internacional	PCT/SE01/01450
	Fecha inicio fase nacional	28/01/2003
	Trámite	011
	Evento	379
	Actuación	330
	Folios	001

Como resultado del examen de forma, realizado con fundamento en 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 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 acredite la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.
- ☐ 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. 28-k) Decisión 486).

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 CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha 11 de febrero de 2020.