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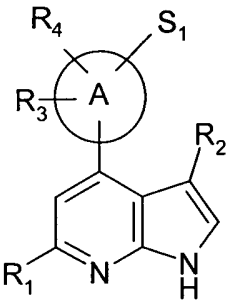
(54) **Title:** 1H-PYRROLO[2,3-B]PYRIDINE DERIVATIVES USEFUL AS HSP90 INHIBITORS



(I)

(57) **Abstract:** Compounds of formula (I) have HSP90 inhibitory activity: ring A is an aryl or heteroaryl ring or ring system; R1 is hydrogen, fluoro, chloro, bromo, or a radical of formula (1A): -X-Alk^1-$(Z)_m$-$(Alk^2)_n$-Q (IA) wherein X is a bond, -O-, -S-, -S(O)-, $-SO_2-$, or -NH-, Z is -O-, -S-, -(C=O)-, -(C=S)-, -S(O)-, $-SO_2-$, $-NR^A-$, or, in either orientation -C(=O)O-, -C(=O)NR^A-, -C(=S)NR^A-, $-SO_2NR^A-$, -NR^AC(=O)-, or -$NR^A SO_2-$ wherein R^A is hydrogen or C_1-C_6 alkyl in which one or more hydrogens is optionally substituted by fluorine;Alk^1 and AIk^2 are optionally substituted divalent C_1-C_3 alkylene:or C_2-C_3 alkenylene radicals, m and n are independently 0 or 1, and Q is hydrogen or an optionally substituted carbocyclic or heterocyclic radical; R_2 is cyano (-CN), fluoro, chloro, bromo, methyl, ethyl, -OH, $-CH_2OH$, $-C(=O)NH_2$,-C(=O)H, $-C(=O)CH_3$, or $-NH_2$; R_3 and R_4 are independently selected from hydrogen, fluoro, chloro, bromo, cyano (-CN), C_1-C_3alkyl optionally substituted with one or more fluorine substituents, C_1-C_3alkoxy optionally substituted with one or more fluorine substituents, $-CH=CH_2$, -C≡CH, cyclopropyl and $-NH_2$, or R_3 and R_4 together represent methylenedioxy ($-OCH_2O-$) or ethylenedioxy ($-OCH_2CH_2O-$) in either of which one or more hydrogens are optionally replaced by fluorine; S_1 is as defined in the description.

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1H-PYRROLO[2,3-B]PYRIDINE DERIVATIVES USEFUL AS HSP90 INHIBITORS

This invention relates to aryl- or heteroaryl-substituted aza-indole (ie aryl- or heteroaryl-substituted 1H-pyrrolo[2,3-b]pyridine) compounds having HSP90 inhibitory activity, to the use of such compounds in medicine, in relation to diseases which are responsive to inhibition of HSP90 activity such as cancers, and to pharmaceutical compositions containing such compounds.

Background to the invention

Molecular chaperones maintain the appropriate folding and conformation of proteins and are crucial in regulating the balance between protein synthesis and degradation. They have been shown to be important in regulating many important cellular functions, such as cell proliferation and apoptosis (Jolly and Morimoto, 2000; Smith et al., 1998; Smith, 2001).

Heat Shock Proteins (Hsps)

Exposure of cells to a number of environmental stresses, including heat shock, alcohols, heavy metals and oxidative stress, results in the cellular accumulation of a number of chaperones, commonly known as heat shock proteins (Hsps). Induction of Hsps protects the cell against the initial stress insult, enhances recovery and leads to maintenance of a stress tolerant state. It has also become clear, however, that certain Hsps may also play a major molecular chaperone role under normal, stress-free conditions by regulating the correct folding, degradation, localization and function of a growing list of important cellular proteins.

A number of multigene families of Hsps exist, with individual gene products varying in cellular expression, function and localization. They are classified according to molecular weight, e.g., Hsp70, Hsp90, and Hsp27. Several diseases in humans can be acquired as a result of protein misfolding (reviewed in Tytell et al., 2001; Smith et al., 1998). Hence the development of therapies which disrupt the molecular chaperone machinery may prove to be beneficial. In some conditions (e.g., Alzheimer's disease, prion diseases and Huntington's disease), misfolded proteins can cause protein aggregation resulting in neurodegenerative disorders. Also, misfolded proteins may result in loss of wild type protein function, leading to deregulated molecular and physiological functions in the cell.

Hsps have also been implicated in cancer. For example, there is evidence of differential expression of Hsps which may relate to the stage of tumour progression (Martin et al., 2000; Conroy et al., 1996; Kawanishi et al., 1999; Jameel et al., 1992; Hoang et al., 2000; Lebeau et al., 1991). As a result of the involvement of Hsp90 in various critical oncogenic pathways and the discovery that certain natural products with anticancer activity are targeting this molecular chaperone suggests that inhibiting the function of Hsp90 may be useful in the treatment of cancer. To this end, the first in class natural product 17AAG is currently in Phase II clinical trials.

Hsp90

Hsp90 constitutes about 1-2% of total cellular protein. In cells, it forms dynamic multi-protein complexes with a wide variety of accessory proteins (referred to as co-chaperones) which appear responsible for regulating the chaperone function. It is essential for cell viability and it exhibits dual chaperone functions (Young et al., 2001). When cells undergo various environmental cellular stresses, Hsp90 forms a core component of the cellular stress response by interacting with many proteins after their native conformation has been altered. Environmental stresses, such as heat shock, heavy metals or alcohol, generate localised protein unfolding. Hsp90 (in concert with other chaperones) binds these unfolded proteins allowing adequate refolding and preventing non-specific aggregation (Smith et al., 1998). In addition, recent results suggest that Hsp90 may also play a role in buffering against the effects of mutation, presumably by correcting the inappropriate folding of mutant proteins (Rutherford and Lindquist, 1998). However, Hsp90 also has an important regulatory role. Under normal physiological conditions, together with its endoplasmic reticulum homologue GRP94, Hsp90 plays a housekeeping role in the cell, maintaining the conformational stability and maturation of many client proteins. These can be subdivided into three groups: (a) steroid hormone receptors (e.g. estrogen receptor, progesterone receptor) (b) Ser/Thr or tyrosine kinases (e.g. Her2, Raf-1, CDK4, and Lck), and (c) a collection of apparently unrelated proteins, e.g. mutant p53 and the catalytic subunit of telomerase hTERT. It has also been shown recently that Hsp90 is responsible for stabilising and activating mutated kinases where the wild type kinase is not an Hsp90 client (for an example see the B-Raf story published in da Rocha Dias et al., 2005). All of these proteins play key regulatory roles in many physiological and biochemical processes in the cell. New client

proteins of Hsp90 are being constantly identified; see http://www.picard.ch/downloads/Hsp90interactors.pdf for the most up to date list.

The highly conserved Hsp90 family in humans consists of four genes, namely the cytosolic Hsp90α and Hsp90β isoforms (Hickey et al., 1989), GRP94 in the endoplasmic reticulum (Argon et al., 1999) and Hsp75/TRAP1 in the mitochondrial matrix (Felts et al., 2000). Apart from the differences in sub-cellular localisation, very little is known about the differences in function between Hsp90α/β, GRP94 and TRAP1. Initial reports suggesting that certain client proteins were chaperoned by a specific Hsp90 (e.g. Her2 by Grp94 alone) appear to have been erroneous.

Hsp90 participates in a series of complex interactions with a range of client and regulatory proteins (Smith, 2001). Although the precise molecular details remain to be elucidated, biochemical and X-ray crystallographic studies (Prodromou et al., 1997; Stebbins et al., 1997) carried out over the last few years have provided increasingly detailed insights into the chaperone function of Hsp90.

Following earlier controversy on this issue, it is now clear that Hsp90 is an ATP-dependent molecular chaperone (Prodromou et al, 1997), with dimerisation of the nucleotide binding domains being essential for ATP hydrolysis, which is in turn essential for chaperone function (Prodromou et al, 2000a). Binding of ATP results in the formation of a toroidal dimer structure in which the N terminal domains are brought into closer contact with each other resulting in a conformational switch known as the 'clamp mechanism' (Prodromou and Pearl, 2000b). This conformational switching is, in part, regulated by the various co-chaperones associated with Hsp90 (Siligardi et al., 2004).

Known Hsp90 Inhibitors

The first class of Hsp90 inhibitors to be discovered was the benzoquinone ansamycin class, which includes the compounds herbimycin A and geldanamycin. They were shown to reverse the malignant phenotype of fibroblasts transformed by the v-*Src* oncogene (Uehara et al., 1985), and subsequently to exhibit potent antitumour activity in both *in vitro* (Schulte et al., 1998) and *in vivo* animal models (Supko et al., 1995).

Immunoprecipitation and affinity matrix studies have shown that the major mechanism of action of geldanamycin involves binding to Hsp90 (Whitesell et al., 1994; Schulte and Neckers, 1998). Moreover, X-ray crystallographic studies have shown that geldanamycin competes at the ATP binding site and inhibits the intrinsic ATPase activity of Hsp90 (Prodromou et al., 1997; Panaretou et al., 1998). This interruption of the chaperone cycle (through blockage of the ATP turnover) causes the loss of the co-chaperone p23 from the complex and the targeting of the client proteins for degradation via the ubiquitin proteasome pathway. 17-Allylamino, 17-demethoxygeldanamycin (17AAG) retains the property of Hsp90 inhibition resulting in client protein depletion and antitumour activity in cell culture and xenograft models (Schulte et al, 1998; Kelland et al, 1999), but has significantly less hepatotoxicity than geldanamycin (Page et al, 1997). Of interest, 17AAG has been shown to be much more active on tumour cells than its affinity for purified Hsp90 would suggest. This has lead to the suggestion that tumour cells (but not non-tumourigenic cells) contain a high-affinity conformation of Hsp90 to which 17AAG binds more tightly, and confers tumour selectivity on Hsp90 inhibitors (Kamal et al., 2003). 17AAG is currently being evaluated in Phase II clinical trials.

Radicicol is a macrocyclic antibiotic shown to reverse the malignant phenotype of v-*Src* and v-*Ha-Ras* transformed fibroblasts (Kwon et al, 1992; Zhao et al, 1995). It was shown to degrade a number of signalling proteins as a consequence of Hsp90 inhibition (Schulte et al., 1998). X-ray crystallographic data confirmed that radicicol also binds to the N terminal domain of Hsp90 and inhibits the intrinsic ATPase activity (Roe et al., 1998). Radicicol lacks antitumour activity *in vivo* due to the unstable chemical nature of the compound.

Coumarin antibiotics are known to bind to bacterial DNA gyrase at an ATP binding site homologous to that of the Hsp90. The coumarin, novobiocin, was shown to bind to the carboxy terminus of Hsp90, i.e., at a different site to that occupied by the benzoquinone ansamycins and radicicol which bind at the N-terminus (Marcu et al., 2000b). However, this still resulted in inhibition of Hsp90 function and degradation of a number of Hsp90-chaperoned signalling proteins (Marcu et al., 2000a). Geldanamcyin cannot bind Hsp90 subsequent to novobiocin; this suggests that some interaction between the N and C

terminal domains must exist and is consistent with the view that both sites are important for Hsp90 chaperone properties.

A purine-based Hsp90 inhibitor, PU3, has been shown to result in the degradation of signalling molecules, including Her2, and to cause cell cycle arrest and differentiation in breast cancer cells (Chiosis et al., 2001). Recent studies have identified other purine-based compounds with activity against Her2 and activity in cell growth inhibition assays (Dymock et al 2004; Kasibhatla et al 2003; Llauger et al 2005).

Patent publications WO 2004/050087, WO 2004/056782, WO 2004/072051, WO 2004/096212, WO 2005/000300, WO 2005/021552, WO 2005/034950, WO 2005/063222; WO 2005/028434; WO 2005/061461, WO2006/008503 WO 2006/0010594 WO 2006/0010595 WO 2006/0014744 WO 2006/018082 WO 2006/039977 WO 2006/051808 WO 2006/055760 WO 2006/075095 WO 2006/079789 WO 2006/084030 and WO 2006/087077 also relate to inhibition of Hsp90.

Hsp90 as a Therapeutic Target

Due to its involvement in regulating a number of signalling pathways that are crucially important in driving the phenotype of a tumour, and the discovery that certain bioactive natural products exert their effects via Hsp90 activity, the molecular chaperone Hsp90 is currently being assessed as a new target for anticancer drug development (Neckers et al., 1999).

The predominant mechanism of action of geldanamycin, 17AAG, and radicicol involves binding to Hsp90 at the ATP binding site located in the N-terminal domain of the protein, leading to inhibition of the intrinsic ATPase activity of Hsp90 (Prodromou et al., 1997; Stebbins et al., 1997; Panaretou et al., 1998).

Inhibition of Hsp90 ATPase activity by 17AAG induces the loss of p23 from the chaperone-client protein complex interrupting the chaperone cycle. This leads to the formation of a Hsp90-client protein complex that targets these client proteins for degradation via the ubiquitin proteasome pathway (Neckers et al., 1999; Whitesell & Lindquist, 2005). Treatment with Hsp90 inhibitors leads to selective degradation of

important proteins (for example Her2, Akt, estrogen receptor and CDK4) involved in cell proliferation, cell cycle regulation and apoptosis, processes which are fundamentally important in cancer.

The preclinical development of 17AAG as an anticancer agent has been well documented (Sausville et al., 2003) and is currently undergoing Phase II clinical trials. Phase I clinical trials results have been recently published (Banerji et al., 2005; Goetz et al., 2005; Ramanathan et al., 2005 and Grem et al., 2005). Of all these trials, the one conducted by Banerji et al. proved the most positive with a maximum dose of 450mg/m2/week achieved with PD marker responses in the majority of patients and possible antitumour activity in two patients

Inhibition of Hsp90 function has been shown to cause selective degradation of important signalling proteins involved in cell proliferation, cell cycle regulation and apoptosis, processes which are fundamentally important and which are commonly deregulated in cancer (Hostein et al., 2001). An attractive rationale for developing drugs against this target for use in the clinic is that by simultaneously depleting proteins associated with the transformed phenotype, one may obtain a strong antitumour effect and achieve a therapeutic advantage against cancer versus normal cells. These events downstream of Hsp90 inhibition are believed to be responsible for the antitumour activity of Hsp90 inhibitors in cell culture and animal models (Schulte et al., 1998; Kelland et al., 1999).

Recent work has shown that the acetylation status of Hsp90 also plays a role in the control of the chaperone cycle. Inhibition of HDAC6 by either small molecule inhibitors or through siRNA gene targeting interrupts the chaperone cycle. Such treatments cause client protein degradation in a fashion analogous to small molecule ATP site inhibitors (Kovacs et al, 2005; Aoyagi & Archer, 2005).

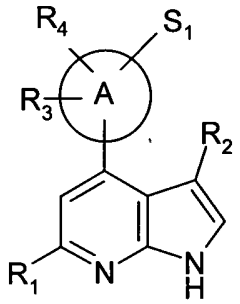
Brief description of the invention

This invention is based on the finding that a class of aryl- or heteroaryl-substituted aza-indole compounds has Hsp90 inhibitory activity, and is of interest in the treatment of diseases responsive to inhibition of Hsp90 activity.

Patent publication WO 2006/046023 is concerned with ortho-condensed pyridine and pyrimidine derivatives (eg purines) as protein kinase inhibitors. The definition of the compounds with which that publication is concerned is very broad, but no aryl- or heteroaryl-substituted aza-indole compounds are particularized or exemplified therein. Also, since the publication is concerned with protein kinase inhibitors, it provides no information concerning the activity of 4-aryl or 4-heteroaryl aza-indole derivatives against Hsp90.

Detailed description of the invention

In one broad aspect the present invention provides a compound of formula (I), or a salt, N-oxide, hydrate, or solvate thereof:



(I)

wherein

ring A is an aryl or heteroaryl ring or ring system;

R_1 is hydrogen, fluoro, chloro, bromo, or a radical of formula (1A):

$$-X\text{-}Alk^1\text{-}(Z)_m\text{-}(Alk^2)_n\text{-}Q \quad (IA)$$

wherein

X is a bond, –O-, -S- -S(O)-, $-SO_2$-, or -NH-,

Z is –O-, -S-, -(C=O)-, -(C=S)-, -S(O)-, $-SO_2$-, $-NR^A$-, or, in either orientation -C(=O)O-, $-C(=O)NR^A$- , $-C(=S)NR^A$-, $-SO_2NR^A$-, $-NR^AC(=O)$-, or $-NR^ASO_2$- wherein R^A is hydrogen or C_1-C_6 alkyl in which one or more hydrogens is optionally substituted by fluorine;

Alk^1 and Alk^2 are optionally substituted divalent C_1-C_3 alkylene or C_2-C_3 alkenylene radicals,

m, and n are independently 0 or 1, and

Q is hydrogen or an optionally substituted carbocyclic or heterocyclic radical;

$\mathbf{R_2}$ is cyano (-CN), fluoro, chloro, bromo, methyl, ethyl, -OH, $-CH_2OH$, $-C(=O)NH_2$, $-C(=O)H$, $-C(=O)CH_3$, or $-NH_2$;

$\mathbf{R_3}$ **and** $\mathbf{R_4}$ are independently selected from hydrogen, fluoro, chloro, bromo, cyano (-CN), C_1-C_3alkyl optionally substituted with one or more fluorine substituents, C_1-C_3alkoxy optionally substituted with one or more fluorine substituents, $-CH=CH_2$, $-C\equiv CH$, cyclopropyl and $-NH_2$, or R_3 and R_4 together represent methylenedioxy ($-OCH_2O-$) or ethylenedioxy ($-OCH_2CH_2O-$) in either of which one or more hydrogens are optionally replaced by fluorine;

$\mathbf{S_1}$ is hydrogen, or a substituent selected from fluoro, chloro, bromo, cyano (-CN), C_1-C_3alkyl optionally substituted with one or more fluorine substituents, C_1-C_3alkoxy optionally substituted with one or more fluorine substituents, $-CH=CH_2$, $-C\equiv CH$, cyclopropyl and –NH2, or S_1 and R_3, or S_1 and R_4, together represent methylenedioxy ($-OCH_2O-$) or ethylenedioxy (($-OCH_2$ CH_2O-) in either of which one or more hydrogens are optionally replaced by fluorine; or S_1 is a radical of formula (IB):

$$-(Alk^3)_p-(Z^1)_q-(Alk^4)_r-Q^1 \qquad \text{(IB)}$$

wherein

p, q and **r** are independently 0 or 1;

(a) when p is 0 or 1, and q is 1, and r is 0 or 1:

$\mathbf{Z^1}$ **is selected from** the group of divalent radicals consisting of (i) -S-, -(C=O)-, -(C=S)-, -S(O)- and $-SO_2-$ and (ii) $-N(R^A)C(=O)-*$ wherein the bond marked * is attached to Q^1 and (iii) in either orientation, $-C(=O)O-$, $-C(=S)NR^A-$, and $-SO_2NR^A-$; **and** $\mathbf{Q^1}$ **is** (i) hydrogen or an optional substituent; or (ii) an optionally substituted carbocyclic or heterocyclic radical; or (iii) a radical $-CH_2[O(CH_2)_w]_xZ^2$ wherein Z^2 is H, -OH or $-O(C_1$-C_3alkyl) wherein x and w are independently 1, 2 or 3; or

(b) when p is 1, and q is 1, and r is 0 or 1:

Z^1 is –O-, **and Q^1 is** (i) hydrogen or an optional substituent which is not linked to $-(Alk^3)_p-(Z^1)_q-(Alk^4)_r-$ through a nitrogen atom; or (ii) an optionally substituted carbocyclic radical; or (iii) an optionally substituted heterocyclic ring of 5 or 6 ring atoms which is not linked to $-(Alk^3)_p-(Z^1)_q-(Alk^4)_r-$ through a ring nitrogen; or (iv) a radical $–CH_2[O(CH_2)_w]_xZ^2$ wherein Z^2 is H, -OH or $–O(C_1-C_3alkyl)$ wherein x and w are independently 1, 2 or 3. or

(c) when p is 1, and q is 1, and r is 0 or 1:

Z^1 is $-NR^A-$ or $-C(=O)N(R^A)-*$ wherein the bond marked * is attached to Q^1 **and Q^1 is** a radical $–CH_2[O(CH_2)_w]_xZ^2$ wherein Z^2 is H, -OH or $–O(C_1-C_3alkyl)$ wherein x and w are independently 1, 2 or 3. or

(d) when p is 0, and q is 1, and r is 0 or 1:

Z^1 is –O- or $-NR^A-$ **and Q^1 is** (i) hydrogen or an optional substituent which is not linked to $-(Alk^3)_p-(Z^1)_q-(Alk^4)_r-$ through a nitrogen atom; or (ii) Q^1 and R^A, taken together with the nitrogen to which they are attached form an optionally substituted heterocyclic ring of 5 or 6 ring atoms; or (iii) a radical $–CH_2[O(CH_2)_w]_xZ^2$ wherein Z^2 is H, -OH or $–O(C_1-C_3alkyl)$ wherein x and w are independently 1, 2 or 3; or

(e) when p is 0 or 1, q is 0, and r is 0 or 1:

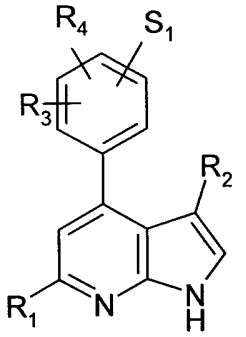
Q^1 is (i) hydrogen or an optional substituent which is not linked to $-(Alk^3)_p-(Z^1)_q-(Alk^4)_r-$ through a nitrogen atom or (ii) an optionally substituted carbocyclic radical; or (iii) an optionally substituted heterocyclic of 5 or 6 ring atoms which is not linked to $-(Alk^3)_p-(Z^1)_q-(Alk^4)_r-$ through a ring nitrogen; or (iv) a radical $–CH_2[O(CH_2)_w]_xZ^2$ wherein Z^2 is H, -OH or $–O(C_1-C_3alkyl)$ wherein x and w are independently 1, 2 or 3;

R^A is hydrogen or C_1-C_3 alkyl optionally substituted with one or more fluorine substituents; and

Alk^3 and Alk^4 are divalent C_1-C_3 alkylene or C_2-C_3 alkenylene radicals, each optionally substituted by one or two substituents selected from fluoro, chloro, C_1-

C_3alkyl optionally substituted with one or more fluorine substituents, C_1-C_3alkoxy optionally substituted with one or more fluorine substituents.

In another broad aspect, the invention provides a compound of formula (IC), or a salt, N-oxide, hydrate, or solvate thereof:



(IC)

wherein

R_1, R_2, R_3 and **R_4** are as defined in relation to formula (I) above, and

S_1 is hydrogen, or a substituent selected from fluoro, chloro, bromo, cyano (-CN), C_1-C_3alkyl optionally substituted with one or more fluorine substituents, C_1-C_3alkoxy optionally substituted with one or more fluorine substituents, -CH=CH_2, -C≡CH, cyclopropyl and –NH_2, or S_1 and R_3, or S_1 and R_4, together represent methylenedioxy (–OCH_2O-) or ethylenedioxy ((–OCH_2 CH_2O-) in either of which one or more hydrogens are optionally replaced by fluorine; or S_1 is a radical of formula (IB):

$$-(Alk^3)_p-(Z^1)_q-(Alk^4)_r-Q^1 \qquad \text{(IB)}$$

wherein

p, q and **r** are independently 0 or 1;

Z^1 is –O-, -S-, -(C=O)-, -(C=S)-, -S(O)-, -SO_2-, -NR^A-, or, in either orientation, -C(=O)N(R^A)- or -SO_2NR^A-;

Q^1 is (i) hydrogen or an optional substituent; or (ii) an optionally substituted carbocyclic or heterocyclic radical; or (iii) a radical –$CH_2[O(CH_2)_w]_xZ^2$ wherein Z^2 is H, -OH or –O(C_1-C_3alkyl) wherein x and w are independently 1, 2 or 3;

R^A is hydrogen or C_1-C_3 alkyl optionally substituted with one or more fluorine substituents; and

Alk^3 and Alk^4 are divalent C_1-C_3 alkylene or C_2-C_3 alkenylene radicals, each optionally substituted by one or two substituents selected from fluoro, chloro, C_1-C_3alkyl optionally substituted with one or more fluorine substituents, C_1-C_3alkoxy optionally substituted with one or more fluorine substituents.

In another aspect, the invention provides the use of a compound of formula (I) or (IC), or a salt, N-oxide, hydrate, or solvate thereof in the preparation of a composition for inhibition of HSP90 activity in vitro or in vivo:

The invention also provides a method of treatment of diseases which are responsive to inhibition of HSP90 activity in mammals, which method comprises administering to the mammal an amount of a compound as defined above effective to inhibit said HSP90 activity.

The in vivo use, and method, of the invention is applicable to the treatment of diseases in which HSP90 activity is implicated, including use for immunosuppression or the treatment of viral disease, inflammatory diseases such as rheumatoid arthritis, asthma, multiple sclerosis, Type I diabetes, lupus, psoriasis and inflammatory bowel disease; cystic fibrosis angiogenesis-related disease such as diabetic retinopathy, haemangiomas, and endometriosis; or for protection of normal cells against chemotherapy-induced toxicity; or diseases where failure to undergo apoptosis is an underlying factor; or protection from hypoxia-ischemic injury due to elevation of Hsp70 in the heart and brain; scrapie/CJD, Huntingdon's or Alzheimer's disease. Use for the treatment of cancer is especially indicated.

As used herein, the term "(C_a-C_b)alkyl" wherein a and b are integers refers to a straight or branched chain alkyl radical having from a to b carbon atoms. Thus when a is 1 and b is 6, for example, the term includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl and n-hexyl.

As used herein the term "divalent (C_a-C_b)alkylene radical" wherein a and b are integers refers to a saturated hydrocarbon chain having from a to b carbon atoms and two unsatisfied valences.

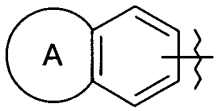
As used herein the term "(C_a-C_b)alkenyl" wherein a and b are integers refers to a straight or branched chain alkenyl moiety having from a to b carbon atoms having at least one double bond of either E or Z stereochemistry where applicable. The term includes, for example, vinyl, allyl, 1- and 2-butenyl and 2-methyl-2-propenyl.

As used herein the term "divalent (C_a-C_b)alkenylene radical" refers to a hydrocarbon chain having from a to b carbon atoms, at least one double bond, and two unsatisfied valences.

As used herein the term "cycloalkyl" refers to a saturated carbocyclic radical having from 3-8 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

As used herein the term "cycloalkenyl" refers to a carbocyclic radical having from 3-8 carbon atoms containing at least one double bond, and includes, for example, cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl.

As used herein the term "aryl" refers to a mono-, bi- or tri-cyclic carbocyclic aromatic radical, and includes aromatic monocyclic or bicyclic carbocyclic radicals fused to a non aromatic carbocyclic or heterocyclic ring. Illustrative of such radicals are phenyl, biphenyl and napthyl, and radicals of the formula:



wherein ring A (i) is optionally substituted, (ii) has 5 or 6 ring members including the carbons of the phenyl ring to which it is fused, and (iii) has at least one heteroatom O, S or N hetero atom as a ring member.

As used herein the term "carbocyclic" refers to a cyclic radical whose ring atoms are all carbon, and includes aryl, cycloalkyl, and cycloalkenyl radicals.

As used herein the term "heteroaryl" refers to a mono-, bi- or tri-cyclic aromatic radical containing one or more heteroatoms selected from S, N and O. Illustrative of such radicals are thienyl, benzthienyl, furyl, benzfuryl, pyrrolyl, imidazolyl, benzimidazolyl, thiazolyl, benzthiazolyl, isothiazolyl, benzisothiazolyl, pyrazolyl, oxazolyl, benzoxazolyl, isoxazolyl, benzisoxazolyl, isothiazolyl, triazolyl, benztriazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, indolyl and indazolyl.

As used herein the unqualified term "heterocyclyl" or "heterocyclic" includes "heteroaryl" as defined above, and in particular refers to a mono-, bi- or tri-cyclic non-aromatic radical containing one or more heteroatoms selected from S, N and O, and to groups consisting of a monocyclic non-aromatic radical containing one or more such heteroatoms which is covalently linked to another such radical or to a monocyclic carbocyclic radical. Illustrative of such radicals are pyrrolyl, furanyl, thienyl, piperidinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrimidinyl, morpholinyl, piperazinyl, indolyl, morpholinyl, benzfuranyl, pyranyl, isoxazolyl, benzimidazolyl, methylenedioxyphenyl, ethylenedioxyphenyl, maleimido and succinimido groups.

Unless otherwise specified in the context in which it occurs, the term "substituted" as applied to any moiety herein means substituted with at least one substituent, for example selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy, hydroxy(C_1-C_6)alkyl, mercapto, mercapto(C_1-C_6)alkyl, (C_1-C_6)alkylthio, monocyclic carbocyclic of 3-6 ring carbon atoms, monocyclic heterocyclic of 5 or 6 ring atoms, halo (including fluoro and chloro), trifluoromethyl, trifluoromethoxy, nitro, nitrile (-CN), oxo, -COOH, -$COOR^A$, -COR^A, -SO_2R^A, -$CONH_2$, -SO_2NH_2, -$CONHR^A$, -SO_2NHR^A, -$CONR^AR^B$, -$SO_2NR^AR^B$, -NH_2, -NHR^A, -NR^AR^B, -$OCONH_2$, -$OCONHR^A$, -$OCONR^AR^B$, -$NHCOR^A$, -$NHCOOR^A$, -NR^BCOOR^A, -$NHSO_2OR^A$, -$NR^BSO_2OR^A$, -$NHCONH_2$, -NR^ACONH_2, -$NHCONHR^B$, -NR^ACONHR^B, -$NHCONR^AR^B$, or -$NR^ACONR^AR^B$ wherein R^A and R^B are independently a (C_1-C_6)alkyl group in which one or more nitrogens are optionally replaced by fluorine. In the case where the optional substituent contains an alkyl radical, that alkyl radical may be substituted by one or more fluorines, and/or by a monocyclic carbocyclic group of 3-6 ring carbon atoms, or a monocyclic heterocyclic group of 5 or 6 ring atoms. In the case where the optional substituent is or comprises a monocyclic carbocyclic group of 3-6 ring carbon atoms, or a monocyclic heterocyclic group of 5 or 6 ring atoms, that ring may itself be substituted by any of the non-cyclic optional substituents listed above. An

"optional substituent" may be one of the substituent groups encompassed in the above description.

As used herein the term "salt" includes base addition, acid addition and quaternary salts. Compounds of the invention which are acidic can form salts, including pharmaceutically or veterinarily acceptable salts, with bases such as alkali metal hydroxides, e.g. sodium and potassium hydroxides; alkaline earth metal hydroxides e.g. calcium, barium and magnesium hydroxides; with organic bases e.g. N-ethyl piperidine, dibenzylamine and the like. Those compounds (I) which are basic can form salts, including pharmaceutically or veterinarily acceptable salts with inorganic acids, e.g. with hydrohalic acids such as hydrochloric or hydrobromic acids, sulphuric acid, nitric acid or phosphoric acid and the like, and with organic acids e.g. with acetic, tartaric, succinic, fumaric, maleic, malic, salicylic, citric, methanesulphonic and p-toluene sulphonic acids and the like.

For a review on suitable salts, see Handbook of Pharmaceutical Salts: Properties, Selection, and Use by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and a stoichiometric amount of one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

Compounds with which the invention is concerned which may exist in one or more stereoisomeric form, because of the presence of asymmetric atoms or rotational restrictions, can exist as a number of stereoisomers with R or S stereochemistry at each chiral centre or as atropisomeres with R or S stereochemistry at each chiral axis. The invention includes all such enantiomers and diastereoisomers and mixtures thereof.

So-called 'pro-drugs' of the compounds of formula (I) or (IC) are also within the scope of the invention. Thus certain derivatives of compounds of formula (I) or (IC) which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of formula (I) or (IC) having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in Pro-drugs as Novel Delivery

Systems, Vol. 14, ACS Symposium Series (T. Higuchi and W. Stella) and Bioreversible Carriers in Drug Design, Pergamon Press, 1987 (ed. E. B. Roche, American Pharmaceutical Association).

Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of formula (I) or (IC) with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in Design of Prodrugs by H. Bundgaard (Elsevier, 1985).

Also included within the scope of the invention are metabolites of compounds of formula (I) or (IC), that is, compounds formed *in vivo* upon administration of the drug. Some examples of metabolites include

(i) where the compound of formula (I) or (IC) contains a methyl group, an hydroxymethyl derivative thereof ($-CH_3$ -> $-CH_2OH$):

(ii) where the compound of formula (I) or (IC) contains an alkoxy group, an hydroxy derivative thereof (-OR -> -OH);

(iii) where the compound of formula (I) or (IC) contains a tertiary amino group, a secondary amino derivative thereof ($-NR^1R^2$ -> $-NHR^1$ or $-NHR^2$);

(iv) where the compound of formula (I) or (IC) contains a secondary amino group, a primary derivative thereof ($-NHR^1$ -> $-NH_2$);

(v) where the compound of formula (I) or (IC) contains a phenyl moiety, a phenol derivative thereof (-Ph -> -PhOH); and

(vi) where the compound of formula (I) or (IC) contains an amide group, a carboxylic acid derivative thereof (-$CONH_2$ -> COOH).

The group R_1 in compounds (I) and (IC)

When R_1 is a radical of formula (1A):

$$-X\text{-}Alk^1\text{-}(Z)_m\text{-}(Alk^2)_n\text{-}Q \quad (IA)$$

X may be –O-, -S- -S(O)-, -SO_2-, or -NH-. At present –O- and –S- are preferred;

when present, Z may be –O-, -S-, -(C=O)-, -(C=S)-, -S(O)-, -SO_2-, –NR^A-, or, in either orientation -C(=O)O-, -C(=O)NR^A- , -C(=S)NR^A-, -SO_2NR^A-, -NR^AC(=O)-, or -NR^ASO_2- wherein R^A is hydrogen or C_1-C_6 alkyl. At present –NR^A- is preferred;

Alk^1 (and Alk^2 when present) may be, for example –CH_2-, -CH_2CH_2-, –$CH_2CH_2CH_2$-,–$CH(CH_3)CH_2$- or -CH_2CH=CH-;

m and n are independently 0 or 1. Thus, in one class of radicals (IA), m and n are both 0. In another class of radicals (IA), m is 1 and n is 0. In a further class of radicals (IA), m is 0 and n is 1;

Q may be hydrogen or an optionally substituted carbocyclic or heterocyclic radical. Examples of carbocyclic radicals Q include phenyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Examples of heterocyclic radicals Q include heteroaryl radicals such as pyridyl, thienyl and furanyl, and non-aromatic heterocyclic radicals such as piperidinyl, piperazinyl and morpholinyl.

Currently it is preferred that Alk^1, Alk^2 and Q (when carbocyclic or heterocyclic) are unsubstituted. However, examples of substituents which may be present in Alk^1, Alk_2 and Q (when carbocyclic or heterocyclic) include methyl, ethyl, n- or isopropyl, vinyl, allyl, methoxy, ethoxy, n-propyloxy, isopropyloxy, benzyloxy,

allyloxy, cyanomethoxy chloro, bromo, cyano, formyl, methyl-, ethyl-, or n-propyl-carbonyloxy, methyl- or ethylaminocarbonyl, and substituents of formula $-O(CH_2)_aZ^1$ wherein a is 1, 2 or 3 and Z^1 is a primary, secondary, tertiary or cyclic amino group, or a C_1-C_6alkoxy group, and substituents of formula $-(Alk^3)_bZ^1$ wherein Alk^3 is a divalent straight or branched chain (C_1-C_3) alkylene, b is 0 or 1, and Z^1 is a primary, secondary, tertiary or cyclic amino group, or a C_1-C_6alkoxy group.

In one class of compounds (I) of the invention R_1 is methoxy, ethoxy, methylthio or ethylthio.

The group R_2 in compounds (I) and (IC)

At present, it is preferred that R_2 is cyano (-CN).

The ring A in Compounds (I)

Ring A is an aryl or heteroaryl ring or ring system, for example phenyl, thienyl, benzthienyl, furyl, benzfuryl, pyrrolyl, imidazolyl, benzimidazolyl, thiazolyl, benzthiazolyl, isothiazolyl, benzisothiazolyl, pyrazolyl, oxazolyl, benzoxazolyl, isoxazolyl, benzisoxazolyl, isothiazolyl, triazolyl, benztriazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, indolyl or indazolyl. Currently it is preferred that ring A is phenyl.

The groups R_3 and R_4 in compounds (I) and (IC)

R_3 and R_4 are independently selected from hydrogen, fluoro, chloro, bromo, cyano (-CN), C_1-C_3alkyl optionally substituted with one or more fluorine substituents, C_1-C_3alkoxy optionally substituted with one or more fluorine substituents, $-CH=CH_2$, $-C\equiv CH$, cyclopropyl and $-NH_2$, or R_3 and R_4 together represent methylenedioxy ($-OCH_2O-$) or ethylenedioxy ($-OCH_2CH_2O-$) in either of which one or more hydrogens are optionally replaced by fluorine. However at least one of R_3 and R_4 should preferably be other than hydrogen. Presently preferred is the case where one or both of R_3 and R_4 is/are selected from fluoro, chloro, methyl or methoxy. Preferred positions for R_3 and R_4 when ring A is phenyl are the para and ortho positions.

The group S_1 in Compounds (I)

When S_1 is other than hydrogen, and ring A is phenyl, it is presently preferred that S_1 be in the meta position of the ring.

In a first subset of compounds (I) of the invention, S_1 is hydrogen, or a substituent selected from fluoro, chloro, bromo, cyano (-CN), C_1-C_3alkyl optionally substituted with one or more fluorine substituents, C_1-C_3alkoxy optionally substituted with one or more fluorine substituents, -CH=CH_2, -C≡CH, cyclopropyl and –NH_2, or S_1 and R_3, or S_1 and R_4, together represent methylenedioxy (–OCH_2O-) or ethylenedioxy (–OCH_2CH_2O-) in either of which one or more hydrogens are optionally replaced by fluorine;

In a second subset of compounds (I) of the invention, S_1 is a radical of formula (IB):

$$-(Alk^3)_p-(Z^1)_q-(Alk^4)_r-Q^1 \qquad (IB)$$

wherein p, q, r, Alk^3, Alk^4, Z^1 and Q^1 are as defined in relation to formula (I) above. In such compounds, Alk^3 and Alk^4 are divalent C_1-C_3 alkylene or C_2-C_3 alkenylene radicals, each optionally substituted by one or two substituents selected from fluoro, chloro, C_1-C_3alkyl optionally substituted with one or more fluorine substituents, C_1-C_3alkoxy optionally substituted with one or more fluorine substituents. Examples of radicals Alk^3 and Alk^4, when present, are example –CH_2-, -CH_2CH_2-, –$CH_2CH_2CH_2$-, –$CH(CH_3)CH_2$-, – $CH_2CH(CH_3)CH_2$-, -CH_2CH=CH-; –$CH(OCH_3)CH_2$-, and – $CH_2CH(OCH_3)CH_2$-,

In this second subset of compounds (I) of the invention there are five specific combinations (a)-(e) of p, q, r, Alk^3, Alk^4, Z^1 and Q^1:

Case (a) arises when p is 0 or 1, and q is 1, and r is 0 or 1. In case (a), Z^1 is selected from the group of divalent radicals consisting of (i) -S-, -(C=O)-, -(C=S)-, -S(O)- and -SO_2- and (ii) -N(R^A)C(=O)-* wherein the bond marked * is attached to Q^1 and (iii) in either orientation, -C(=O)O-, -C(=S)NR^A-, and -SO_2NR^A-; and Q^1 is (i) hydrogen or an optional substituent; or (ii) an optionally substituted carbocyclic or heterocyclic radical; or (iii) a radical –$CH_2[O(CH_2)_w]_xZ^2$ wherein Z^2 is H, -OH or –O(C_1-C_3alkyl) wherein x and w are independently 1, 2 or 3.

R^A, when present in Z^1 and when other than hydrogen may be, for example, methyl, ethyl, n-or iso-propyl, or trifluoromethyl.

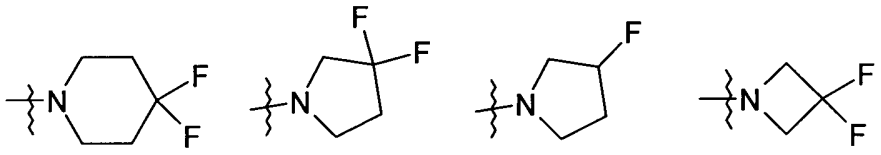
When other than hydrogen, Q^1 may be, for example

an primary, secondary or tertiary amino substituent, for example $-NR^AR^B$ wherein R^A and R^B are independently selected from hydrogen and C^1-C_3alkyl in which one or more hydrogens is optionally replaced by fluorine, for example methylamino, dimethylamino, ethylamino, diethylamino, n- or iso-propylamino, or N-methyl-N-ethylamino and N-(1,1,1-trifluoroethyl)-N-ethylamino,

a non-amino optional substituent, for example chloro, C_1-C_3alkoxy, cyano or acetyl; or a cyclopropyl, cylopenyl or cyclohexyl group;

an optionally substitued phenyl group, for example wherein optional substituents are selected from cyano (-CN), fluoro, chloro, bromo, methyl, ethyl, -OH, -CH_2OH, -$C(=O)NH_2$, -C(=O)H, -$C(=O)CH_3$, and -NH_2;

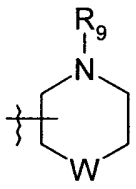
a cyclic amino group such as morpholino, piperidinyl, piperazinyl or methylpiperidinyl or a fluoro substituted cyclic amino group such as those of formulae (A)-(D):



A B C D

a saturated carbocylic group such as cyclopropyl, cyclopentyl, cyclohexyl or norbornyl;

a heterocyclic group such as any of those heteroaryl groups referred to above as examples of ring A, or a non aromatic heterocyclic group such as one having the formula E:



E

wherein W is $-CH_2-$, -O-, -S- or $-NR_9$, and R_9 is hydrogen , methyl, ethyl or n- or iso-propyl; or

a radical $-CH_2[O(CH_2)_w]_xZ^2$ wherein Z^2 is H, -OH or $-OCH_3$ wherein x and w are independently 1, 2 or 3. Such radicals include the polyether radicals $-O-(CH_2)_{1-3}OH$, $-O-(CH_2)_{1-3}O(C_1-C_3alkyl)$, $-O-(CH_2)_{1-3}-O-(CH_2)_{1-3}OH$, and $-O-(CH_2)_{1-3}-O-(CH_2)_{1-3}O(C_1-C_3alkyl)$,

Case (b) arises when p is 1, and q is 1, and r is 0 or 1 and Z^1 is –O-. In case (b) Q^1 is (i) hydrogen or an optional substituent which is not linked to $-(Alk^3)_p-(Z^1)_q-(Alk^4)_r-$ through a nitrogen atom; or (ii) an optionally substituted carbocyclic radical; or (iii) an optionally substituted heterocyclic ring of 5 or 6 ring atoms which is not linked to $-(Alk^3)_p-(Z^1)_q-(Alk^4)_r-$ through a ring nitrogen; or (iv) a radical $-CH_2[O(CH_2)_w]_xZ^2$ wherein Z^2 is H, -OH or $-O(C_1-C_3alkyl)$ wherein x and w are independently 1, 2 or 3.

In this case (b), when other than hydrogen, Q^1 may be, for example

a non-amino optional substituent, for example chloro, C_1-C_3alkoxy, cyano or acetyl; or a cyclopropyl, cylopenyl or cyclohexyl group;

an optionally substitued phenyl group, for example wherein optional substituents are selected from cyano (-CN), fluoro, chloro, bromo, methyl, ethyl, -OH, $-CH_2OH$, $-C(=O)NH_2$, -C(=O)H, $-C(=O)CH_3$, and $-NH_2$;

a saturated carbocylic group such as cyclopropyl, cyclopentyl, cyclohexyl or norbornyl;

a heterocyclic group such as any of those heteroaryl groups referred to above as examples of ring A, or a non aromatic heterocyclic group such as one having formula E defined above; or

a radical $-CH_2[O(CH_2)_w]_xZ^2$ wherein Z^2 is H, -OH or $-OCH_3$ wherein x and w are independently 1, 2 or 3. Such radicals include the polyether radicals $-O-(CH_2)_{1-3}OH$, $-O-(CH_2)_{1-3}O(C_1-C_3alkyl)$, $-O-(CH_2)_{1-3}-O-(CH_2)_{1-3}OH$, and $-O-(CH_2)_{1-3}-O-(CH_2)_{1-3}O(C_1-C_3alkyl)$.

Case (c) arises when p is 1, and q is 1, and r is 0 or 1 and Z^1 is $-NR^A-$ or $-C(=O)N(R^A)-*$ wherein the bond marked * is attached to Q^1. In this case (c):

R^A when other than hydrogen may be, for example, methyl, ethyl, n-or iso-propyl, or trifluoromethyl; and

Q^1 is a radical $-CH_2[O(CH_2)_w]_xZ^2$ wherein Z^2 is H, -OH or $-O(C_1-C_3alkyl)$ wherein x and w are independently 1, 2 or 3. Such radicals include the polyether radicals $-O-(CH_2)_{1-3}OH$, $-O-(CH_2)_{1-3}O(C_1-C_3alkyl)$, $-O-(CH_2)_{1-3}-O-(CH_2)_{1-3}OH$, and $-O-(CH_2)_{1-3}-O-(CH_2)_{1-3}O(C_1-C_3alkyl)$.

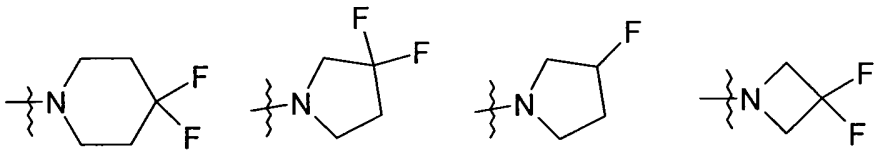
Case (d) arises when p is 0, and q is 1, and r is 0 or 1 and Z^1 is –O- or $-NR^A-$. In this case (d) Q^1 is (i) hydrogen or an optional substituent which is not linked to $-(Alk^3)_p-(Z^1)_q-(Alk^4)_r-$ through a nitrogen atom; or (ii) Q^1 and R^A, taken together with the nitrogen to which they are attached form an optionally substituted heterocyclic ring of 5 or 6 ring atoms; or (iii) a radical $-CH_2[O(CH_2)_w]_xZ^2$ wherein Z^2 is H, -OH or $-OCH_3$ wherein x and w are independently 1, 2 or 3. In this case (d) R^A when other than hydrogen may be, for example, methyl, ethyl, n-or iso-propyl, or trifluoromethyl; and Q^1 may be, for example:

a non-amino optional substituent, for example chloro, C_1-C_3alkoxy, cyano or acetyl; or a cyclopropyl, cylopentyl or cyclohexyl group;

a radical $-CH_2[O(CH_2)_w]_xZ^2$ wherein Z^2 is H, -OH or $-OCH_3$ wherein x and w are independently 1, 2 or 3. Such radicals include the polyether radicals

$-O-(CH_2)_{1-3}OH$, $-O-(CH_2)_{1-3}O(C_1-C_3alkyl)$, $-O-(CH_2)_{1-3}-O-(CH_2)_{1-3}OH$, and $-O-(CH_2)_{1-3}-O-(CH_2)_{1-3}O(C_1-C_3alkyl)$, or

Q^1 and R^A, taken together with the nitrogen to which they are attached form an optionally substituted heterocyclic ring of 5 or 6 ring atoms, for example a cyclic amino group such as morpholino, piperidinyl, piperazinyl or methylpiperidinyl or a fluoro substituted cyclic amino group such as those of formulae (A)-(D):



A B C D

Case (e) arises when p is 0 or 1, q is 0, and r is 0 or 1. In this case, Q^1 is (i) hydrogen or an optional substituent which is not linked to $-(Alk^3)_p-(Z^1)_q-(Alk^4)_r-$ through a nitrogen atom or (ii) an optionally substituted carbocyclic radical; or (iii) an optionally substituted heterocyclic of 5 or 6 ring atoms which is not linked to $-(Alk^3)_p-(Z^1)_q-(Alk^4)_r-$ through a ring nitrogen; or (iv) a radical $-CH_2[O(CH_2)_w]_xZ^2$ wherein Z^2 is H, -OH or $-OCH_3$ wherein x and w are independently 1, 2 or 3. In this case (e), Q^1 may be, for example:

a non-amino optional substituent, for example chloro, C_1-C_3alkoxy, cyano or acetyl; or a cyclopropyl, cylopentyl or cyclohexyl group;

a heterocyclic group such as any of those heteroaryl groups referred to above as examples of ring A, or a non aromatic heterocyclic group such as one having formula E defined above; or

a radical $-CH_2[O(CH_2)_w]_xZ^2$ wherein Z^2 is H, -OH or $-OCH_3$ wherein x and w are independently 1, 2 or 3. Such radicals include the polyether radicals $-O-(CH_2)_{1-3}OH$, $-O-(CH_2)_{1-3}O(C_1-C_3alkyl)$, $-O-(CH_2)_{1-3}-O-(CH_2)_{1-3}OH$, and $-O-(CH_2)_{1-3}-O-(CH_2)_{1-3}O(C_1-C_3alkyl)$.

The group S_1 in Compounds (IC)

In compounds (IC) of the invention, it is presently preferred that S_1 be in the meta position of the ring.

As in the case of compounds (I), in a first subset of compounds (IC) of the invention, S_1 is hydrogen, or a substituent selected from fluoro, chloro, bromo, cyano (-CN), C_1-C_3alkyl optionally substituted with one or more fluorine substituents, C_1-C_3alkoxy optionally substituted with one or more fluorine substituents, -CH=CH_2, -C≡CH, cyclopropyl and –NH_2, or S_1 and R_3, or S_1 and R_4, together represent methylenedioxy (–OCH_2O-) or ethylenedioxy (–OCH_2CH_2O-) in either of which one or more hydrogens are optionally replaced by fluorine;

In a second subset of compounds (IC) of the invention, S_1 is a radical of formula (IB):

$$-(Alk^3)_p-(Z^1)_q-(Alk^4)_r-Q^1 \qquad (IB)$$

wherein

p, q and **r** are independently 0 or 1;

Z^1 is –O-, -S-, -(C=O)-, -(C=S)-, -S(O)-, -SO_2-, -NR^A-, or, in either orientation, -C(=O)N(R^A)- or -SO_2NR^A-;

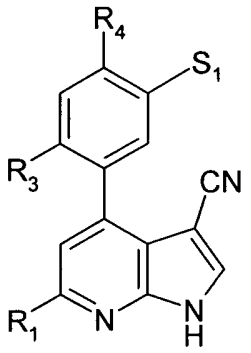
Q^1 is (i) hydrogen or an optional substituent; or (ii) an optionally substituted carbocyclic or heterocyclic radical; or (iii) a radical –$CH_2[O(CH_2)_w]_xZ^2$ wherein Z^2 is H, -OH or –O(C_1-C_3alkyl) wherein x and w are independently 1, 2 or 3;

R^A is hydrogen or C_1-C_3 alkyl optionally substituted with one or more fluorine substituents; and

Alk^3 and Alk^4 are divalent C_1-C_3 alkylene or C_2-C_3 alkenylene radicals, each optionally substituted by one or two substituents selected from fluoro, chloro, C_1-C_3alkyl optionally substituted with one or more fluorine substituents, C_1-C_3alkoxy optionally substituted with one or more fluorine substituents.

In compounds (IC) of the invention, when S_1 is a radical of formula (IB), Z^1, Q^1, R^A, Alk^3 and Alk_4 therein may be any of those radicals or groups defined and discussed in relation to compounds (I), cases (a), (b), (c), (d) or (e) above.

One particular sub-class of compounds of the invention consists of those of formula (ID):



(ID)

and salts, N-oxides, hydrates, or solvates thereof, wherein:

R_1 and S_1 are independently selected from (a) hydrogen, methoxy, ethoxy, methylthio or ethylthio; (b) a group of formula $-X^1$-Alk^5-$(CO)_wNR^CR^D$ wherein w is 0 or 1, X^1 is –O- or –S-, Alk^5 is a straight or branched chain C_1-C_3alkylene radical, R^C is C_1-C_3alkyl and R^D is C_1-C_3alkyl or hydroxyl(C_1-C_3alkyl)-; and (c) a group of formula $-X^1$-Alk^5-Ar wherein X^1 is –O- or –S-, Alk^5 is a straight or branched chain C_1-C_3alkylene radical, and Ar is phenyl or a 5- or 6-memnbered heteroaryl ring wherein at least one hetero atom is nitrogen; PROVIDED THAT R_1 and S_1 are not both hydrogen;

R_3 is fluoro, chloro, bromo or methyl; and

R_4 is fluoro, chloro, bromo methyl, ethyl, isopropyl, methoxy, or cyano.

Specific examples of compounds of the invention include those of the Examples herein.

There are multiple synthetic strategies for the synthesis of the compounds (I) with which the present invention is concerned, but all rely on known chemistry, known to the synthetic organic chemist. Thus, compounds according to formula (I) or (IC) can be synthesised according to procedures described in the standard literature and are well-known to the one skilled in the art. Typical literature sources are "*Advanced organic chemistry*", 4th Edition (Wiley), J March, "*Comprehensive Organic Transformation*", 2nd Edition (Wiley), R.C. Larock , "*Handbook of Heterocyclic Chemistry*", 2nd Edition (Pergamon), A.R. Katritzky), review articles such as found in "*Synthesis*", "*Acc. Chem.*

Res." , "*Chem. Rev*", or primary literature sources identified by standard literature searches online or from secondary sources such as "*Chemical Abstracts*" or "*Beilstein*". Such literature methods include those of the preparative Examples herein, and methods analogous thereto. In general, compounds of the invention may be prepared by methods as described in the Examples herein, or by methods analogous to those described ion the Examples herein.

The compounds of the invention are inhibitors of HSP90 and are useful in the treatment of diseases which are responsive to inhibition of HSP90 activity such as cancers; viral diseases such as Hepatitis C (HCV) (Waxman, 2002); Immunosuppression such as in transplantation (Bijlmakers, 2000 and Yorgin, 2000); Anti-inflammatory diseases (Bucci, 2000) such as Rheumatoid arthritis, Asthma, MS, Type I Diabetes, Lupus, Psoriasis and Inflammatory Bowel Disease; Cystic fibrosis (Fuller, 2000); Angiogenesis-related diseases (Hur, 2002 and Kurebayashi, 2001): diabetic retinopathy, haemangiomas, psoriasis, endometriosis and tumour angiogenesis. Also an Hsp90 inhibitor of the invention may protect normal cells against chemotherapy-induced toxicity and be useful in diseases where failure to undergo apoptosis is an underlying factor. Such an Hsp90 inhibitor may also be useful in diseases where the induction of a cell stress or heat shock protein response could be beneficial, for example, protection from hypoxia-ischemic injury due to elevation of Hsp70 in the heart (Hutter, 1996 and Trost, 1998) and brain (Plumier, 1997 and Rajder, 2000). An Hsp90 inhibitor - induced increase in Hsp70 levels could also be useful in diseases where protein misfolding or aggregation is a major causal factor, for example, neurogenerative disorders such as scrapie/CJD, Huntingdon's and Alzheimer's (Sittler, 2001; Trazelt, 1995 and Winklhofer, 2001)".

Accordingly, the invention also includes:
(i) A pharmaceutical or veterinary composition comprising a compound of formula (I) or (IC) above, together with a pharmaceutically or veterinarily acceptable carrier.

(ii) The use of a compound a compound of formula (I) or (IC) above in the preparation of a composition for composition for inhibition of HSP90 activity in vitro or in vivo.

(iii). A method of treatment of diseases or conditions which are responsive to inhibition of HSP90 activity in mammals which method comprises administering to the mammal an

amount of a compound of formula (I) or (IC) above effective to inhibit said HSP90 activity.

It will be understood that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the causative mechanism and severity of the particular disease undergoing therapy. In general, a suitable dose for orally administrable formulations will usually be in the range of 0.1 to 3000 mg, once, twice or three times per day, or the equivalent daily amount administered by infusion or other routes. However, optimum dose levels and frequency of dosing will be determined by clinical trials as is conventional in the art.

The compounds with which the invention is concerned may be prepared for administration by any route consistent with their pharmacokinetic properties. The orally administrable compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For topical application to the skin, the drug may be made up into a cream, lotion or ointment. Cream or ointment formulations which may be used for the drug are conventional formulations well known in the art, for example as described in standard textbooks of pharmaceutics such as the British Pharmacopoeia.

The active ingredient may also be administered parenterally in a sterile medium. Depending on the vehicle and concentration used, the drug can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle.

Compounds of the invention may be administered together with other classes opf pharmaceutically active drugs. For example, for the treatment of cancers, combination therapy with two or more different classes of anticancer agent is a recognised and widespread practice. The present compounds may be used in such combinationtherapy, particularly where the other drug(s) have a mode of action different from HSP90 inhibition.

The following examples illustrate the preparation and activities of specific compounds of the invention and are not intended to be limiting of the full scope of the invention.

General Procedures

All reagents obtained from commercial sources were used without further purification. Anhydrous solvents were obtained from commercial sources and used without further drying. Flash chromatography was performed with pre-packed silica gel cartridges (Strata SI-1; 61Å, Phenomenex, Cheshire UK or IST Flash II, 54Å, Argonaut, Hengoed, UK). Thin layer chromatography was conducted with 5 x 10 cm plates coated with Merck Type 60 F_{254} silica gel.

The compounds of the present invention were characterized by Liquid chromatography / mass spectrometry (LCMS) using a Hewlett Packard 1100 series LCMS/MSD linked to quadripole detector (ionization mode: electron spray positive or negative; column: Phenomenex Luna 3u C18(2) 30 x 4.6 mm; Buffer A prepared by dissolving 1.93g

ammonium acetate in 2.5 L HPLC grade H_20 and adding 2 mL formic acid. Buffer B prepared by adding 132 mL buffer A to 2.5 L of HPLC grade acetonitrile and adding 2 mL formic acid; elution gradient 95:5 to 5:95 buffer A : buffer B over 3.75 minutes or 7.5 minutes. Flow rate = 2.0 mL/min. Retention Times are reported in minutes. Ionisation is positive unless otherwise stated.

Nuclear magnetic resonance (NMR) analysis was performed with a Brucker DPX-400 MHz NMR spectrometer. The spectral reference was the known chemical shift of the solvent. Proton NMR data is reported as follows: chemical shift (δ) in ppm, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, dd = doublet of doublet, br = broad), integration, coupling constant.

Some compounds of the invention were purified by preparative HPLC. Preparative HPLC purifications were performed on a Waters FractionLynx MS Autopurification system with a Gemini® 5 µM C18(2), 100 mm × 20 mm i.d. column from Phenomenex, running at a flow rate of 20 mL min^{-1} with UV diode array detection (210 – 400 nm) and mass-directed collection. Gradients used for each compound are shown in Table 1.

At pH 4:Solvent A: L HPLC grade Water + 10mM ammonium acetate + 0.08% v/v formic acid.

Solvent B: 95% v/v HPLC grade acetonitrile + 5% v/v Solvent A + 0.08% v/v formic acid.

At pH 9:Solvent A: HPLCS grade Water + 10 mM ammonium acetate + 0.08% v/v ammonia solution.

Solvent B: 95% v/v HPLC grade acetonitrile + 5% v/v Solvent A + 0.08% v/v ammonia solution..

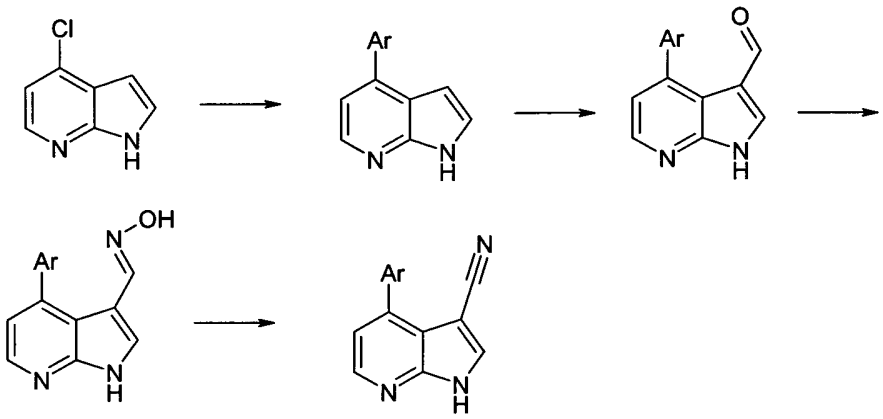
The mass spectrometer was a Waters Micromass ZQ2000 spectrometer operating in positive or negative ion electrospray ionisation modes, with a molecular weight scan range of 150 to 1000.

Table 1 Preparative HPLC gradients

Time /min	%B for Compound no.			
	8	**9**	**11**	**12**
0.0	5	5	5	5
0.5	20	25	30	35
7.0	40	45	50	55
7.5	95	95	95	95
9.5	95	95	95	95
10	5	5	5	5

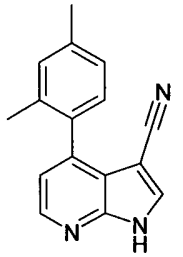
IUPAC chemical names were generated using AutoNom Standard.

Some compounds of the invention can be made (by way of example) by following the route outlined in scheme 1. Experimental Methods, reagents and product isolation methods will be known to those skilled in the art of organic synthesis. It is understood that other methods can also be used.



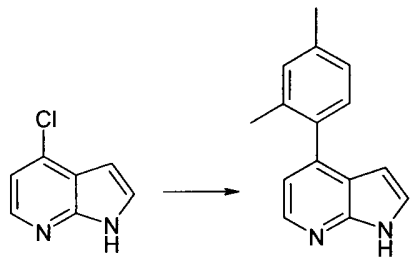
Scheme 1

Example 1
4-(2,4-Dimethyl-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile



Step1.

4-(2,4-Dimethyl-phenyl)-1H-pyrrolo[2,3-b]pyridine

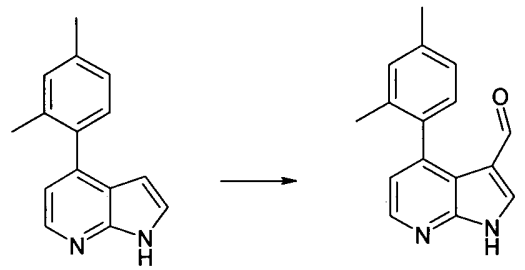


Bis(tri-t-butylphosphine)palladium(0) was added to a suspension of 4-Chloro-1H-Pyrrolo[2,3-b]pyridine, 2,4-Dimethylphenylboronic acid and potassium fluoride in 1,4-Dioxan under a nitrogen atmosphere. The reaction mixture heated at ~80^{0}C, for ~ 2hrs. The suspension was allowed to cool and diluted with ethyl acetate, the phases were separated and the organic phase was washed with water, saturated aqueous sodium chloride solution, then dried over anhydrous sodium sulphate and concentrated to a pale yellow solid. The crude product was purified by column chromatography on silica gel, eluting with mixtures of dichloromethane and methanol. The resulting product was re-purified by column chromatography on silica gel , eluting with mixtures of ethyl acetate and hexane, to afford title compound as a pale yellow solid.

LCMS retention time = 2.468 minutes; *m/z* = 233.1 $[M+H]^+$ (Run time 3.75mins)

Step 2

4-(2,4-Dimethyl-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde



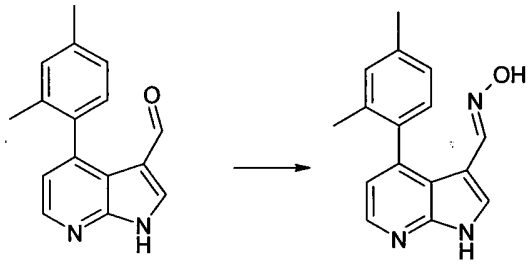
DMF was added slowly to cooled (ice-water bath) phosphorous oxychloride and the mixture stirred. 4-(2,4-Dimethyl-phenyl)-1H-pyrrolo[2,3-b]pyridine was added and the suspension heated at 110^{0}C, for 18hrs. The resulting suspension was allowed to cool

and water added the mixture was then neutralised with aqueous sodium hydroxide and extracted with ethyl acetate. The organic extracts were washed with water and saturated aqueous sodium chloride solution, the solution was dried over anhydrous sodium sulphate and concentrated to a pale yellow solid. The crude product was purified by column chromatography on silica gel, eluting with mixtures of dichloromethane and methanol. The crude product was re-purified by column chromatography on silica gel, eluting with mixtures of ethyl acetate and hexane, to give a pale yellow solid.

LCMS retention time = 2.22 minutes; *m/z* = 251.1 $[M+H]^+$ (Run time 3.75mins)

Step 3

4-(2,4-Dimethyl-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde oxime

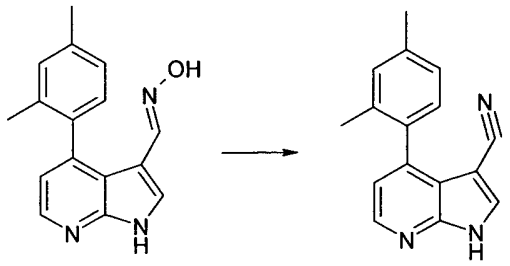


Hydroxylamine hydrochloride was added to a suspension of 4-(2,4-Dimethyl-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde in ethanol. Sodium acetate was added and the suspension heated at ~90^{0}C, for ~ 90mins. The suspension was allowed to cool and concentrated, water was added and the mixture extracted with ethyl acetate. The organic extracts were washed with water and saturated aqueous sodium chloride solution, the solution was dried over anhydrous sodium sulphate and concentrated to a pale brown solid.

LCMS retention time = 2.147 minutes; *m/z* = 266.1 $[M+H]^+$ (Run time 3.75mins)

Step 5

4-(2,4-Dimethyl-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile



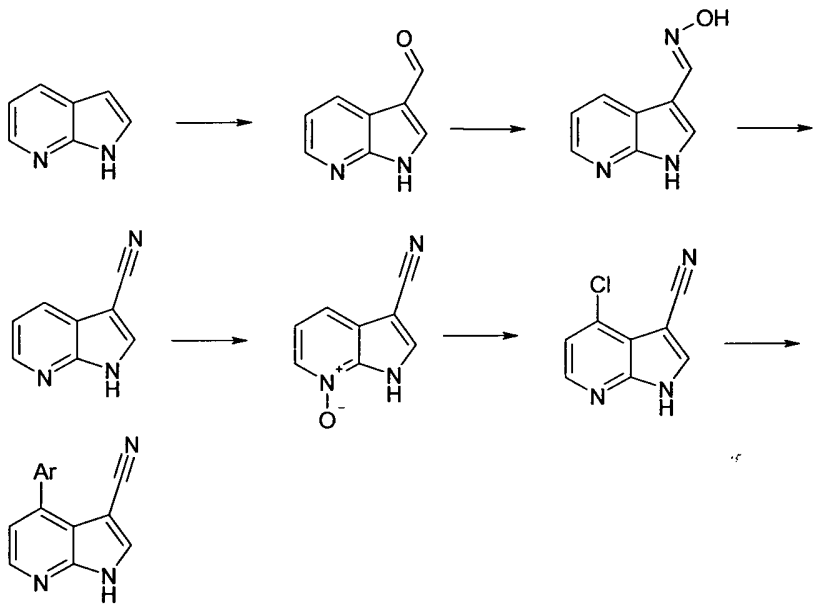
Thionyl chloride was added to a suspension of 4-(2,4-Dimethyl-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde oxime in dichloromethane, at ~0°C (ice/ water), the resulting solution was stirred at room temperature for ~60mins. to give an off-white suspension. The suspension was concentrated in vacuo and saturated aqueous sodium hydrogen carbonate solution added the mixture extracted with ethyl acetate, the extracts were washed with water and saturated aqueous sodium chloride solution, the solution was dried over anhydrous sodium sulphate and concentrated to a pale brown solid. The crude product was re-purified by preparative HPLCMS, to give the product as an off-white solid.

LCMS retention time = 2.262 minutes; *m/z* = 248.1 $[M+H]^+$ (Run time 3.75mins)

^{1}H NMR (400 MHz, DMSO-d_6) δ 2.06 (s, 3H), 2.35 (s, 3H), 7.07 (d, 1H, J = 5.0 Hz), 7.11 (m, 2H), 7.12 (brs, 1H), 8.41 (d, 1H, J = 5.0 Hz), 8.42 (s, 1H), 12.89 (brs, 1H).

This compound had activity 'A' in the fluorescence polarization assay described below.

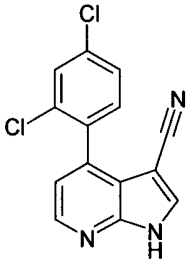
Some compounds of the invention can be made (by way of example) by following the route outlined in scheme 2. Experimental Methods, reagents and product isolation methods will be known to those skilled in the art of organic synthesis. It is understood that other methods can also be used.



Scheme 2

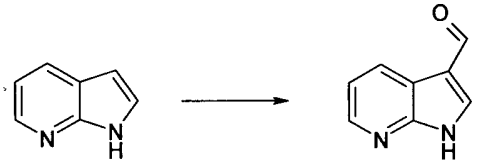
Example 2

4-(2,4-Dichloro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile



Step1

1H-Pyrrolo[2,3-b]pyridine-3-carbaldehyde

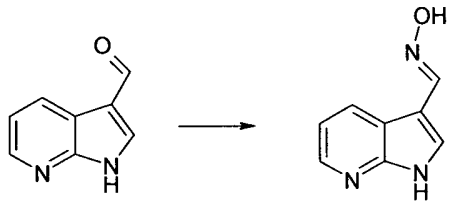


7-Azaindole was added to a solution of hexamethylenetetramine (2 equivalents) in water /acetic acid mixture (1:2). The resulting solution was heated under reflux for ~3hrs. to give a dark yellow solution. The solution was allowed to cool and poured into water, to give a white suspension. Solids were removed by filtration and washed with water, to give an off-white powder after being dried *in vacuo*.

LCMS retention time = 1.366 minutes; *m/z* = 147.0 $[M+H]^+$ (Run time 3.75mins)

Step 2

1H-Pyrrolo[2,3-b]pyridine-3-carbaldehyde oxime

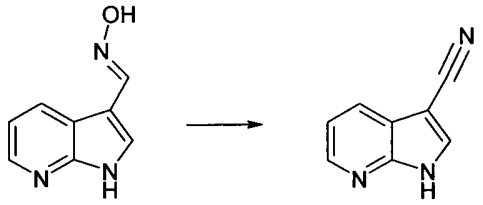


Aqueous hydroxylamine was added to a suspension of the 1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde in water and the suspension heated to 100^{0}C for ~60mins to give an off-white suspension. The suspension was allowed to cool to ambient temperature and then further cooled (ice / water bath). Solids were removed by filtration and washed with water and dried *in vacuo*.

LCMS retention time = 1.273 minutes; *m/z* = 162.0 $[M+H]^+$ (Run time 3.75mins)

Step 3

1H-Pyrrolo[2,3-b]pyridine-3-carbonitrile

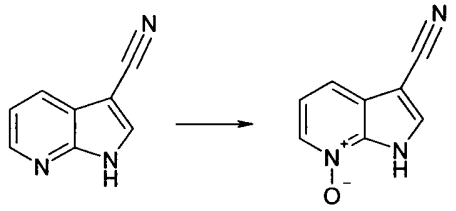


A suspension of the1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde oxime in acetic anhydride was heated to 140^{0}C, for ~3hrs. The resulting solution was allowed to cool and poured into water to give an off-white suspension, the solids were removed by filtration and washed with water, the crude solid was re-crystallised from boiling water to give an off-white solid. Solids were removed by filtration and washed with water to give a pale brown powder and dried *in vacuo*.

LCMS retention time = 1.578 minutes, *m/z* = 144.1 $[M+H]^+$ (Run time 3.75mins)

Step 4

7-Oxy-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile

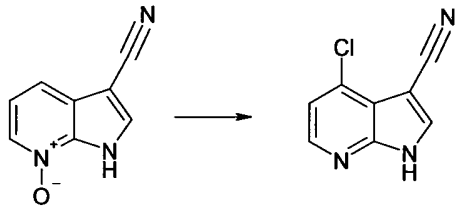


A suspension of the1H-pyrrolo[2,3-b]pyridine-3-carbonitrile in chloroform was cooled (ice / water bath). m-Chloroperoxybenzoic acid was added and the suspension stirred, room temperature for ~18hrs. to give an off-white suspension. Methanesulphonic acid (1.5 equivalents) was added to give a pale yellow solution, diethyl ether was then added and the solution cooled (ice/ water) to afford an off-white precipitate. Solids were removed by filtration and washed with diethyl ether and dried in vacuo to afford the product as the methansulphonate salt.

LCMS retention time = 1.085 minutes; *m/z* = 160.1 $[M+H]^+$ (Run time 3.75mins)

Step 5

4-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile

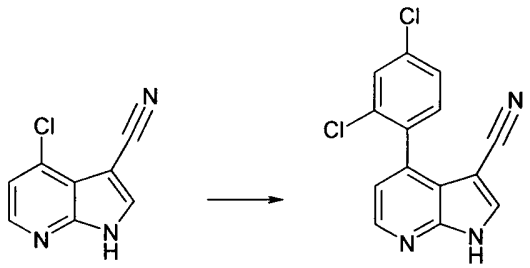


Methanesulphonyl chloride (2 equivalents) was added to a suspension of the 7-Oxy-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile methanesulphonate salt in DMF and the suspension heated, 80^{0}C, for ~2hrs. to give a pale brown solution. The resulting solution was allowed to cool and poured into water to give a pale yellow suspension. The solids were removed by filtration and washed with water and hexane, to give an off-white solid which was dried in vacuo.

LCMS retention time = 1.841 minutes; *m/z* = 178.0 $[M+H]^+$ (Run time 3.75mins)

Step 6

4-(2,4-Dichloro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile



Bis(tri-t-butylphosphine)palladium(0) was added to a suspension of 4-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile, 2,4-Dichlorophenylboronic acid and potassium fluoride in 1,4-Dioxan under a nitrogen atmosphere. The mixture heated at ~95^{0}C, for ~24hrs. The suspension was allowed to cool and diluted with ethyl acetate, the mixture washed with water and saturated aqueous sodium chloride solution, the solution was dried over anhydrous sodium sulphate and concentrated to a pale yellow solid. The crude product was purified by column chromatography on silica gel, eluting with mixtures of dichloromethane and methanol. The crude product was re-purified by preparative HPLC (pH 4), to give the product as a pale brown solid.

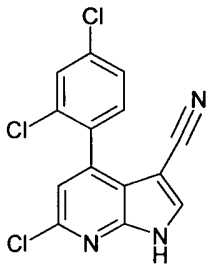
LCMS retention time = 2.315 minutes; *m/z* = 288.0 / 290.0 $[M+H]^+$ (Run time 3.75mins)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.20 (d, 1H, J = 4.8 Hz), 7.51 (d, 1H, J = 8.2 Hz), 7.58 (dd, 1H, J = 8.2, 2.0 Hz), 7.83 (d, 1H, J = 2.0 Hz), 8.48 (d, 1H, J = 5.0 Hz), 13.03 (brs, 1H)

This compound had activity 'A' in the fluorescence polarization assay described below.

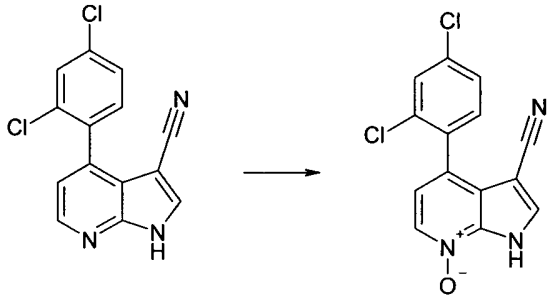
Example 3

6-Chloro-4-(2,4-dichloro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile



Step1

4-(2,4-Dichloro-phenyl)-7-Oxy-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile

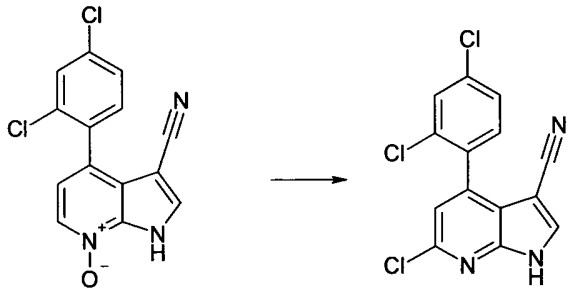


A suspension of the 4-(2,4-dichloro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile in chloroform was cooled (ice / water). m-Chloroperoxybenzoic acid was added and the suspension stirred at room temperature for ~18hrs. The resulting solution was concentrated to an orange gum. The crude product was purified by column chromatography, silica, eluting with mixtures of dichloromethane and methanol.

LCMS retention time = 1.973 minutes; *m/z* = 304.0 / 306.0 $[M+H]^+$ (Run time 3.75mins)

Step 2

6-Chloro-4-(2,4-dichloro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile



Methanesulphonyl chloride (2 equivalents) was added to a suspension of the 4-(2,4-Dichloro-phenyl)-7-Oxy-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile in DMF and the suspension heated at 80°C, for ~2hrs. to give a pale brown solution. The resulting solution was allowed to cool and poured into water, the mixture was extracted with ethyl acetate and the extracts were washed with water and saturated aqueous sodium chloride solution, the solution was dried over anhydrous sodium sulphate and concentrated to a pale brown solid. The crude product was purified by preparative HPLC (pH4) to give the product as an off-white solid.

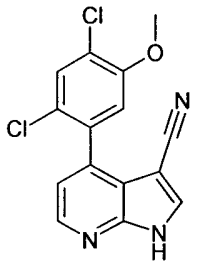
LCMS retention time = 2.577 minutes; *m/z* = 322 $[M+H]^+$ (Run time 3.75mins)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.36 (s, 1H), 7.55 (d, 1H, J = 8.1 Hz), 7.60 (dd, 1H, J = 8.1, 2.0 Hz), 7.85 (d, 1H, J = 2.0 Hz), 8.53 (brs, 1H), 13.34 (brs, 1H)

This compound had activity 'A' in the fluorescence polarization assay described below.

Example 4

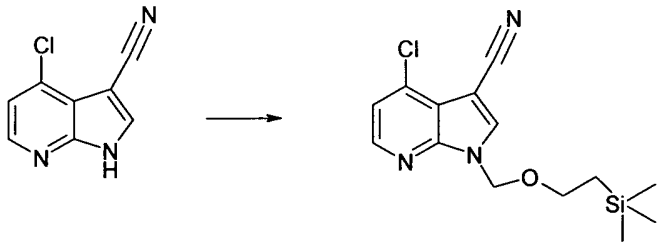
4-(2,4-Dichloro-5-methoxy-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile



This compound was made by way of the route outlined in scheme 2, with the exception of the pyrrolo nitrogen being protected prior to the cross coupling step.

Step 1

4-Chloro-1-(2-trimethylsilanyl-ethoxymethyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile

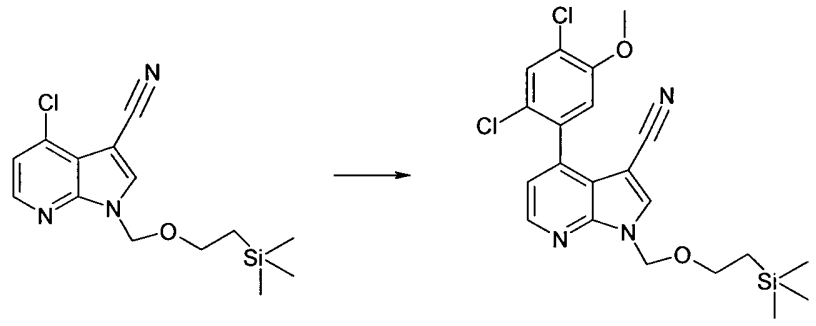


Sodium hydride (60% dispersion in mineral oil) was added to a cooled (ice / water bath) suspension of 4-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile in THF and the mixture stirred for ~60mins. 2-(Trimethylsilyl)ethoxymethyl chloride was added and the mixture stirred for ~2hrs. The suspension was diluted with ethyl acetate and the mixture washed with water and saturated aqueous sodium chloride solution, the solution was dried over anhydrous sodium sulphate and concentrated to a pale brown gum. The crude product was purified by column chromatography on silica gel, eluting with mixtures of ethyl acetate and hexane.

LCMS retention time = 2.728 minutes; *m/z* = 308.1 $[M+H]^+$ (Run time 3.75mins)

Step 2

4-(2,4-Dichloro-5-methoxy-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile

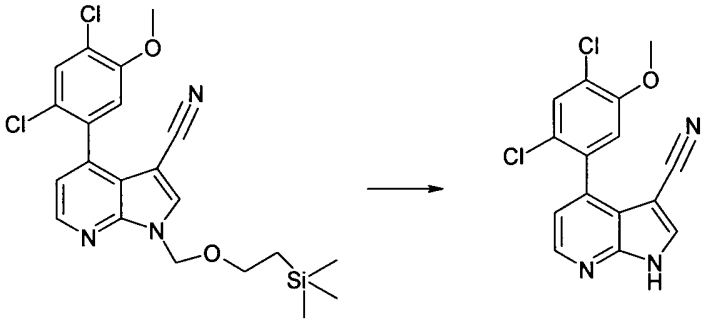


1,1'-Bis(diphenylphosphino)ferrorecene palladium(II) chloride was added to a suspension of 4-chloro-1-(2-trimethylsilanyl-ethoxymethyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile and 2,4-Dichloro-5-methoxyphenylboronic acid in 1,4-Dioxan under a nitrogen atmosphere. Aqueous potassium phosphate (2M) was added and the mixture heated at ~95^{0}C, for ~ 24hrs. The suspension was allowed to cool and diluted with ethyl acetate, the mixture washed with water and saturated aqueous sodium chloride solution, the solution was dried over anhydrous sodium sulphate and concentrated to a dark brown gum. The crude product was purified by column chromatography, silica, eluting with mixtures of ethyl acetate and hexane.

LCMS retention time = 2.863 minutes; *m/z* = 448.1 / 450.1 $[M+H]^+$ (Run time 3.75mins)

Step 3

4-(2,4-Dichloro-5-methoxy-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile



Tetrabutylammonium fluoride (1M in THF) was added to a solution of 4-(2,4-dichloro-5-methoxy-phenyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile and ethylenediamine (1.5 equivalents) in THF, under a nitrogen atmosphere and the solution heated at ~65^{0}C, for ~ 18hrs. The solution was allowed to cool and

diluted with ethyl acetate. The phases were separated and the organic phase was washed with water, saturated aqueous sodium chloride solution then dried over anhydrous sodium sulphate and concentrated to a pale yellow solid. The crude product was purified by column chromatography on silica gel, eluting with mixtures of ethyl acetate and hexane.

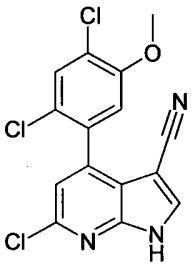
LCMS retention time = 2.310 minutes; m/z = 318.1 / 320.05 $[M+H]^+$ (Run time 3.75mins)

^1H NMR (400 MHz, DMSO-d_6) δ 3.59 (s, 3H), 7.25 (d, 1H, J = 4.8 Hz), 7.29 (s, 1H), 7.78 (s, 1H), 8.48 (d, 1H, J = 4.8 Hz), 8.50 (s, 1H), 13.03 (brs, 1H).

This compound had activity 'A' in the fluorescence polarization assay described below.

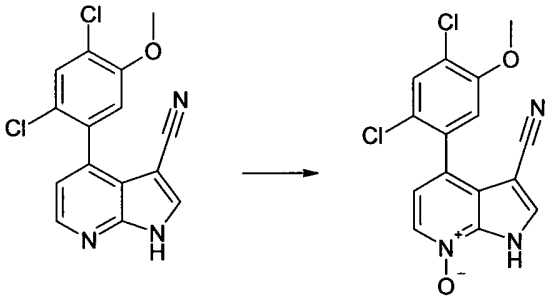
Example 5

6-Chloro-4-(2,4-dichloro-5-methoxy-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile



Step 1

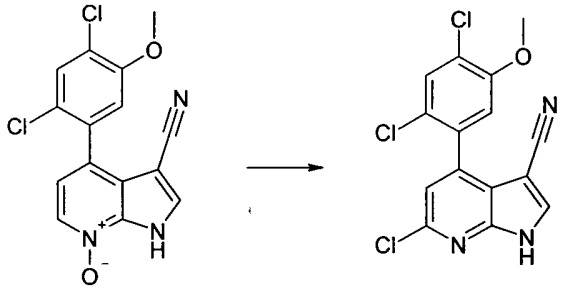
4-(2,4-Dichloro-5-methoxy-phenyl)-7-Oxy-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile



A suspension of the 4-(2,4-dichloro-5-methoxy-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile in chloroform was cooled (ice/water). m-Chloroperbenzoic acid was added and the suspension stirred at room temperature for ~18hrs. The resulting solution was

concentrated to an orange gum and this crude product was purified by column chromatography on silica gel, eluting with mixtures of dichloromethane and methanol.
LCMS retention time = 1.967 minutes; m/z = 334.0 / 336.0 $[M+H]^+$ (Run time 3.75mins)

Step 2
6-Chloro-4-(2,4-dichloro-5-methoxy-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile

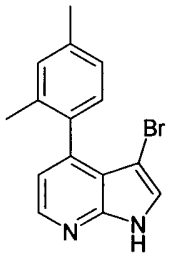


The title compound was prepared by way of the method outlined for example 3 step 2.
product was purified by Preparative HPLC (pH4).
LCMS retention time = 2.568 minutes; *m/z* = 352 $[M+H]^+$ (Run time 3.75mins)

This compound had activity 'A' in the fluorescence polarization assay described below.

Example 6

3-Bromo-4-(2,4-dimethyl-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile



N-Bromosuccinimide was added to a solution of 4-(2,4-dimethyl-phenyl)-1H-pyrrolo[2,3-b]pyridine (example 1 step 1) in dichloromethane, and the solution stirred for ~90mins. The solution was diluted with dichloromethane and washed with water and saturated aqueous sodium chloride solution. The phases were separated dried over anhydrous sodium sulphate and concentrated to a red / orange gum. The crude product was purified by column chromatography on silica gel, eluting with mixtures of ethyl acetate

and hexane. The crude product was re-purified by preparative HPLC (pH4), to give the product as a pale brown solid.

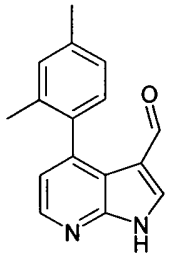
LCMS retention time = 2.569 minutes; *m/z* = 301.0 / 303.0 $[M+H]^+$ (Run time 3.75mins).

^1H NMR (400 MHz, DMSO-d_6) δ 1.96 (s, 3H), 2.34 (s, 3H), 6.86 (d, 1H, J = 4.8 Hz), 7.06 (m, 2H), 7.11 (s, 1H), 7.64 (d, 1H, J = 2.) Hz), 8.29 (d, 1H, J = 4.8 Hz), 12.16 (brs, 1H).

This compound had activity 'B' in the fluorescence polarization assay described below.

Example 7

4-(2,4-Dimethyl-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde



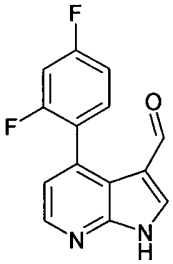
This compound was prepared by the methods outlined in example 1 steps 1 and 2, using 2,4-dimethyl-phenyl-boronic acid for step 1 (cross coupling).

LCMS retention time = 2.22 minutes; *m/z* = 251.1 $[M+H]^+$ (Run time 3.75mins).

This compound had activity 'A' in the fluorescence polarization assay described below.

Example 8

4-(2,4-Difluorol-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde



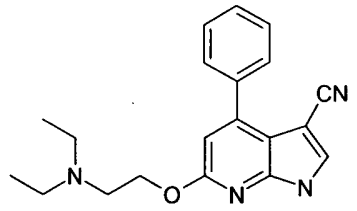
This compound was prepared by the methods outlined in example 1 steps 1 and 2, using 2,4-difluoro-pheny-boronic acid for step 1 (cross coupling).

LCMS retention time = 2.05 minutes; *m/z* = 259 $[M+H]^+$ (Run time 3.75mins).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.18 (dd, 1H J = 8.5, 2.6 Hz), 7.21 (d, 1H, J = 4.8 Hz), 7.31 (dt, 1H, J = 10, 2.6 Hz), 7.51 (m, 1H), 8.44 (d, 1H, J = 4.8 Hz), 8.52 (s, 1H), 9.60 (s, 1H), 12.96 (brs, 1H).

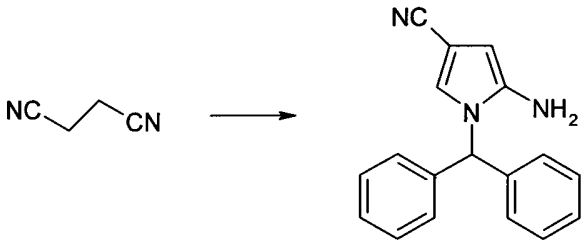
Example 9

6-(2-Diethylamino-ethoxy)-4-phenyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile



Step1

5-Amino-1-benzohydryl-1H-pyrrole-3-carbonitrile

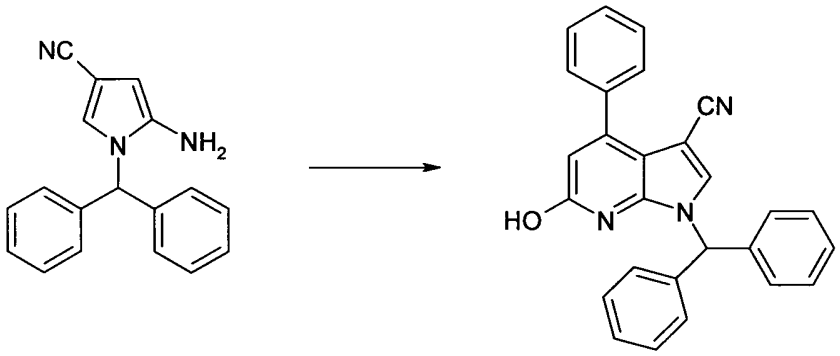


A solution of ethyl formate (4.0 mL) and succininitrile (4.0 g, 49.9 mmol) in THF (80 mL) was added dropwise to an ice bath cooled solution of potassium tert butoxide in THF (50 mL) under a nitrogen atmosphere. The resulting suspension was stirred at ambient temperature for 30 minutes. The solvent was removed *in vacuo* and the residual solid was suspended in water (20 mL) and amino diphenyl methane was added dropwise. Acetic acid (20 mL) was then added and the reaction mixture was heated to 100 °C for 10 minutes. The mixture was cooled to ambient temperature and water (150 mL) was added and the mixture was extracted with diethyl ether. (200 mL) and the phases separated. The ether extracts were washed sequentially with 2.0 M aqueous sodium hydroxide solution (75 mL) water (2 x 75 mL) and saturated sodium chloride solution (75 mL). The organic phase was dried over sodium sulphate, filtered and the filtrate solvents

evaporated *in vacuo* to leave a dark brown gum. The residue was dissolved in ethanol (50 mL) and sodium ethoxide (6.8 g) was added and the resulting solution stirred at ambient temperature for 60 minutes. Water (250 mL) was added and the mixture then extracted with diethyl ether (200 mL). The phases were separated and the organic phase washed with water (250 mL) and saturated sodium chloride solution (150 mL). The organic phase was dried over sodium sulphate, filtered and the filtrate solvents evaporated *in vacuo* to afford a dark-brown solid (8.1 g).

Step 2

1-Benzhydryl-6-hydroxy-4-phenyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile

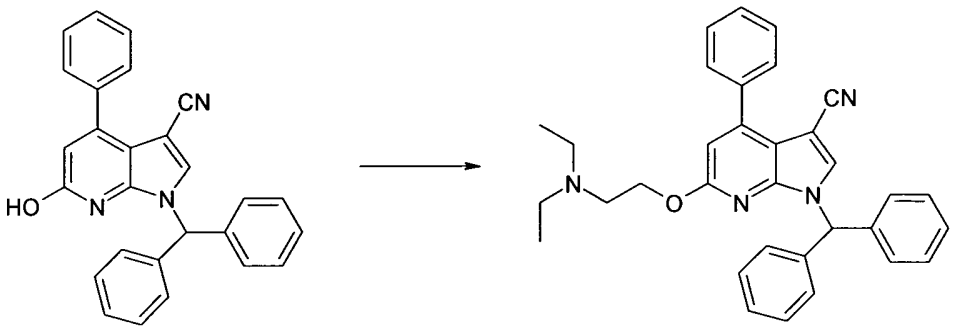


3-Oxo-3-phenyl-propionic acid ethyl ester (3.85 g) was added to a suspension of 5-amino-1-benzhydryl-1H-pyrrole-3-cabonitrile (5.5 g) in 1-butanol (80 mL) and the suspension stirred. Hydrochloric acid (6N, 1.0 mL) was added and the mixture was heated at 120 ^{0}C, for 2 hrs and then the resulting solution was allowed to cool and concentrated to a dark purple gum. The crude product was purified by column chromatography on silica, gel eluting with dichloromethane to give the product as a pale-brown solid (3.25 g).

LCMS retention time = 2.653 minutes; *m/z* = 402.2 $[M+H]^{+}$ (Run time 3.75mins)

Step 3

1-Benzhydryl-6-(2-diethylamino-ethoxy)-4-phenyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile

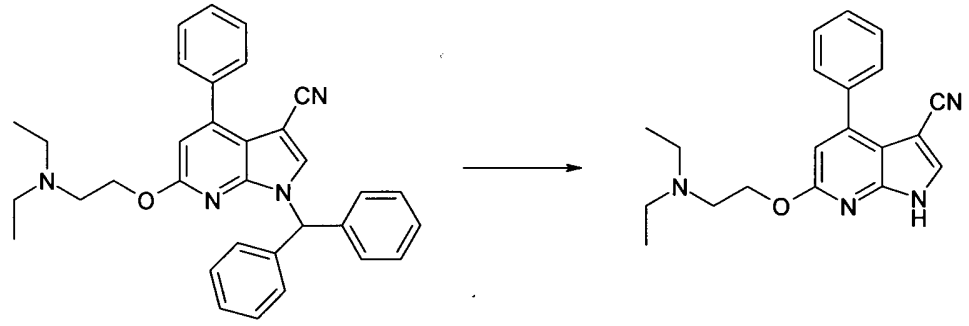


Cesium carbonate (3.25 g) was added to a solution of 1-Benzhydryl-6-hydroxy-4-phenyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (2.0 g) in acetone (30 mL) and the suspension stirred. 2-Bromo-N,N-diethylethylamine hydrochloride (2.0 g) was added and the suspension was heated at 70 ^{0}C, for 90 mins. The resulting suspension was allowed to cool and ethyl acetate (250 mL) was added. The organic phase was washed with water (1 x 100 mL) then saturated aqueous sodium chloride solution (100 mL). The organic phase was dried over anhydrous sodium sulphate and concentrated to a dark brown gum (2.0 g) which solidified on standing.

LCMS retention time = 2.106 minutes; *m/z* = 501.3 $[M+H]^+$ (Run time 3.75mins)

Step 4

6-(2-Diethylamino-ethoxy)-4-phenyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile



A solution of potassium *tert*-butoxide (1.0 g) in THF (20 mL) was added to a solution of 1-Benzhydryl-6-methoxy-4-phenyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile in DMSO (2.5 mL) and the suspension stirred at ambient temperature for 60 mins. Saturated aqueous ammonium chloride solution (50 mL) was added and the mixture extracted with ethyl acetate (250 mL). The organic phase was separated and washed with water (2 x 50 mL) then saturated aqueous sodium chloride solution (75 mL). The aqueous phase was

dried over anhydrous sodium sulphate, filtered and the filtrate solvents removed *in vacuo* to leave an orange gum. The crude product was purified by flash chromatography on silica gel (70 g) eluting with dichloromethane / methanol mixture (9 : 1) to afford the a brown gum which was triturated with diethyl ether : hexane (1 : 9) mixture, filtered and dried *in vacuo* to afford the product (250 mg) as a light-brown solid.

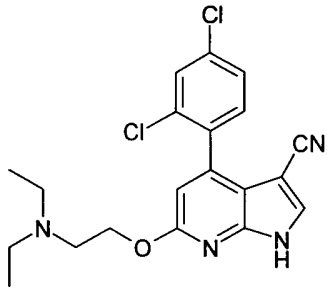
LCMS retention time = 1.620 minutes; *m/z* = 335.2 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ 0.99 (t, 6H, J = 7.1 Hz), 2,58 (m, 4H), 2.84 (m, 2H), 4.38 (t, 2H, J = 6.0 Hz), 6.64 (s, 1H), 7.47 – 7.54 (m, 3H), 7.57 – 7.61 (m, 2H), 8.23 (s, 1H), 12.73 (brs, 1H).

This compound had activity 'C' in the fluorescence polarization assay described below.

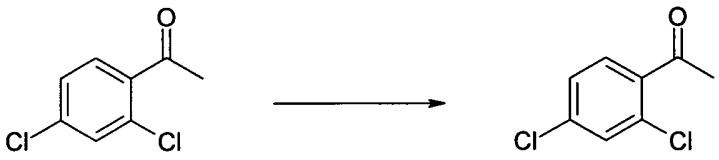
Example 10

4-(2,4-Dichloro-phenyl)-6-(2-diethylamino-ethoxy)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile



Step 1

1-(2,4-dichloro-phenyl) ethanone

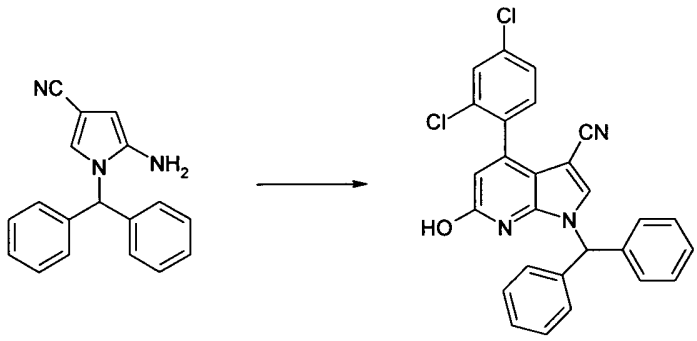


Sodium Hydride (60% dispersion in mineral oil) (4.0 g) was added in portions to a solution of 2,4-dichloroacetophenone (8.8 g) in diethyl carbamate (90 mL) under a nitrogen atmosphere. The mixture was heated to 80 °C for 3 hrs. The mixture was cooled to ambient temperature and then poured into a mixture of water (300 mL) and

acetic acid (10 mL). The mixture was extracted with diethyl ether (3 x 100 mL) and the combined organic extracts were washed with water (2 x 100 mL), then saturated sodium chloride solution (100 mL). The organic phase was dried over anhydrous sodium sulphate, filtered and the filtrate solvents removed in vacuo to afford an orange oil which was purified by distillation under reduced pressure (1 mm Hg) to afford the product (9.88 g) as a pale yellow oil.

Step 2

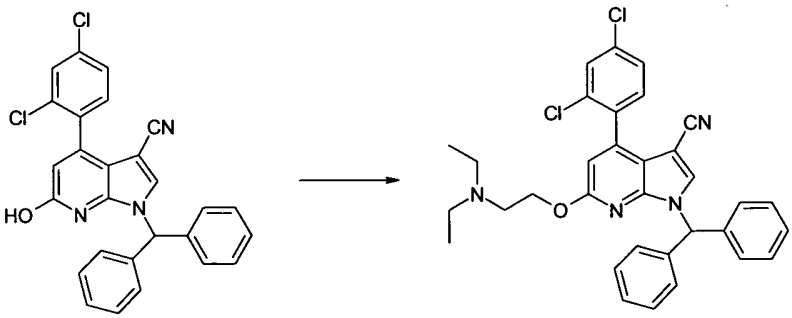
1-Benzhydryl-6-hydroxy-4-(2,4-dichlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile



This compound was made utilizing the method of example 9 step 2 using 5-Amino-1-benzohydryl-1H-pyrrole-3-carbonitrile and 1-(2,4-dichloro-phenyl) ethanone.
LCMS retention time = 2.733 minutes; *m/z* = 470.1, 472.1 $[M+H]^+$.

Step 3

1-Benzhydryl-4-(2,4-dichlorophenyl)-6-(2-diethylamino-ethoxy)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile

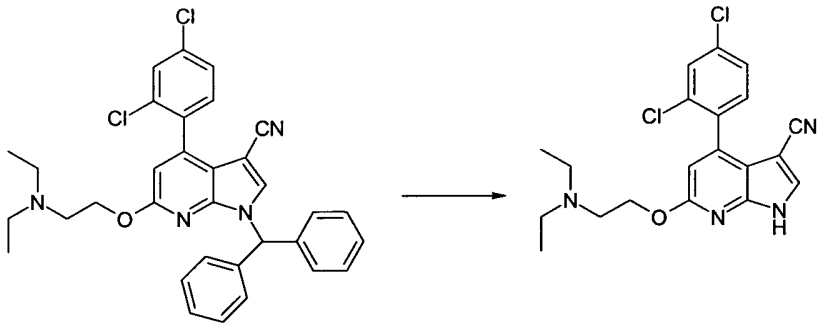


This compound was made by way of the methods utilized for example 9 step 3.

LCMS retention time = 2.219 minutes; *m/z* = 569.2, 571.2 $[M+H]^+$.

Step 4

4-(2,4-Dichloro-phenyl)-6-(2-diethylamino-ethoxy)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile



This compound was made by way of the method utilized for example 9 step 4.

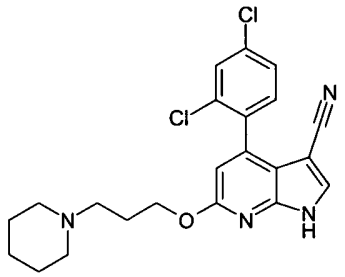
LCMS retention time = 2.842 minutes; *m/z* = 403.1, 405.1 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ 0.99 (t, 6H, J = 7.4 Hz), 2.61 (q, 4H, J = 7.4 Hz), 2.86 (t, 2H, J = 6.1 Hz), 4.39 (t, 2H, J = 6.1 Hz), 6.62 (s, 1H), 7.49 (d, 1H, J = 8.3 Hz), 7.56 (dd, 1H, J = 8.3, 2.0 Hz), 7.80 (d, 1H, J = 2.0 Hz), 8.19 (s, 1H), 8.26 (s, 1H)

This compound had activity 'B' in the fluorescence polarization assay described below.

Example 11

4-(2,4-Dichloro-phenyl)-6-(3-piperidin-1-yl-propoxy)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile



This compound was made by way of the methods utilised for the preparation of the compounds of example 9 and 10. Thus 1-Benzhydryl-4-(2,4-dichlorophenyl)-6-(2-diethylamino-ethoxy)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (example 10, step 2) was

reacted with 1-(chloropropoxy piperidine hydrochloride then the benzhydryl protecting group removed bythe method outlined in example 9 step 4 to afford a crude product which was purified by preparative HPLC to give the title compound (example 11) as a light brown solid.

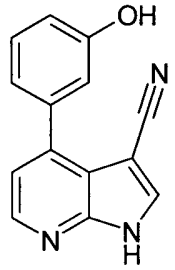
LCMS retention time = 1.895 minutes; *m/z* = 429.3, 431.1 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ 1.38 (m, 2H), 1.48 (m. 4H), 1.91 (m, 2H), 2.33 (m, 4H), 2.39 (t, 2H, J = 7.0z), 4.33 (t, 2H, J = 7.0 Hz), 6.62 (s, 1H), 7.49 (d, 1H, J = 8.2 Hz), 7.56 (dd, 1H, J = 8.2 Hz, 2.0 Hz), 7.79 (d, 1H, J = 2.0 Hz), 8.18 (s, 1H), 12.70 (brs, 1H).

This compound had activity 'B' in the fluorescence polarization assay described below.

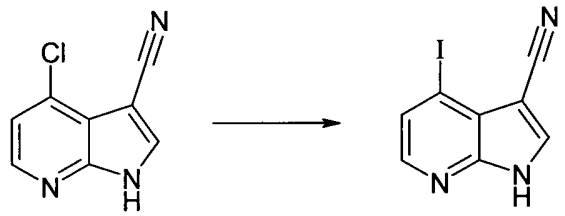
Example 12

4-(3-Hydroxy-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile



Step 1

4-iodo-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile

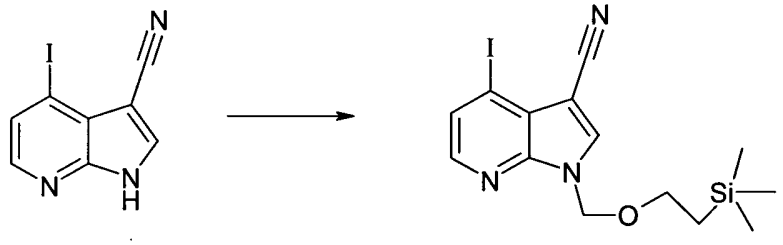


Acetyl chloride (1.5 mL) was added to a suspension of 4-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (1.8 g) and sodium Iodide (7.5 g) in acetonitrile (40 mL) and the suspension was heated to 80 °C for 18 hrs. Ethyl acetate (400 mL) was added and the organic phase was washed sequentially with water (100 mL) 10% (w/v) aqueous sodium thiosulphate solution (100 mL), water (2 x 100 mL) and saturated aqueous sodium

chloride solution (100 mL). The organic phase was dried over sodium sulphate and filtered and filtrate solvents removed in vacuo to give a yellow solid, which was suspended in methanolic ammonia (2M, 35 mL) and stirred for 30 minutes. Methanol was removed *in vacuo* and the residual solid was triturated with diethyl ether to afford product (2.4 g) as a brown powder.

Step 2

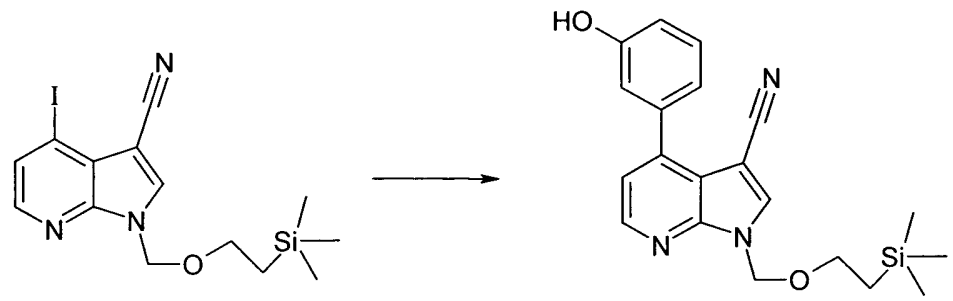
4-iodo-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile



Sodium hydride (400 mg) was added to a suspension of the azaindole (1.5g) in THF (40 mL) at 0 °C under a nitrogen atmosphere. The mixture was stirred for 90 mins at ambiet temperature. The reaction mixture was recooled to 0 °C and 2-(trimethylsilyl)-ethoxy methyl chloride (1.5 mL) was added and the solution was stirred for 2 hours at . Ethyl acetate was added and the organic phase was washed with water (2 x 100 mL) and saturated aqueous sodium chloride solution (100 mL). The organic phase was dried over sodium sulphate, filtered and the filtrate solvents removed in vacuo to afford a yellow solid. The crude product was purified by flash chromatography eluting with ethyl acetate : hexane mixture (1:9) to afford the product (1.7 g) as a colorless solid.

Step 3

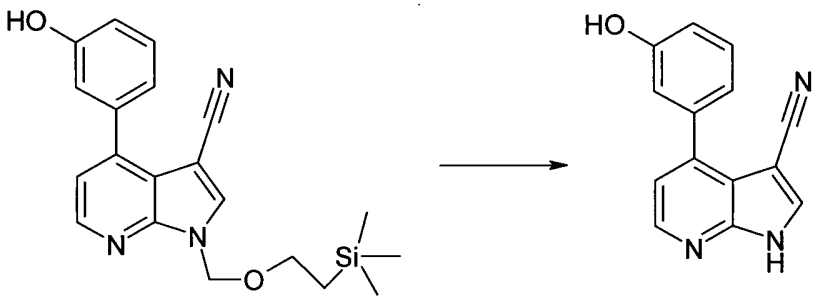
4-(3-hydroxy-phenyl)-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile



Potassium phosphate (5.1 g) was added to a suspension of 3-hydroxyphenyl boronic acid (1.1 g) and 4-iodo-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (1.6 g) in 1,4-dioxane (20 mL) under a nitrogen atmosphere. Dichloro-bis-(triphenylphosphine) palladium II (105 mg) was added and the reaction mixture was heated to 95 °C for 18 hr. The suspension was allowed to cool and ethyl acetate (150 mL) was added and the mixture was washed sequentially with saturated ammonium chloride solution (50 mL), water (2 x 50 mL) and saturated aqueous sodium chloride solution (50 mL). The organic phase was dried over sodium sulphate, filtered and filtrate solvents removed in vacuo to afford a brown gum. The crude product was purified by flash chromatography eluting with ethyl acetate : hexane mixture (1:2) to afford the product (1.4 g) as a colorless solid.

Step 4

4-(3-Hydroxy-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile



The compound was made by the method utilized for example 4 step 3.

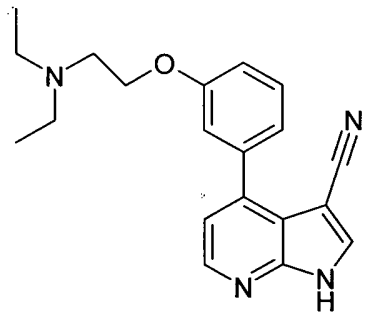
LCMS retention time = 1.810 minutes; *m/z* = 236.1 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ 6.88 (dd, 1H, J = 7.4, 2.5 Hz), 6.91 (t, 1H, J = 2.5 Hz), 7.00 (d, 1H, J = 7.8 Hz), 7.20 (d, 1H, J = 4.8 Hz), 7.31 (t, 1H, J = 7.8 Hz), 8.41 (d, 1H, J = 4.8 Hz), 8.50 (s, 1H), 9,65 (brs, 1H), 12.96 (brs, 1H).

This compound had activity 'B' in the fluorescence polarization assay described below.

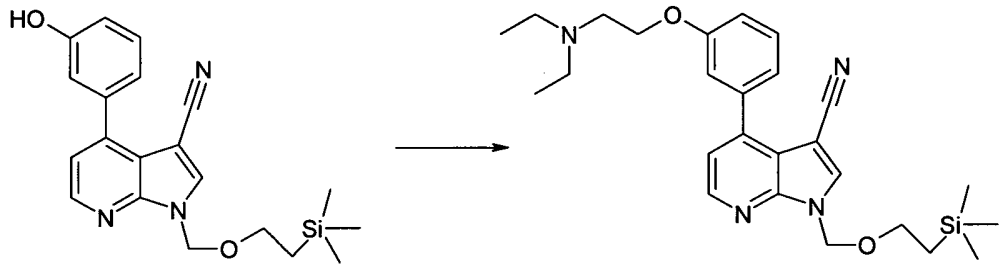
Example 13

4-[3-(2-Diethylamino-ethoxy)-phenyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile



Step 1

4-[3-(2-Diethylamino-ethoxy)-phenyl]-1-(2-trimethylsilanyl-ethoxymethyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile

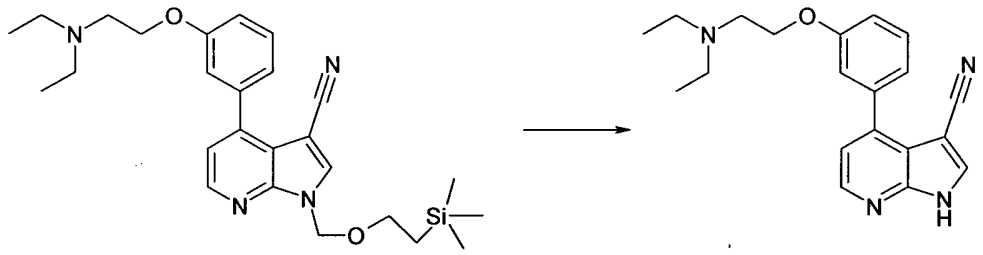


A solution of diisopropylazodicarboxylate (0.15 mL) in THF (2.5 mL) was added to a solution of 4-(3-hydroxy-phenyl)-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (180 mg) and triphenyl phosphine (200 mg) in THF (10 mL) under a nitrogen atmosphere. A solution of 2-diethylamino ethanol (0.10 mL) in THF (2.5 mL) was then added and the mixture stirred at ambient temperature for 18 hr. The product was purified by ion exchange chromatography (SCX-II), followed by flash

chromatography on silica gel (20 g) eluting with ethyl acetate to give the product (190 mg) as a pale brown gum.

Step 2

4-[3-(2-Diethylamino-ethoxy)-phenyl]-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile



The compound was made by the method utilized for example 4 step 3.

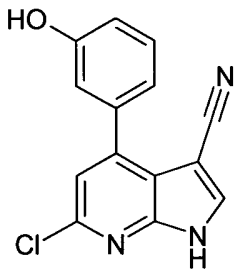
LCMS retention time = 1.56 minutes; *m/z* = 335.2 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ 0.97 (t, 6H, J = 7.1 Hz), 2,55 (q, 4H, J = 7.1 Hz)), 2.81 (t, 2H, J = 6.1 Hz)), 4.13 (t, 2H, J = 6.1 Hz), 7.04 (m, 1H), 7.15 (m, 1H), 7.17 (m, 1H), 7.27 (d, 1H, J = 4.8 Hz), 7.42 (t, 1H, J = 7.8 Hz), 8.43 (d, 1H, J = 4.8 Hz), 8.52 (s, 1H), 12.95 (brs, 1H).

This compound had activity 'B' in the fluorescence polarization assay described below.

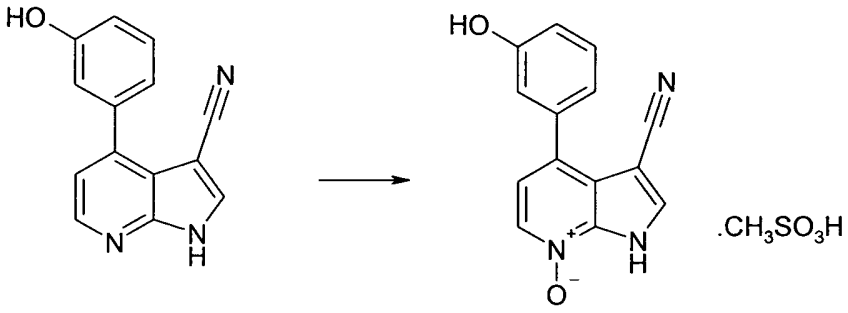
Example 14

6-Chloro-4-(3-hydroxy-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile



Step 1

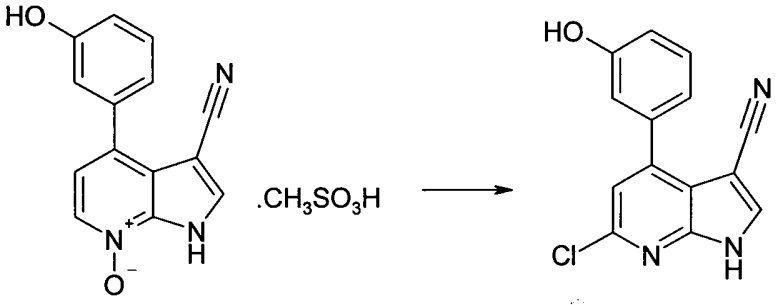
4-(3-hydroxy-phenyl)-7-oxo-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile methane sulphonate



4-(3-Hydroxy-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (850 mg) was added to a solution of meta-chloroperoxybenzoic acid (ca 77%;1.6 g) in dichloromethane (40 mL). The reaction mixture was stirred for ca. 100 hrs affording a yellow suspension. Methane sulphonic acid (0.5 mL) was added affording a yellow solution. Diethyl ether was added and the mixture stirred to afford a yellow suspension, which was filtered, washed with ether and dried in vacuo to give the product (560 mg) as a yellow powder.

Step 2

6-Chloro-4-(3-hydroxy-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile



Methane sulfonyl chloride (1.0 mL) was added to a solution of 4-(3-hydroxy-phenyl)-7-oxo-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile methane sulphonate (550 mg) in DMF (10 mL) and the mixture was heated at 80 °C for 90 mins. The resulting solution was allowed to cool to ambient temperature and then poured into water (100 mL) and the suspension was made basic by addition of aqueous ammonia, and stirred for 10 min. The solids were collected by filtration and then purified by flash chromatography on silica gel, eluting with dichloromethane / methanol (19:1) to give a pale brown solid (300 mg).

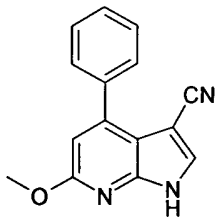
LCMS retention time = 2.09 minutes; *m/z* = 270 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ 6.91 (dd, 1H, J = 8.1, 2.4 Hz), 6.97 (t, 1H, J = 2.4 Hz), 7.02 (d, 1H, J = 8.1 Hz), 7.28 (s, 1H), 7.33 (t, 1H, J = 7.8 Hz), 8.54 (s, 1H), 9.72 (s, 1H), 13.17 (brs, 1H).

This compound had activity 'A' in the fluorescence polarization assay described below.

Example 15

6-methoxy-4-(-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile



This compound was made by way of the methods utilized for example 9, using dimethyl sulphate to alkylate 1-Benzhydryl-6-hydroxy-4-phenyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (example 9 step 3).

LCMS retention time = 2.34 minutes; *m/z* = 250.1 $[M+H]^+$.

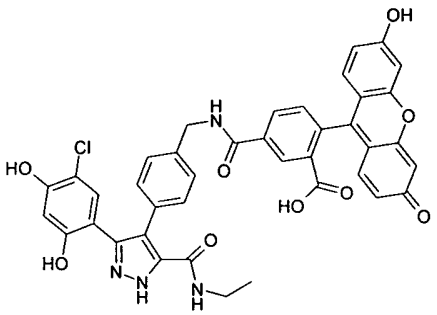
^1H NMR (400 MHz, DMSO-d_6) δ 3.93 (s, 1H), 6.68 (s, 1H), 7.49-7.62 (m, 3H), 7.58-7.62 (m, 2H), 8.24 (d, 1H, J = 3.0 Hz), 12.77 (brs, 1H).

This compound had activity 'A' in the fluorescence polarization assay described below.

Fluorescence Polarization Assay

Fluorescence polarization {also known as fluorescence anisotropy} measures the rotation of a fluorescing species in solution, where the larger molecule the more polarized the fluorescence emission. When the fluorophore is excited with polarized light, the emitted light is also polarized. The molecular size is proportional to the polarization of the fluorescence emission.

The fluoroscein-labelled probe –



binds to HSP90 { full-length human, full-length yeast or N-terminal domain HSP90 } and the anisotropy {rotation of the probe:protein complex} is measured.

Test compound is added to the assay plate, left to equilibrate and the anisotropy measured again. Any change in anisotropy is due to competitive binding of compound to HSP90, thereby releasing probe.

Materials

Chemicals are of the highest purity commercially available and all aqueous solutions are made up in AR water.

1) Costar 96-well black assay plate #3915
2) Assay buffer of (a)100mM Tris pH7.4; (b) 20mM KCl; (c) 6mM $MgCl_2$. Stored at room temperature.
3) BSA (bovine serum albumen) 10 mg/ml (New England Biolabs # B9001S)
4) 20 mM probe in 100 % DMSO stock concentration. Stored in the dark at RT. Working concentration is 200 nM diluted in AR water and stored at 4 °C. Final concentration in assay 80 nM.
5) E. coli expressed human full-length HSP90 protein, purified >95% (see, e.g., Panaretou et al., 1998) and stored in 50µL aliquots at -80°C .

Protocol

1) Add 100µl 1x buffer to wells 11A and 12A (=FP BLNK)

2) Prepare assay mix – all reagents are kept on ice with a lid on the bucket as the probe is light-sensitive.

		i. Final Conc^{n}
• 1x Hsp90 FP Buffer	10 ml	1x
• BSA 10mg/ml (NEB)	5.0 µl	5 µg/ml
• Probe 200µM	4.0 µl	80 nM
• Human full-length Hsp90	6.25 µl	200 nM

3) Aliquot 100µl assay mix to all other wells
4) Seal plate and leave in dark at room temp for 20 minutes to equilibrate

Compound Dilution Plate – 1 x 3 dilution series

1) In a clear 96-well v-bottom plate – {# VWR 007/008/257} add 10 µl 100% DMSO to wells B1 to H11
2) To wells A1 to A11 add 17.5µl 100% DMSO
3) Add 2.5 µl cpd to A1. This gives 2.5 mM {50x} stock cpd – assuming cpds 20 mM.
4) Repeat for wells A2 to A10. Control in columns 11 and 12.
5) Transfer 5 µl from row A to row B- not column 12. Mix well.
6) Transfer 5 µl from row B to row C. Mix well.
7) Repeat to row G.
8) Do not add any compound to row H – this is the 0 row.
9) This produces a 1x3 dilution series from 50 µM to 0.07 µM.
10) In well B12 prepare 20 µl of 100 µM standard compound.
11) After first incubation the assay plate is read on a Fusion™ α-FP plate reader (Packard BioScience, Pangbourne, Berkshire,UK).
12) After the first read, 2 µl of diluted compound is added to each well for columns 1 to 10. In column 11 {provides standard curve} only add compound B11 – H11. Add 2 µl of 100mM standard cpd to wells B12 – H12 {is positive control }
13) The Z' factor is calculated from zero controls and positive wells. It typically gives a value of 0.7 – 0.9.

The compounds tested in the above assay were assigned to one of two activity ranges, namely

A: FP IC_{50} < 1.0 μM

B: FP IC_{50} > 1.0 μM < 10 μM

C: FP IC_{50} > 10.0 μM,

and those assignments are reported above.

A growth inhibition assay was also employed for the evaluation of candidate HSP90 inhibitors:

Assessment of cytotoxicity by Sulforhodamine B (SRB) assay: calculation of 50% inhibitory concentration (IC_{50}).

Day 1

1) Determine cell number by haemocytometer.
2) Using an 8 channel multipipettor, add 160μl of the cell suspension (3600 cells/well or 2 x 10^4 cells/ml) to each well of a 96-well microtitre plate.
3) Incubate overnight at 37°C in a CO_2 incubator.

Day 2

4) Stock solutions of drugs are prepared, and serial dilutions of each drug are performed in medium to give final concentrations in wells.
5) Using a multipipettor, 40μl of drug (at 5x final concentration) is added to quadruplicate wells.
6) Control wells are at either side of the 96 well plates, where 40μl of medium is added.
7) Incubate plates in CO_2 incubator for 4 days (48 hours).

Day 6

8) Tip off medium into sink and immerse plate slowly into 10% ice cold trichloroacetic acid (TCA). Leave for about 30mins on ice.
9) Wash plates three times in tap water by immersing the plates into baths of tap water and tipping it off.
10) Dry in incubator.
11) Add 100µl of 0.4% SRB in 1%acetic acid to each well (except the last row (right hand)of the 96 well plate, this is the 0% control, ie no drug, no stain. The first row will be the 100% control with no drug, but with stain). Leave for 15 mins.
12) Wash off unbound SRB stain with four washes of 1% acetic acid.
13) Dry plates in incubator.
14) Solubilise SRB using 100µl of 10mM Tris base and put plates on plate shaker for 5 mins.
15) Determine absorbance at 540nm using a plate reader. Calculate mean absorbance for quadruplicate wells and express as a percentage of value for control, untreated wells.
16) Plot % absorbance values versus log drug concentration and determine the IC_{50}.

The compounds tested in the above assay were assigned to one of two activity ranges, namely A = IC_{50} <50µM; B = IC_{50} >50µM. By way of example the compound of example 5 had activity in the "A" range".

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A number of publications are cited above in order to more fully describe and disclose the invention and the state of the art to which the invention pertains. Full citations for these references are provided below. Each of these references is incorporated herein by reference in its entirety into the present disclosure.

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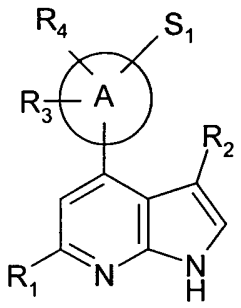
Claims:

1. A compound of formula (I), or a salt, N-oxide, hydrate, or solvate thereof:



(I)

wherein

ring A is an aryl or heteroaryl ring or ring system;

R_1 is hydrogen, fluoro, chloro, bromo, or a radical of formula (1A):

$$-X\text{-}Alk^1\text{-}(Z)_m\text{-}(Alk^2)_n\text{-}Q \quad (IA)$$

wherein

X is a bond, –O-, -S- -S(O)-, $-SO_2$-, or -NH-,

Z is –O-, -S-, -(C=O)-, -(C=S)-, -S(O)-, $-SO_2$-, $-NR^A$-, or, in either orientation -C(=O)O-, -C(=O)NR^A- , -C(=S)NR^A-, $-SO_2NR^A$-, -NR^AC(=O)-, or -NR^ASO_2- wherein R^A is hydrogen or C_1-C_6 alkyl in which one or more hydrogens is optionally substituted by fluorine;

Alk^1 and Alk^2 are optionally substituted divalent C_1-C_3 alkylene or C_2-C_3 alkenylene radicals,

m and n are independently 0 or 1, and

Q is hydrogen or an optionally substituted carbocyclic or heterocyclic radical;

R_2 is cyano (-CN), fluoro, chloro, bromo, methyl, ethyl, -OH, $-CH_2OH$, $-C(=O)NH_2$, -C(=O)H, $-C(=O)CH_3$, or $-NH_2$;

R_3 and R_4 are independently selected from hydrogen, fluoro, chloro, bromo, cyano (-CN), C_1-C_3alkyl optionally substituted with one or more fluorine substituents, C_1-C_3alkoxy optionally substituted with one or more fluorine substituents, $-CH=CH_2$, -C≡CH, cyclopropyl and $–NH_2$, or R_3 and R_4 together represent methylenedioxy

(–OCH_2O-) or ethylenedioxy (–OCH_2CH_2O-) in either of which one or more hydrogens are optionally replaced by fluorine;

S_1 is hydrogen, or a substituent selected from fluoro, chloro, bromo, cyano (-CN), C_1-C_3alkyl optionally substituted with one or more fluorine substituents, C_1-C_3alkoxy optionally substituted with one or more fluorine substituents, -$CH=CH_2$, -C≡CH, cyclopropyl and –NH_2, or S_1 and R_3, or S_1 and R_4, together represent methylenedioxy (–OCH_2O-) or ethylenedioxy ((–OCH_2 CH_2O-) in either of which one or more hydrogens are optionally replaced by fluorine; or S_1 is a radical of formula (IB):

$$-(Alk^3)_p-(Z^1)_q-(Alk^4)_r-Q^1 \qquad (IB)$$

wherein

p, q and **r** are independently 0 or 1;

(a) when p is 0 or 1, and q is 1, and r is 0 or 1:

Z^1 is selected from the group of divalent radicals consisting of (i) -S-, -(C=O)-, -(C=S)-, -S(O)- and -SO_2- and (ii) -$N(R^A)C(=O)$-* wherein the bond marked * is attached to Q^1 and (iii) in either orientation, -C(=O)O-, -$C(=S)NR^A$-, and -SO_2NR^A-; **and Q^1 is** (i) hydrogen or an optional substituent; or (ii) an optionally substituted carbocyclic or heterocyclic radical; or (iii) a radical –$CH_2[O(CH_2)_w]_xZ^2$ wherein Z^2 is H, -OH or –O(C_1-C_3alkyl) wherein x and w are independently 1, 2 or 3; or

(b) when p is 1, and q is 1, and r is 0 or 1:

Z^1 is –O-, **and Q^1 is** (i) hydrogen or an optional substituent which is not linked to -$(Alk^3)_p$-$(Z^1)_q$-$(Alk^4)_r$- through a nitrogen atom; or (ii) an optionally substituted carbocyclic radical; or (iii) an optionally substituted heterocyclic ring of 5 or 6 ring atoms which is not linked to -$(Alk^3)_p$-$(Z^1)_q$-$(Alk^4)_r$- through a ring nitrogen; or (iv) a radical –$CH_2[O(CH_2)_w]_xZ^2$ wherein Z^2 is H, -OH or –O(C_1-C_3alkyl) wherein x and w are independently 1, 2 or 3. or

(c) when p is 1, and q is 1, and r is 0 or 1:

Z^1 is $-NR^A-$ or $-C(=O)N(R^A)-$* wherein the bond marked * is attached to Q^1 **and Q^1 is** a radical $-CH_2[O(CH_2)_w]_xZ^2$ wherein Z^2 is H, -OH or $-O(C_1-C_3alkyl)$ wherein x and w are independently 1, 2 or 3. or

(d) when p is 0, and q is 1, and r is 0 or 1:

Z^1 is –O- or $-NR^A-$ **and Q^1 is** (i) hydrogen or an optional substituent which is not linked to $-(Alk^3)_p-(Z^1)_q-(Alk^4)_r-$ through a nitrogen atom; or (ii) Q^1 and R^A, taken together with the nitrogen to which they are attached form an optionally substituted heterocyclic ring of 5 or 6 ring atoms; or (iii) a radical $-CH_2[O(CH_2)_w]_xZ^2$ wherein Z^2 is H, -OH or $-O(C_1-C_3alkyl)$ wherein x and w are independently 1, 2 or 3; or

(e) when p is 0 or 1, q is 0, and r is 0 or 1:

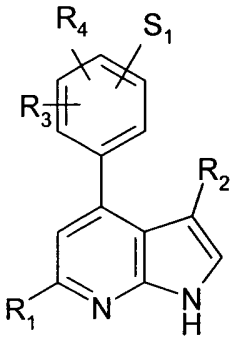
Q^1 is (i) hydrogen or an optional substituent which is not linked to $-(Alk^3)_p-(Z^1)_q-(Alk^4)_r-$ through a nitrogen atom or (ii) an optionally substituted carbocyclic radical; or (iii) an optionally substituted heterocyclic of 5 or 6 ring atoms which is not linked to $-(Alk^3)_p-(Z^1)_q-(Alk^4)_r-$ through a ring nitrogen; or (iv) a radical $-CH_2[O(CH_2)_w]_xZ^2$ wherein Z^2 is H, -OH or $-O(C_1-C_3alkyl)$ wherein x and w are independently 1, 2 or 3;

R^A is hydrogen or C_1-C_3 alkyl optionally substituted with one or more fluorine substituents; and

Alk^3 and Alk^4 are divalent C_1-C_3 alkylene or C_2-C_3 alkenylene radicals, each optionally substituted by one or two substituents selected from fluoro, chloro, C_1-C_3alkyl optionally substituted with one or more fluorine substituents, C_1-C_3alkoxy optionally substituted with one or more fluorine substituents.

2. A compound as claimed in claim 1 wherein ring A is a phenyl ring.

3. A compound of formula (IC), or a salt, N-oxide, hydrate, or solvate thereof:



(IC)

wherein

R_1, R_2, R_3 and R_4 are as defined in claim 1, and

S_1 is hydrogen, or a substituent selected from fluoro, chloro, bromo, cyano (-CN), C_1-C_3alkyl optionally substituted with one or more fluorine substituents, C_1-C_3alkoxy optionally substituted with one or more fluorine substituents, -CH=CH_2, -C≡CH, cyclopropyl and –NH_2, or S_1 and R_3, or S_1 and R_4, together represent methylenedioxy (–OCH_2O-) or ethylenedioxy ((–OCH_2CH_2O-) in either of which one or more hydrogens are optionally replaced by fluorine;

or S_1 is a radical of formula (IB):

$$-(Alk^3)_p-(Z^1)_q-(Alk^4)_r-Q^1 \qquad \text{(IB)}$$

wherein

p, q and **r** are independently 0 or 1;

Z^1 is –O-, -S-, -(C=O)-, -(C=S)-, -S(O)-, -SO_2-, -NR^A-, or, in either orientation, -C(=O)N(R^A)- or -SO_2NR^A-;

Q^1 is (i) hydrogen or an optional substituent; or (ii) an optionally substituted carbocyclic or heterocyclic radical; or (iii) a radical –$CH_2[O(CH_2)_w]_xZ^2$ wherein Z^2 is H, -OH or –O(C_1-C_3alkyl) wherein x and w are independently 1, 2 or 3;

R^A is hydrogen or C_1-C_3 alkyl optionally substituted with one or more fluorine substituents; and

Alk^3 and Alk^4 are divalent C_1-C_3 alkylene or C_2-C_3 alkenylene radicals, each optionally substituted by one or two substituents selected from fluoro, chloro, C_1-C_3alkyl optionally substituted with one or more fluorine substituents, C_1-C_3alkoxy optionally substituted with one or more fluorine substituents.

4. A compound as claimed in claim 1 or claim 2 wherein R_1 and S_1 are independently selected from (a) hydrogen, methoxy, ethoxy, methylthio or ethylthio; (b) a group of formula $-X^1$-Alk^5-$(CO)_wNR^CR^D$ wherein w is 0 or 1, X^1 is –O- or –S-, Alk^5 is a straight or branched chain C_1-C_3alkylene radical, R^C is C_1-C_3alkyl and R^D is C_1-C_3alkyl or hydroxyl(C_1-C_3alkyl)-; and (c) a group of formula $-X^1$-Alk^5-Ar wherein X^1 is –O- or –S-, Alk^5 is a straight or branched chain C_1-C_3alkylene radical, and Ar is phenyl or a 5- or 6-memnbered heteroaryl ring wherein at least one hetero atom is nitrogen

5. A compound as claimed in any of the preceding claims wherein R_1 is methoxy, ethoxy, methylthio or ethylthio.

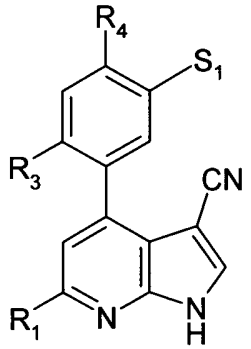
6. A compound as claimed in any of the preceding claims wherein R_2 is cyano (-CN).

7. A compound as claimed any of claims 2 to 6 wherein R_3 is in the ortho position and R_4 in the para position.

8. A compound as claimed in any of claims 2 to 7 wherein S_1 is in the meta position of the phenyl ring.

9. A compound as claimed in any of the preceding claims wherein R_3 and/or R_4 is selected from fluoro, chloro, bromo and methyl.

10. A compound as claimed in claim 1 having formula (ID):



(ID)

or a salt, N-oxide, hydrate, or solvate thereof, wherein:

R_1 and S_1 are independently selected from (a) hydrogen, methoxy, ethoxy, methylthio or ethylthio; (b) a group of formula $-X^1$-Alk^5-$(CO)_wNR^CR^D$ wherein w is 0 or 1, X^1 is –O- or –S-, Alk^5 is a straight or branched chain C_1-C_3alkylene radical, R^C is C_1-C_3alkyl and R^D is C_1-C_3alkyl or hydroxyl(C_1-C_3alkyl)-; and (c) a group of formula $-X^1$-Alk^5-Ar wherein X^1 is –O- or –S-, Alk^5 is a straight or branched chain C_1-C_3alkylene radical, and Ar is phenyl or a 5- or 6-memnbered heteroaryl ring wherein at least one hetero atom is nitrogen; PROVIDED THAT R_1 and S_1 are not both hydrogen;

R_3 is fluoro, chloro, bromo or methyl; and

R_4 is fluoro, chloro, bromo methyl, ethyl, isopropyl, methoxy, or cyano.

11. A compound as claimed in claim 1 which is the subject of any of the Examples herein.

12. A pharmaceutical or veterinary composition comprising a compound as claimed in any of claims 1 to 11, together with one or more pharmaceutically or veterinarily acceptable carriers and/or excipients.

13. The use of a compound as claimed in any of claims 1 to 11 in the preparation of a composition for inhibition of HSP90 activity in vitro or in vivo

14. A method of treatment of diseases which are responsive to inhibition of HSP90 activity in mammals, which method comprises administering to the mammal an amount of a compound as claimed in any of claims 1 to 13 effective to inhibit said HSP90 activity.

15. The use as claimed in claim 13 or a method as claimed claim 14 for immunosuppression or the treatment of viral disease, inflammatory diseases such as rheumatoid arthritis, asthma, multiple sclerosis, Type I diabetes, lupus, psoriasis and inflammatory bowel disease; cystic fibrosis angiogenesis-related disease such as diabetic retinopathy, haemangiomas, and endometriosis; or for protection of normal cells against chemotherapy-induced toxicity; or diseases where failure to undergo apoptosis is

an underlying factor; or protection from hypoxia-ischemic injury due to elevation of Hsp70 in the heart and brain; scrapie/CJD, Huntingdon's or Alzheimer's disease.

16. The use as claimed in claim 13 or a method as claimed claim 14, for the treatment of cancer.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2007/003133

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/437 A61P35/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FR 2 880 540 A (AVENTIS PHARMA SA SA [FR]) 14 July 2006 (2006-07-14) claims 1,8	1-16
P,X	WO 2007/090141 A (SMITHKLINE BEECHAM CORP [US]; TANG JUN [US]; NAKANO MASATO [JP]; HAMAJ) 9 August 2007 (2007-08-09) claim 1; examples 13,14; general intermediates 6,7;	1-16
P,X	WO 2007/084667 A (OSI PHARMACEUTICAL INC [US]; ARNOLD LEE D [US]; CHEN XIN [US]; DONG HA) 26 July 2007 (2007-07-26) claim 1; compounds 131, 137, 139, 147, 148, 153, 154, 156, 158-162	1-16

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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 November 2007	26/11/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	MORIGGI, J

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2007/003133

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2007/076423 A (SMITHKLINE BEECHAM CORP [US]; SEEFELD MARK ANDREW [US]; HAMAJIMA TOSHI) 5 July 2007 (2007-07-05) claim 1; example 89	1-16
P,X	WO 2007/002433 A (PLEXXIKON INC [US]; IBRAHIM PRABHA N [US]; ARTIS DEAN R [US]; BREMER R) 4 January 2007 (2007-01-04) page 449; compound P0031	1-16
P,X	WO 2006/090261 A (PFIZER PROD INC [US]; KAUFFMAN GOSS STRYKER [US]; LI CHAO [US]; LIPPA) 31 August 2006 (2006-08-31) claim 1; example 17	1-16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2007/003133

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 14 and a part of claim 16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2007/003133

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 2880540 A	14-07-2006	EP 1838322 A2	03-10-2007
		WO 2006075095 A2	20-07-2006
WO 2007090141 A	09-08-2007	NONE	
WO 2007084667 A	26-07-2007	NONE	
WO 2007076423 A	05-07-2007	NONE	
WO 2007002433 A	04-01-2007	AR 054624 A1	04-07-2007
		WO 2007002325 A1	04-01-2007
WO 2006090261 A	31-08-2006	NONE	