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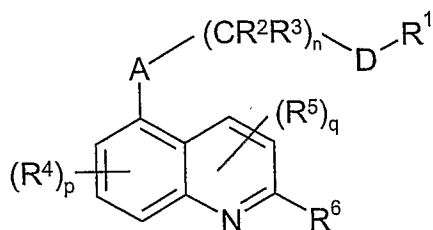
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(54) Title: QUINOLINE DERIVATIVES AS P2X7 RECEPTOR ANTAGONIST AND THEIR USE IN THE TREATMENT OF RHEUMATOID ARTHRITIS, OSTEOARTHRITIS, COPD AND IBD



(I)

(57) Abstract: The invention provides compounds of formula (I), processes for their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions, and their use in therapy, wherein A, D, R¹, R², R³, R⁴, R⁵, R⁶, n, p and q are as defined in the specification.

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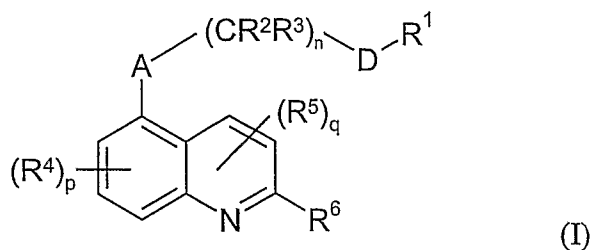
The present invention relates to quinoline derivatives, processes for their preparation,
5 pharmaceutical compositions containing them, a process for preparing pharmaceutical
compositions, and their use in therapy.

The P2X₇ receptor (previously known as P2Z receptor), which is a ligand-gated ion
channel, is present on a variety of cell types, largely those known to be involved in the
10 inflammatory/immune process, specifically, macrophages, mast cells and lymphocytes
(T and B). Activation of the P2X₇ receptor by extracellular nucleotides, in particular
adenosine triphosphate, leads to the release of interleukin-1 β (IL-1 β) and giant cell
formation (macrophages/microglial cells), degranulation (mast cells) and proliferation
(T cells) and apoptosis and L-selectin shedding (lymphocytes). P2X₇ receptors are also
15 located on antigen-presenting cells (APC), keratinocytes, salivary acinar cells (parotid
cells), hepatocytes and mesangial cells.

It would be desirable to make compounds effective as P2X₇ receptor antagonists for use in
the treatment of inflammatory, immune or cardiovascular diseases, in the aetiologies of
20 which the P2X₇ receptor may play a role.

P2X₇ antagonists comprising quinoliny1 groups are known from WO2003/080579, WO
2004/106305 and WO2005/009968. In each of these disclosures it is necessary for the
compounds to contain either a carbocyclyl-alkylamido or a heterocyclyl-alkylamido group.
25 In contrast, the present invention provides compounds active as P2X₇ antagonists
comprising an aryl- or heteroaryl-heteroalkylamido group.

In accordance with the present invention, there is therefore provided a compound of
formula (I), or a pharmaceutically acceptable salt thereof,
30



wherein

n is 1, 2 or 3;

when n is 1, A represents NHC(O) or NHC(S);

5 when n is 2 or 3, A represents NHC(O), C(O)NH, NHC(S) or C(S)NH;

D represents O, S or NR⁷, wherein R⁷ represents hydrogen, C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl or C₁₋₆ haloalkyl;

10 R¹ represents a 6-10 membered aryl, or a 5-10 membered heteroaryl ring, which aryl or heteroaryl ring may be optionally substituted by one or more substituents independently selected from halogen, cyano, C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, NR⁸R⁹, S(O)₀₋₂R¹⁰, S(O)₂NR¹¹R¹², C(O)NR¹³R¹⁴, CO₂R¹⁵, NR¹⁶S(O)₂R¹⁷, C(O)R¹⁸, NR¹⁹C(O)R²⁰, NR²¹C(O)NR²²R²³, NR²⁴S(O)₂NR²⁵R²⁶ and OR²⁷;

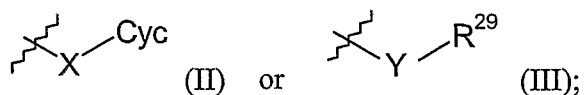
15 within each grouping CR²R³, R² and R³ each independently represent hydrogen, halogen, C₁₋₃ alkyl, C₁₋₃ hydroxyalkyl or C₁₋₃ haloalkyl;

p represents 0, 1, 2 or 3; each R⁴ independently represents halogen, cyano, C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl or C₁₋₆ haloalkyl;

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q represents 0, 1 or 2; each R⁵ independently represents halogen, cyano, C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl or C₁₋₆ haloalkyl;

25 R⁶ represents a group



wherein X represents a bond, O, S, NR^{30} or a C_{1-4} alkylene which C_{1-4} alkylene may be optionally substituted by one or more substituents independently selected from halogen, hydroxy and C_{1-4} alkoxy;

5 Cyc represents a 3-8 membered carbocyclic or a 4-8 membered heterocyclic ring, which ring may be optionally substituted by one or more substituents R^{28} , wherein each substituent R^{28} is independently selected from halogen, cyano, $=\text{O}$, $\text{S}(\text{O})_2\text{R}^{31}$, $\text{C}(\text{O})\text{R}^{32}$, CO_2R^{33} , $\text{C}(\text{O})\text{NR}^{34}\text{R}^{35}$, $\text{NR}^{36}\text{C}(\text{O})\text{R}^{37}$, $\text{S}(\text{O})_2\text{NR}^{38}\text{R}^{39}$, $\text{NR}^{40}\text{S}(\text{O})_2\text{R}^{41}$, OR^{42} , SR^{43} , $\text{NR}^{44}\text{R}^{45}$, Z^1 or a C_{1-6} alkyl group which C_{1-6} alkyl group may be optionally substituted by one or
 10 more substituents independently selected from halogen, hydroxyl, C_{1-6} alkoxy, $\text{NR}^{46}\text{R}^{47}$, $\text{S}(\text{O})_0-2\text{R}^{48}$, $\text{C}(\text{O})\text{R}^{49}$, CO_2R^{50} , $\text{C}(\text{O})\text{NR}^{51}\text{R}^{52}$, $\text{NR}^{53}\text{C}(\text{O})\text{R}^{54}$, $\text{S}(\text{O})_2\text{NR}^{55}\text{R}^{56}$, $\text{NR}^{57}\text{S}(\text{O})_2\text{R}^{58}$ and Z^2 ;

Y represents a bond, OC_{1-6} alkylene, $\text{S}(\text{O})_0-2\text{C}_{1-6}$ alkylene, $\text{N}(\text{R}^{59})\text{C}_{1-6}$ alkylene or C_{1-6}
 15 alkylene, wherein any alkylene group in Y may be optionally substituted by one or more substituents independently selected from halogen, hydroxy and C_{1-4} alkoxy;

R^{29} represents hydrogen, halogen, hydroxyl, C_{1-6} alkoxy, cyano, $\text{NR}^{60}\text{R}^{61}$, $\text{S}(\text{O})_0-2\text{R}^{62}$, $\text{C}(\text{O})\text{R}^{63}$, CO_2R^{64} , $\text{C}(\text{O})\text{NR}^{65}\text{R}^{66}$, $\text{NR}^{67}\text{C}(\text{O})\text{R}^{68}$, $\text{S}(\text{O})_2\text{NR}^{69}\text{R}^{70}$, $\text{NR}^{71}\text{S}(\text{O})_2\text{R}^{72}$ or Z^3 ;
 20 with the proviso that when Y is a bond R^{29} is not hydrogen;

R^{42} , R^{43} , R^{44} and R^{45} each independently represent hydrogen or a C_{1-6} alkyl group which C_{1-6} alkyl group may be optionally substituted by one or more substituents independently selected from halogen, hydroxyl, C_{1-6} alkoxy, $\text{NR}^{73}\text{R}^{74}$, $\text{S}(\text{O})_0-2\text{R}^{75}$, $\text{C}(\text{O})\text{R}^{76}$, CO_2R^{77} ,
 25 $\text{C}(\text{O})\text{NR}^{78}\text{R}^{79}$, $\text{NR}^{80}\text{C}(\text{O})\text{R}^{81}$, $\text{S}(\text{O})_2\text{NR}^{82}\text{R}^{83}$, $\text{NR}^{84}\text{S}(\text{O})_2\text{R}^{85}$ or Z^4 , or R^{44} and R^{45} , together with the nitrogen atom to which they are both attached, may form a 4-8 membered aliphatic heterocyclic ring, which heterocyclic ring may be optionally substituted by one or more substituents independently selected from halogen, hydroxy, C_{1-6} alkyl, C_{1-6} hydroxyalkyl and C_{1-6} haloalkyl;

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Z^1 , Z^2 , Z^3 and Z^4 each independently represent tetrazole, or a 5-6 membered heterocyclic ring, which heterocyclic ring is substituted by one or more substituents independently

selected from hydroxy, amino, =O, =S, and which heterocyclic ring may further be optionally substituted by one or more substituents independently selected from halogen and C₁₋₆ alkyl;

5 R⁸, R⁹, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R³⁰, R³², R³³, R³⁴, R³⁵, R³⁶, R³⁷, R³⁸, R³⁹, R⁴⁰, R⁴⁶, R⁴⁷, R⁴⁹, R⁵⁰, R⁵¹, R⁵², R⁵³, R⁵⁴, R⁵⁵, R⁵⁶, R⁵⁷, R⁵⁹, R⁶⁰, R⁶¹, R⁶³, R⁶⁴, R⁶⁵, R⁶⁶, R⁶⁷, R⁶⁸, R⁶⁹, R⁷⁰, R⁷¹, R⁷³, R⁷⁴, R⁷⁶, R⁷⁷, R⁷⁸, R⁷⁹, R⁸⁰, R⁸¹, R⁸², R⁸³ and R⁸⁴ each independently represent hydrogen, C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl or C₁₋₆ haloalkyl; or any of R⁸ and R⁹, R¹¹ and R¹², R¹³ and R¹⁴, R²² and R²³, R²⁵ and R²⁶, R³⁴ and R³⁵, R³⁸ and R³⁹, R⁴⁶ and R⁴⁷, R⁵¹ and R⁵², R⁵⁵ and R⁵⁶, R⁶⁰ and R⁶¹, R⁶⁵ and R⁶⁶, R⁶⁹ and R⁷⁰, R⁷³ and R⁷⁴, R⁷⁸ and R⁷⁹, and R⁸² and R⁸³, together with the nitrogen atom to which they are both attached, may form a 4-8 membered aliphatic heterocyclic ring, which heterocyclic ring may be optionally substituted by one or more substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl and C₁₋₆ haloalkyl; and

15 R¹⁰, R¹⁷, R³¹, R⁴¹, R⁴⁸, R⁵⁸, R⁶², R⁷², R⁷⁵ and R⁸⁵ each independently represent C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl or C₁₋₆ haloalkyl; and

20 with the proviso that when R¹ is phenyl, D is O, n is 1, R² is hydrogen, R³ is hydrogen, A is NHC(O), p is 0, q is 0 and R⁶ is methyl, then the phenyl group R¹ must be substituted by at least one substituent other than C₁₋₄ alkyl, chlorine and methoxy.

It will be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It is to be understood that the present invention encompasses all such solvated forms. Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

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In the context of the present specification the term 'Carbocyclic' denotes aliphatic or aromatic carbon rings; 'Cycloalkyl' denotes aliphatic carbon rings (i.e. saturated or

partially saturated rings) for example cyclopropyl, cyclopentyl, cyclohexyl or cyclohexenyl; and 'Aryl' denotes aromatic carbon rings, for example phenyl or naphthyl. The term 'Heterocyclic' denotes aliphatic or aromatic rings comprising at least one heteroatom selected from the group comprising nitrogen, oxygen and sulfur; or an *N*-oxide thereof, or an *S*-oxide or *S*-dioxide thereof.

The term 'Heteroaryl' denotes aromatic rings comprising at least one heteroatom selected from the group comprising nitrogen, oxygen and sulfur; or an *N*-oxide thereof, or an *S*-oxide or *S*-dioxide thereof: examples of heteroaryl groups include furyl, thienyl, pyrrolyl, thiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, benzo[*b*]furyl (also known as benzfuryl), benzo[*b*]thienyl (also known as benz[*b*]thienyl, benzothienyl or benzo[*b*]thiophenyl), 2,3-dihydrobenz[*b*]thienyl (for example in a 1-dioxo-2,3-dihydrobenz[*b*]thienyl moiety), indazolyl, benzimidazolyl, benztriazolyl, benzoxazolyl, benzthiazolyl, 1,2,3-benzothiadiazolyl, an imidazopyridinyl (such as imidazo[1,2-*a*]pyridinyl), a thienopyridinyl (for example thieno[3,2-*b*]pyridin-6-yl, thieno[2,3-*c*]pyridin-2-yl or thieno[3,2-*c*]pyridin-2-yl), thieno[3,2-*d*]pyrimidin-6-yl, 1,2,3-benzoxadiazolyl, benzo[1,2,3]thiadiazolyl, 2,1,3-benzothiadiazolyl, benzofurazan (also known as 2,1,3-benzoxadiazolyl), quinoxalinyl, a pyrazolopyridine (for example 1*H*-pyrazolo[3,4-*b*]pyridinyl), quinolinyl, isoquinolinyl, a naphthyridinyl (for example [1,6]naphthyridinyl or [1,8]naphthyridinyl) or a benzothiazinyl; or an *N*-oxide thereof, or an *S*-oxide or *S*-dioxide thereof. The term 'Aliphatic heterocyclic ring' denotes a saturated or partially saturated monocyclic ring comprising at least one heteroatom selected from the group comprising nitrogen, oxygen and sulphur: or an *N*-oxide thereof, or an *S*-oxide or *S*-dioxide thereof: for example pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, homopiperazinyl, homopiperidinyl and azetidiny.

25

In the context of the present specification alkyl groups and moieties may be straight or branched chain and include, for example, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl or tert-butyl. Haloalkyl moieties may contain one or more (e.g. one, two, three, four, five or six) halogen atoms. In the present specification halogen is for example, fluorine, chlorine or bromine. Hydroxyalkyl moieties may contain one or more (e.g. one, two or three) hydroxyl groups. In general, a hydroxyl moiety will not be attached to a carbon atom which is adjacent to a nitrogen atom. In the context of the present specification, where it is

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stated that a group may be optionally substituted by one or more substituents the group may be unsubstituted or substituted; when substituted the group will generally be substituted with one, two or three substituents.

5 In the present invention n represents 1, 2 or 3. In an embodiment of the invention, n represents 1 or 2. In another embodiment, n represents 1.

When n is 1, A represents NHC(O) or NHC(S); and when n is 2 or 3, A represents NHC(O), C(O)NH, NHC(S) or C(S)NH.

10

In an embodiment of the invention, when n is 1, A represents NHC(O); and when n is 2 or 3, A represents NHC(O) or C(O)NH.

In an embodiment of the invention, A represents NHC(O).

15

In the present invention D represents O, S or NR^7 , wherein R^7 represents hydrogen, C_{1-6} alkyl, C_{1-6} hydroxyalkyl or C_{1-6} haloalkyl.

20 In an embodiment of the invention, D represents NR^7 and R^7 represents hydrogen, C_{1-4} alkyl, C_{1-4} hydroxyalkyl or C_{1-4} haloalkyl. In a further aspect of this embodiment, D represents NR^7 , and R^7 represents hydrogen or C_{1-4} alkyl.

R^1 represents a 6-10 membered aryl, or a 5-10 membered heteroaryl ring, which aryl or heteroaryl ring may be optionally substituted by one or more substituents independently
25 selected from halogen, cyano, C_{1-6} alkyl, C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, NR^8R^9 , $\text{S(O)}_{0-2}\text{R}^{10}$, $\text{S(O)}_2\text{NR}^{11}\text{R}^{12}$, $\text{C(O)NR}^{13}\text{R}^{14}$, CO_2R^{15} , $\text{NR}^{16}\text{S(O)}_2\text{R}^{17}$, C(O)R^{18} , $\text{NR}^{19}\text{C(O)R}^{20}$, $\text{NR}^{21}\text{C(O)NR}^{22}\text{R}^{23}$, $\text{NR}^{24}\text{S(O)}_2\text{NR}^{25}\text{R}^{26}$ and OR^{27} .

30 In an embodiment of the invention, R^1 represents phenyl, which phenyl may be optionally substituted by one or more substituents independently selected from halogen, cyano, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} haloalkyl, NR^8R^9 , $\text{S(O)}_{0-2}\text{R}^{10}$, $\text{S(O)}_2\text{NR}^{11}\text{R}^{12}$, $\text{C(O)NR}^{13}\text{R}^{14}$,

CO_2R^{15} , $\text{NR}^{16}\text{S}(\text{O})_2\text{R}^{17}$, $\text{C}(\text{O})\text{R}^{18}$, $\text{NR}^{19}\text{C}(\text{O})\text{R}^{20}$, $\text{NR}^{21}\text{C}(\text{O})\text{NR}^{22}\text{R}^{23}$, $\text{NR}^{24}\text{S}(\text{O})_2\text{NR}^{25}\text{R}^{26}$ and OR^{27} .

In an embodiment of the invention, R^1 represents phenyl, which phenyl may be optionally substituted by one or more substituents independently selected from halogen, cyano, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} haloalkyl, hydroxyl, C_{1-4} alkoxy, amino, C_{1-4} alkylamino and di- $(\text{C}_{1-4}\text{alkyl})$ amino.

In an embodiment of the invention R^1 represents an optionally substituted 5-10 membered heteroaryl ring. When R^1 represents a 5-10 membered heteroaryl ring, examples of heteroaryl rings include pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl.

Within each grouping CR^2R^3 , R^2 and R^3 each independently represent hydrogen, C_{1-3} alkyl, C_{1-3} hydroxyalkyl or C_{1-3} haloalkyl. In an embodiment of the invention, each R^2 and R^3 independently represent hydrogen or C_{1-3} alkyl. In an embodiment of the invention, each R^2 and R^3 independently represent hydrogen.

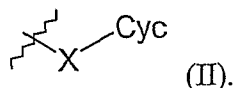
Each R^4 independently represents halogen, cyano, C_{1-6} alkyl, C_{1-6} hydroxyalkyl or C_{1-6} haloalkyl. In an embodiment of the invention, each R^4 independently represents halogen or C_{1-4} alkyl. In an embodiment of the invention, each R^4 independently represents halogen (e.g. fluorine, chlorine or bromine).

In the present invention p is 0, 1, 2 or 3. In an embodiment of the invention p is 0 or 1. In an embodiment of the invention p is 1.

Each R^5 independently represents halogen, cyano, C_{1-6} alkyl, C_{1-6} hydroxyalkyl or C_{1-6} haloalkyl. In an embodiment of the invention, each R^5 independently represents halogen or C_{1-4} alkyl. In an embodiment of the invention, each R^5 independently represents halogen (e.g. fluorine, chlorine or bromine).

In the present invention q is 0, 1 or 2. In an embodiment of the invention q is 0 or 1. In an embodiment of the invention q is 0.

In an embodiment of the invention, R^6 represents a group



5 In an embodiment of the invention, X represents a bond.

In an embodiment of the invention, X represents NR^{30} . In a further aspect of this embodiment, R^{30} represents hydrogen or C_{1-4} alkyl.

10 In an embodiment of the invention, Cyc represents a 4-8 membered heterocyclic ring, which heterocyclic ring may be optionally substituted by one or more substituents R^{28} .

Examples of heterocyclic rings that Cyc may represent include, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, homopiperazinyl, homopiperidinyl, azetidiny, triazinyl,
 15 pyrazolyl and triazolyl. In an embodiment of the invention Cyc represents an optionally substituted pyrrolidinyl or morpholinyl ring.

In the present invention each substituent R^{28} independently represents halogen, cyano, $=O$, $S(O)_2R^{31}$, $C(O)R^{32}$, CO_2R^{33} , $C(O)NR^{34}R^{35}$, $NR^{36}C(O)R^{37}$, $S(O)_2NR^{38}R^{39}$, $NR^{40}S(O)_2R^{41}$,
 20 OR^{42} , SR^{43} , $NR^{44}R^{45}$, Z^1 or a C_{1-6} alkyl group which C_{1-6} alkyl group may be optionally be substituted by one or more substituents independently selected from halogen, hydroxyl, C_{1-6} alkoxy, $NR^{46}R^{47}$, $S(O)_{0-2}R^{48}$, $C(O)R^{49}$, CO_2R^{50} , $C(O)NR^{51}R^{52}$, $NR^{53}C(O)R^{54}$, $S(O)_2NR^{55}R^{56}$, $NR^{57}S(O)_2R^{58}$ and Z^2 .

25 In an embodiment of the invention, each substituent R^{28} is independently selected from halogen, OR^{42} , $NR^{44}R^{45}$ or a C_{1-4} alkyl group, which C_{1-4} alkyl group may be optionally substituted by one or more substituents independently selected from halogen, hydroxyl, C_{1-4} alkoxy, $NR^{46}R^{47}$ and $C(O)NR^{51}R^{52}$. In a further aspect of this embodiment, R^{46} , R^{47} , R^{51} and R^{52} each independently represent hydrogen or a C_{1-4} alkyl group optionally substituted
 30 by one or more substituents independently selected from halogen and hydroxyl.

In the present invention R^{42} , R^{43} , R^{44} and R^{45} each independently represent hydrogen or a C_{1-6} alkyl group which C_{1-6} alkyl group may be optionally substituted by one or more substituents independently selected from halogen, hydroxyl, C_{1-6} alkoxy, $NR^{73}R^{74}$, $S(O)_{0-2}R^{75}$, $C(O)R^{76}$, CO_2R^{77} , $C(O)NR^{78}R^{79}$, $NR^{80}C(O)R^{81}$, $S(O)_2NR^{82}R^{83}$, $NR^{84}S(O)_2R^{85}$ or Z^4 ,
 5 or R^{44} and R^{45} , together with the nitrogen atom to which they are both attached, may form a 4-8 membered aliphatic heterocyclic ring, which heterocyclic ring may be optionally substituted by one or more substituents independently selected from halogen, hydroxy, C_{1-6} alkyl, C_{1-6} hydroxyalkyl and C_{1-6} haloalkyl.

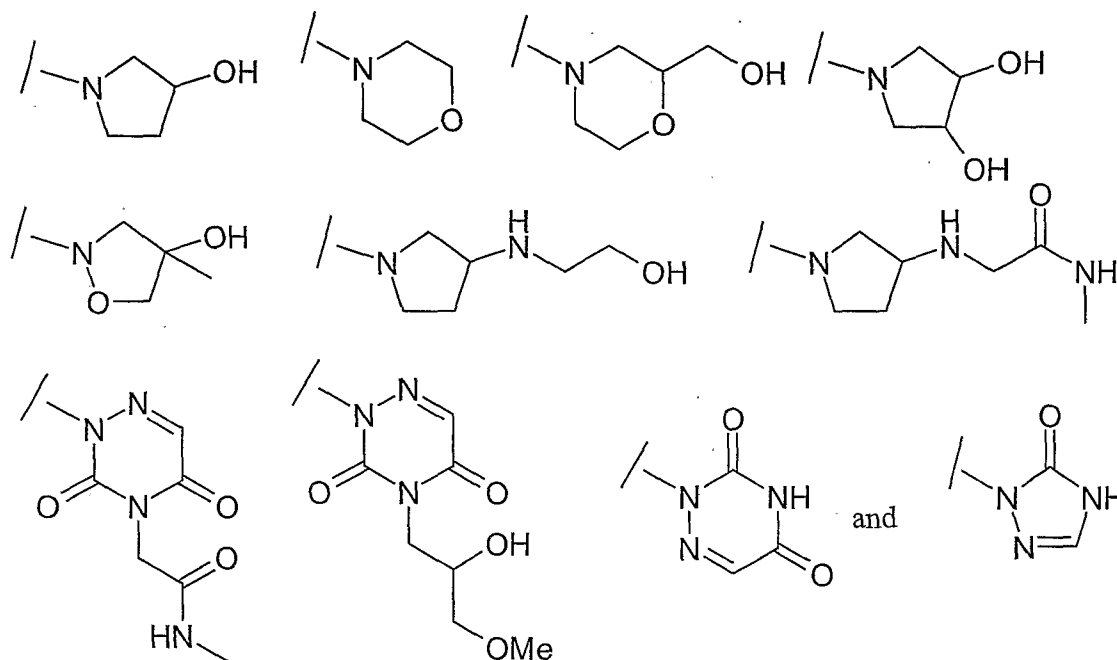
10 In an embodiment of the invention, R^{42} , R^{43} , R^{44} and R^{45} each independently represent hydrogen or a C_{1-4} alkyl group which C_{1-4} alkyl group may be optionally substituted by one or more substituents independently selected from halogen, hydroxyl, C_{1-4} alkoxy, $NR^{73}R^{74}$ and $C(O)NR^{78}R^{79}$. In a further aspect of this embodiment, R^{73} , R^{74} , R^{78} and R^{79} each independently represent hydrogen or a C_{1-4} alkyl group, which C_{1-4} alkyl group may be
 15 optionally substituted by one or more substituents independently selected from halogen and hydroxyl.

In an embodiment of the invention, each substituent R^{28} is independently selected from halogen, OR^{42} , $NR^{44}R^{45}$ or a C_{1-4} alkyl group, which C_{1-4} alkyl group may be optionally
 20 substituted by one or more substituents independently selected from halogen, hydroxyl, C_{1-4} alkoxy, $NR^{46}R^{47}$ and $C(O)NR^{51}R^{52}$;
 R^{42} , R^{44} and R^{45} each independently represent hydrogen or a C_{1-4} alkyl group which C_{1-4} alkyl group may be optionally substituted by one or more substituents independently selected from halogen, hydroxyl, C_{1-4} alkoxy, $NR^{73}R^{74}$ and $C(O)NR^{78}R^{79}$; and
 25 R^{46} , R^{47} , R^{51} , R^{52} , R^{73} , R^{74} , R^{78} and R^{79} each independently represent hydrogen or a C_{1-4} alkyl group which C_{1-4} alkyl group may be optionally substituted by one or more substituents independently selected from halogen and hydroxyl.

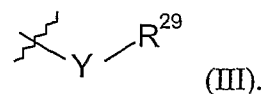
In an embodiment of the invention, each substituent R^{28} is independently selected from
 30 hydroxy, methyl, ethyl, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_2OH$, $-CH_2C(O)OH$, $-NHCH_2C(O)OH$, $-NHCH_2CH_2C(O)OH$, $-CH_2NHCH_3$, $-CH_2NHCH_2CH_2OH$, $-NHCH_2C(O)NHCH_3$, $-NHCH(CH_3)CH_2OH$, $-N(CH_3)CH_2CH(OH)CH_2OH$, -

CH₂CH(OH)CH₂OH, -CH(CH₃)CH(OH)CH₂OH, -CH₂C(O)NHCH₃, -CH₂CH(OH)CH₂OCH₃ and -CH₂C(O)N(CH₃)CH₂CH₂OH. In a further aspect of this embodiment, Cyc represents a pyrrolidiny1 or morpholinyl ring.

5 In an embodiment of the invention, R⁶ represents a group selected from



In an embodiment of the invention, R⁶ represents a group



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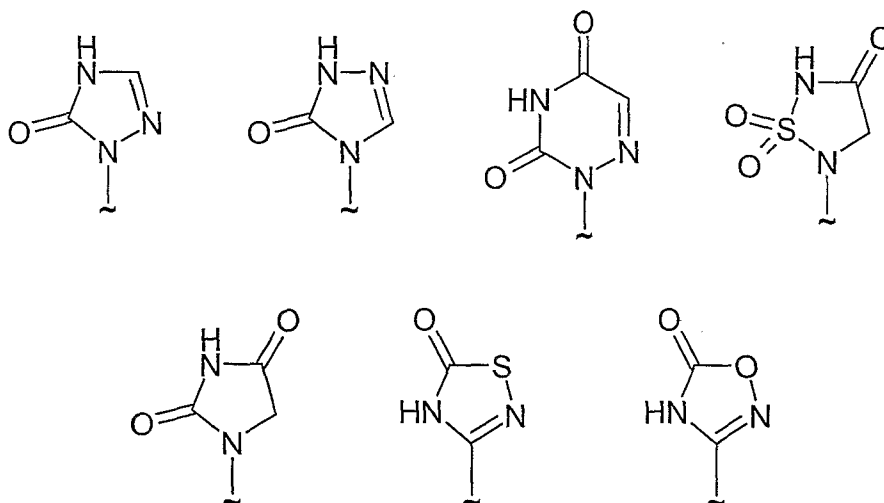
In an embodiment of the invention, Y represents a bond, OC₁₋₄ alkylene, N(R⁵⁹)C₁₋₄ alkylene or C₁₋₄ alkylene, wherein any alkylene group in Y may be optionally substituted by one or more substituents independently selected from halogen, hydroxy and C₁₋₄ alkoxy.

15 In a further aspect of this embodiment R⁵⁹ represents hydrogen or C₁₋₄ alkyl.

In the present invention, R²⁹ represents hydrogen, halogen, hydroxyl, C₁₋₆alkoxy, cyano, NR⁶⁰R⁶¹, S(O)₀₋₂R⁶², C(O)R⁶³, CO₂R⁶⁴, C(O)NR⁶⁵R⁶⁶, NR⁶⁷C(O)R⁶⁸, S(O)₂NR⁶⁹R⁷⁰, NR⁷¹S(O)₂R⁷² or Z³; with the proviso that when Y is a bond R²⁹ is not hydrogen.

In an embodiment of the invention R^{29} represents hydrogen, halogen, hydroxyl, C_{1-4} alkoxy, $NR^{60}R^{61}$ and $C(O)NR^{65}R^{66}$. In a further aspect of this embodiment R^{60} , R^{61} , R^{65} and R^{66} each independently represent hydrogen or a C_{1-4} alkyl group optionally substituted by one or more substituents independently selected from halogen and hydroxyl.

Z^1 , Z^2 , Z^3 and Z^4 each independently represent tetrazole, or a 5-6 membered heterocyclic ring, which heterocyclic ring is substituted by one or more substituents independently selected from hydroxy, amino, $=O$, $=S$, and which heterocyclic ring may further be optionally substituted by one or more substituents independently selected from halogen and C_{1-6} alkyl. Examples of groups that Z^1 , Z^2 , Z^3 and Z^4 may represent include:



In an embodiment of the invention, R^8 , R^9 , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} and R^{27} each independently represent hydrogen or C_{1-4} alkyl. In an embodiment of the invention, R^{10} and R^{17} each independently represent C_{1-4} alkyl.

In an embodiment of the invention, R^{30} represents hydrogen or C_{1-4} alkyl.

In an embodiment of the invention, R^{32} , R^{33} , R^{34} , R^{35} , R^{36} , R^{37} , R^{38} , R^{39} , R^{40} , R^{46} , R^{47} , R^{49} , R^{50} , R^{51} , R^{52} , R^{53} , R^{54} , R^{55} , R^{56} and R^{57} each independently represent hydrogen or C_{1-4} alkyl which C_{1-4} alkyl group may be optionally substituted by one or more substituents

independently selected from halogen and hydroxyl. In an embodiment of the invention, R^{31} , R^{41} , R^{48} and R^{58} each independently represent C_{1-4} alkyl which C_{1-4} alkyl group may be optionally substituted by one or more substituents independently selected from halogen and hydroxyl.

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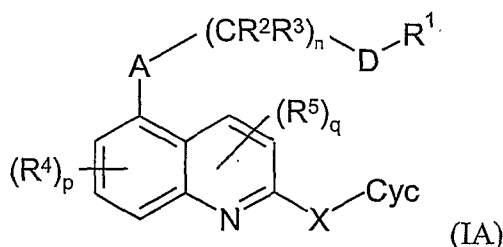
In an embodiment of the invention, R^{59} represents hydrogen or C_{1-4} alkyl.

In an embodiment of the invention, R^{60} , R^{61} , R^{63} , R^{64} , R^{65} , R^{66} , R^{67} , R^{68} , R^{69} , R^{70} and R^{71} each independently represent hydrogen or C_{1-4} alkyl which C_{1-4} alkyl group may be optionally substituted by one or more substituents independently selected from halogen and hydroxyl. In an embodiment of the invention, R^{62} and R^{72} each independently represent C_{1-4} alkyl which C_{1-4} alkyl group may be optionally substituted by one or more substituents independently selected from halogen and hydroxyl.

In an embodiment of the invention, R^{73} , R^{74} , R^{76} , R^{77} , R^{78} , R^{79} , R^{80} , R^{81} , R^{82} , R^{83} and R^{84} each independently represent hydrogen or C_{1-4} alkyl which C_{1-4} alkyl group may be optionally substituted by one or more substituents independently selected from halogen and hydroxyl. In an embodiment of the invention, R^{75} and R^{85} each independently represent C_{1-4} alkyl which C_{1-4} alkyl group may be optionally substituted by one or more substituents independently selected from halogen and hydroxyl.

20

In a further aspect, the present invention provides a compound of formula (IA), or a pharmaceutically acceptable salt thereof,



25

wherein

n is 1;

A represents $NHC(O)$;

D represents O, S or NR^7 , wherein R^7 represents hydrogen or C_{1-4} alkyl;

R^1 represents phenyl, which phenyl may be optionally substituted by one or more substituents independently selected from halogen, cyano, nitro, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} haloalkyl, NR^8R^9 , $\text{S}(\text{O})_{0-2}\text{R}^{10}$, $\text{S}(\text{O})_2\text{NR}^{11}\text{R}^{12}$, $\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, CO_2R^{15} , $\text{NR}^{16}\text{S}(\text{O})_2\text{R}^{17}$, $\text{C}(\text{O})\text{R}^{18}$, $\text{NR}^{19}\text{C}(\text{O})\text{R}^{20}$, $\text{NR}^{21}\text{C}(\text{O})\text{NR}^{22}\text{R}^{23}$, $\text{NR}^{24}\text{S}(\text{O})_2\text{NR}^{25}\text{R}^{26}$ and OR^{27} ;

R^2 and R^3 each independently represent hydrogen or C_{1-3} alkyl;

p represents 0 or 1; R^4 represents halogen or C_{1-4} alkyl;

q represents 0 or 1; R^5 represents halogen or C_{1-4} alkyl;

X represents a bond,

Cyc represents a 4-8 membered heterocyclic ring, which heterocyclic ring may be optionally substituted by one or more substituents R^{28} ;

each substituent R^{28} is independently selected from halogen, OR^{42} , $\text{NR}^{44}\text{R}^{45}$ or a C_{1-4} alkyl group, which C_{1-4} alkyl group may be optionally substituted by one or more substituents independently selected from halogen, hydroxyl, C_{1-4} alkoxy, $\text{NR}^{46}\text{R}^{47}$ and $\text{C}(\text{O})\text{NR}^{51}\text{R}^{52}$;

R^{42} , R^{44} and R^{45} each independently represent hydrogen or a C_{1-4} alkyl group which C_{1-4} alkyl group may be optionally substituted by one or more substituents independently selected from halogen, hydroxyl, C_{1-4} alkoxy, $\text{NR}^{73}\text{R}^{74}$ and $\text{C}(\text{O})\text{NR}^{78}\text{R}^{79}$;

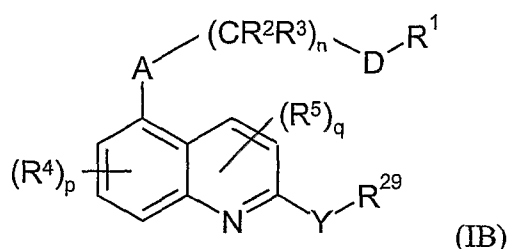
R^{46} , R^{47} , R^{51} , R^{52} , R^{73} , R^{74} , R^{78} and R^{79} each independently represent hydrogen or a C_{1-4} alkyl group which C_{1-4} alkyl group may be optionally substituted by one or more

substituents independently selected from halogen and hydroxyl;

R^8 , R^9 , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} and R^{27} each independently represent hydrogen or C_{1-4} alkyl; and

R^{10} and R^{17} each independently represent C_{1-4} alkyl.

In a further aspect, the present invention provides a compound of formula (IB), or a pharmaceutically acceptable salt thereof,



wherein

n is 1;

A represents NHC(O);

D represents O, S or NR⁷, wherein R⁷ represents hydrogen or C₁₋₄ alkyl;

5 R¹ represents phenyl, which phenyl may be optionally substituted by one or more substituents independently selected from halogen, cyano, nitro, C₁₋₄ alkyl, C₁₋₄ hydroxyalkyl, C₁₋₄ haloalkyl, NR⁸R⁹, S(O)₀₋₂R¹⁰, S(O)₂NR¹¹R¹², C(O)NR¹³R¹⁴, CO₂R¹⁵, NR¹⁶S(O)₂R¹⁷, C(O)R¹⁸, NR¹⁹C(O)R²⁰, NR²¹C(O)NR²²R²³, NR²⁴S(O)₂NR²⁵R²⁶ and OR²⁷; R² and R³ each independently represent hydrogen or C₁₋₃ alkyl;

10 p represents 0 or 1; R⁴ represents halogen or C₁₋₄ alkyl;

q represents 0 or 1; R⁵ represents halogen or C₁₋₄ alkyl;

Y represents a bond, OC₁₋₄alkylene, N(R⁵⁹)C₁₋₄alkylene or C₁₋₄alkylene, wherein any alkylene group in Y may be optionally substituted by one or more substituents independently selected from halogen, hydroxy and C₁₋₄alkoxy;

15 R⁵⁹ represents hydrogen or C₁₋₄ alkyl;

R²⁹ represents hydrogen, halogen, hydroxyl, C₁₋₄alkoxy, NR⁶⁰R⁶¹ and C(O)NR⁶⁵R⁶⁶; with the proviso that when Y is a bond R²⁹ is not hydrogen; and

R⁶⁰, R⁶¹, R⁶⁵ and R⁶⁶ each independently represent hydrogen or a C₁₋₄ alkyl group which C₁₋₄ alkyl group may be optionally substituted by one or more substituents independently
20 selected from halogen and hydroxyl;

R⁸, R⁹, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶ and R²⁷ each independently represent hydrogen or C₁₋₄ alkyl;

R¹⁰ and R¹⁷ each independently represent C₁₋₄ alkyl; and

with the proviso that when R¹ is phenyl, D is O, n is 1, R² is hydrogen, R³ is hydrogen, A is

25 NHC(O), p is 0, q is 0 and YR²⁹ represents methyl, then the phenyl group R¹ must be substituted by at least one substituent other than C₁₋₄ alkyl, chlorine and methoxy.

Pharmaceutically acceptable salts of a compound of formula (I) include, but are not limited to base salts such as an alkali metal salt for example sodium or potassium, an alkaline earth
30 metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, N-methylpiperidine, N-ethylpiperidine, procaine, dibenzylamine, N,N-dibenzylethylamine or amino acids for example lysine. Where the

compound is sufficiently basic, suitable salts include acid addition salts such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or p-toluenesulphonate salt. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions.

In an embodiment of the invention, the compound of formula (I) is selected from:

N-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-2-(phenylamino)-acetamide,
N-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-2-[(3-chlorophenyl)amino]-acetamide,

N-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-2-[(4-chlorophenyl)amino]-acetamide,

N-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-2-[(2-chlorophenyl)amino]-acetamide,

N-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-2-phenoxy-acetamide,

N-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-2-(phenylthio)-acetamide,

N-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-2-[(3-cyanophenyl)amino]-acetamide,

N-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-2-[(4-cyanophenyl)amino]-acetamide,

N-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-2-[(3-fluorophenyl)amino]-acetamide,

N-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-2-[(4-fluorophenyl)amino]-acetamide,

N-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-2-[(3,4-difluorophenyl)amino]-acetamide,

N-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-2-[(3,4-difluorophenyl)amino]-propanamide,

N-[6-Chloro-2-(1,2-dihydroxypropyl)-5-quinolinyl]-2-[(4-fluorophenyl)amino]-acetamide,

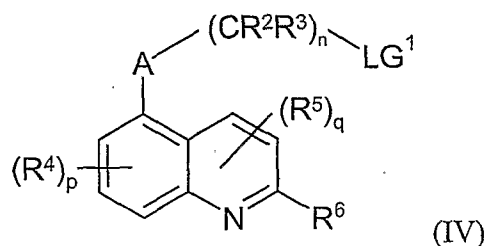
N-(6-Chloro-2-morpholin-4-yl-quinolin-5-yl)-2-(4-fluoro-phenylamino)-acetamide,

N-[6-Chloro-2-(1*H*-pyrazol-3-yl)-quinolin-5-yl]-2-(4-fluoro-phenylamino)-acetamide

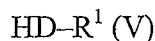
or a pharmaceutically acceptable salt thereof.

The present invention further provides a process for the preparation of a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, which comprises either

- 5 (a) reacting a compound of formula

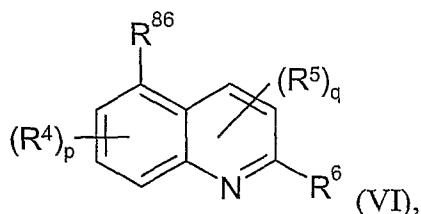


with a compound of formula



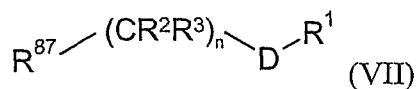
- wherein LG^1 represents a leaving group such as a halogeno or sulphonyloxy group (e.g. a chloro, bromo, iodo, trifluoromethanesulphonyloxy, methanesulphonyloxy or paratoluenesulphonyloxy group) and A, D, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , n, p and q are as defined in formula (I); or
- 10

- (b) reacting a compound of formula



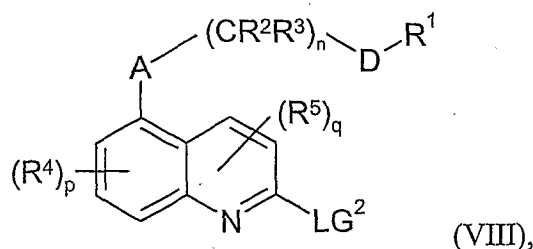
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with a compound of formula

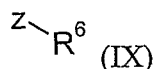


- wherein one of R^{86} and R^{87} represents NH_2 and the other of R^{86} and R^{87} represents CO_2H , COF , COBr or COCl , and D, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , n, p and q are as defined in formula (I); or
- 20

- (c) reacting a compound of formula



with a compound of formula



wherein LG^2 represents a leaving group such as a halogeno or sulphonyloxy group (e.g. a chloro, bromo, iodo, trifluoromethanesulphonyloxy, methanesulphonyloxy or paratoluenesulphonyloxy group), A, D, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , n, p and q are as defined in formula (I), and z either represents hydrogen when R^6 is attached to z at a heteroatom, otherwise when R^6 is attached to z at a carbon atom, z represents a metallic, organometallic or organosilicon group (e.g. copper, lithium, an organoboron group such as $\text{B}(\text{OH})_2$, $\text{B}(\text{O}^i\text{Pr})_2$, BEt_2 or a boronic acid pinacol cyclic ester, or an organotin group such as SnMe_3 or SnBu_3 , or an organosilicon group such as $\text{Si}(\text{Me})\text{F}_2$);

and optionally after (a), (b) or (c), carrying out one or more of the following:

- converting the compound to a further compound of the invention
- forming a pharmaceutically acceptable salt of the compound.

In process (a), the reaction is conveniently carried out in an organic solvent such as *N*-methylpyrrolidinone, acetonitrile or *N,N*-dimethylformamide, optionally in the presence of a base such as potassium carbonate, triethylamine or diisopropylethylamine, and at a temperature in the range from 25°C to 180°C, in particular 80°C to 150°C, either in a microwave or under conventional thermal conditions.

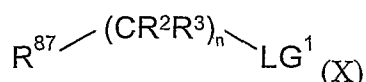
In process (b), the reaction may conveniently be carried out in the presence of a suitable coupling reagent, such as bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBroP) or dicyclohexylcarbodiimide and 1-hydroxybenzotriazole, in the presence of a base such as triethylamine, *N*-methylmorpholine, diisopropylethylamine or potassium carbonate, in a solvent such as dichloromethane, *N*-methylpyrrolidinone, *N,N*-

dimethylformamide or tetrahydrofuran, and at a temperature in the range from 0°C to 150°C, in particular 25°C to 100°C.

In process (c), when z represents hydrogen, the reaction may conveniently be carried out in an organic solvent such as *N*-methylpyrrolidinone, acetonitrile or *N,N*-dimethylformamide, optionally in the presence of a base such as potassium carbonate or triethylamine, and at a temperature in the range from 25°C to 180°C, in particular 50°C to 120°C, either in a microwave or under conventional thermal conditions.

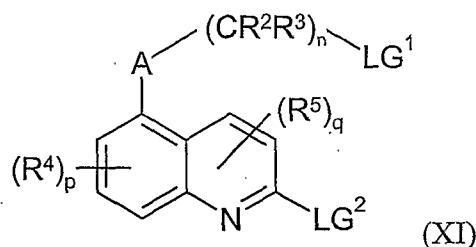
In process (c), when z represents a metallic or organometallic group, the reaction may conveniently be carried out in the presence of a catalyst such as tetrakis(triphenylphosphine)palladium(0), palladium(II) chloride or dichlorobis(triphenylphosphine)palladium(II), in the presence of a solvent such as tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, toluene, methanol, or water, in the presence of a base such as sodium carbonate or potassium carbonate, and at a temperature in the range 10 to 250°C, preferably in the range 60 to 120°C.

Compounds of formula (IV) may be prepared by reacting a compound of formula (VI) as described in (b) above with a compound of formula

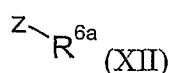


wherein LG¹ is as defined in formula (IV), R⁸⁷ is as defined in formula (VII), and R², R³ and n are as defined in formula (I), optionally in the presence of a suitable coupling reagent, such as bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBroP) or dicyclohexylcarbodiimide and 1-hydroxybenzotriazole, in the presence of a base such as triethylamine, *N*-methylmorpholine, diisopropylethylamine or potassium carbonate, in a solvent such as dichloromethane, *N*-methylpyrrolidinone, *N,N*-dimethylformamide, acetone or tetrahydrofuran, and at a temperature in the range from 0°C to 150°C, in particular 25°C to 100°C.

Alternatively, compounds of formula (IV) may be prepared by reacting a compound of formula



with a compound of formula

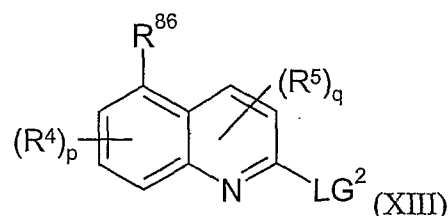


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wherein R^{6a} either represents a group of formula R^6 as defined in formula (I) or a precursor group that may be converted to R^6 by standard chemical transformation, z is as defined in formula (IX), LG^2 is as defined in formula (VIII), LG^1 is as defined in formula (IV), and A , R^2 , R^3 , R^4 , R^5 , n , p and q are as defined in formula (I). When R^{6a} is a precursor group to R^6 , the reaction of (XI) and (XII) is followed by a standard chemical transformation to convert the precursor group to R^6 (e.g. dihydroxylation of an alkene). When z represents hydrogen and R^{6a} is attached to z at a heteroatom, the reaction between a compound of formula (XI) and a compound of formula (XII) may conveniently be carried out in an organic solvent such as *N*-methylpyrrolidinone, acetonitrile or *N,N*-dimethylformamide, optionally in the presence of a base such as potassium carbonate or triethylamine, and at a temperature in the range from 25°C to 180°C, in particular 50°C to 120°C, either in a microwave or under conventional thermal conditions. When z represents a metallic or organometallic group such as an organoboron group (e.g. $\text{B}(\text{OH})_2$ or a boronic acid pinacol cyclic ester) or an organotin group (e.g. SnBu_3), and R^{6a} is attached to z at a carbon atom, the reaction between a compound of formula (XI) and a compound of formula (XII) may conveniently be carried out in the presence of a catalyst such as tetrakis(triphenylphosphine)palladium(0), palladium(II) chloride or dichlorobis(triphenylphosphine)palladium(II), in the presence of a solvent such as tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, toluene, methanol, or water, in the presence of a base such as sodium carbonate or potassium carbonate, and at a temperature in the range 10 to 250°C, preferably in the range 60 to 120°C.

25

Compounds of formula (VI) may be prepared by reacting a compound of formula



with a compound of formula (XII), wherein LG^2 is as defined in formula (VIII), R^{86} is as defined in formula (VI), and R^4 , R^5 , p and q are as defined in formula (I). When R^{6a} is a precursor group to R^6 , the reaction of (XIII) and (XII) is followed by a standard chemical transformation to convert the precursor group to R^6 (e.g. dihydroxylation of an alkene). When z represents hydrogen and R^{6a} is attached to z at a heteroatom, the reaction between a compound of formula (XIII) and a compound of formula (XII) may conveniently be carried out in an organic solvent such as *N*-methylpyrrolidinone, acetonitrile or *N,N*-dimethylformamide, optionally in the presence of a base such as potassium carbonate or triethylamine, and at a temperature in the range from 25°C to 180°C, in particular 50°C to 120°C, either in a microwave or under conventional thermal conditions. When z represents a metallic or organometallic group such as an organoboron group (e.g. $B(OH)_2$ or a boronic acid pinacol cyclic ester) or an organotin group (e.g. $SnBu_3$), and R^{6a} is attached to z at a carbon atom, the reaction between a compound of formula (XIII) and a compound of formula (XII) may conveniently be carried out in the presence of a catalyst such as tetrakis(triphenylphosphine)palladium(0), palladium(II) chloride or dichlorobis(triphenylphosphine)palladium(II), in the presence of a solvent such as tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, toluene, methanol, or water, in the presence of a base such as sodium carbonate or potassium carbonate, and at a temperature in the range 10 to 250°C, preferably in the range 60 to 120°C.

Compounds of formula (VIII) may be prepared by reacting a compound of formula (XIII) with a compound of formula (VII), optionally in the presence of a suitable coupling reagent, such as bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBroP) or dicyclohexylcarbodiimide and 1-hydroxybenzotriazole, in the presence of a base such as triethylamine, *N*-methylmorpholine, diisopropylethylamine or potassium carbonate, in a solvent such as dichloromethane, *N*-methylpyrrolidinone, *N,N*-dimethylformamide or

tetrahydrofuran, and at a temperature in the range from 0°C to 150°C, in particular 50°C to 100°C.

Alternatively, compounds of formula (VIII) may be prepared by reacting a compound of formula (XIII), with a compound of formula (X), and subsequently reacting the product of (X) and (XIII) with a compound of formula (V). The reaction of (X) and (XIII) may be conducted in the presence of a base such as triethylamine, *N*-methymorpholine, diisopropylethylamine or potassium carbonate, and optionally in the presence of a suitable coupling reagent, such as bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBroP) or dicyclohexylcarbodiimide and 1-hydroxybenzotriazole. This reaction may conveniently be conducted in a solvent such as dichloromethane, *N*-methylpyrrolidinone, *N,N*-dimethylformamide or tetrahydrofuran, and at a temperature in the range from 0°C to 150°C. The subsequent reaction with (V) may be conducted in an organic solvent such as *N*-methylpyrrolidinone, acetonitrile or *N,N*-dimethylformamide, optionally in the presence of a base such as potassium carbonate or triethylamine, and at a temperature in the range from 25°C to 180°C, either in a microwave or under conventional thermal conditions.

Compounds of formula (XI) may be prepared by reacting a compound of formula (XIII), with a compound of formula (X), in the presence of a base such as triethylamine, *N*-methymorpholine, diisopropylethylamine or potassium carbonate, and optionally in the presence of a suitable coupling reagent, such as bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBroP) or dicyclohexylcarbodiimide and 1-hydroxybenzotriazole. This reaction may conveniently be conducted in a solvent such as dichloromethane, *N*-methylpyrrolidinone, *N,N*-dimethylformamide or tetrahydrofuran, and at a temperature in the range from 0°C to 150°C.

Compounds of formula (V), (VII), (IX), (X), (XII) and (XIII) are either commercially available, are known in the literature or may be prepared easily using known techniques.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxy, carboxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting

groups. Thus, the preparation of the compounds of formula (I) may involve at a certain stage protection with and/or the removal of one or more protecting groups. The protection and deprotection of functional groups is described in 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991) and 'Protecting Groups', P.J. Kocienski, Georg Thieme Verlag (1994). The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt using conventional methods.

A compound of the invention, or a pharmaceutically acceptable salt thereof, can be used in the treatment of:

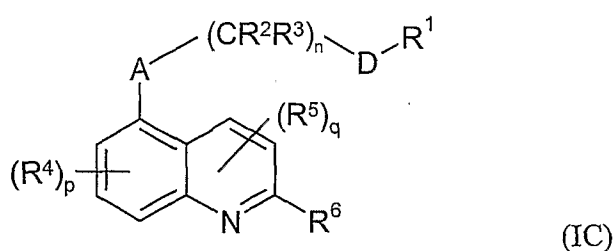
1. respiratory tract: obstructive diseases of the airways including: asthma, including bronchial, allergic, intrinsic, extrinsic, exercise-induced, drug-induced (including aspirin and NSAID-induced) and dust-induced asthma, both intermittent and persistent and of all severities, and other causes of airway hyper-responsiveness; chronic obstructive pulmonary disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema; bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections; complications of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension; antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough; acute and chronic rhinitis including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever); nasal polyposis; acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus;
2. bone and joints: arthritides associated with or including osteoarthritis/osteoarthritis, both primary and secondary to, for example, congenital hip dysplasia; cervical and lumbar spondylitis, and low back and neck pain; rheumatoid arthritis and Still's disease; seronegative spondyloarthropathies including ankylosing spondylitis, psoriatic arthritis, reactive arthritis and undifferentiated spondyloarthropathy; septic arthritis and other infection-related arthropathies and bone disorders such as tuberculosis, including Potts' disease and

- Poncet's syndrome; acute and chronic crystal-induced synovitis including urate gout, calcium pyrophosphate deposition disease, and calcium apatite related tendon, bursal and synovial inflammation; Behcet's disease; primary and secondary Sjogren's syndrome; systemic sclerosis and limited scleroderma; systemic lupus erythematosus, mixed
5 connective tissue disease, and undifferentiated connective tissue disease; inflammatory myopathies including dermatomyositis and polymyositis; polymyalgia rheumatica; juvenile arthritis including idiopathic inflammatory arthritides of whatever joint distribution and associated syndromes, and rheumatic fever and its systemic complications; vasculitides including giant cell arteritis, Takayasu's arteritis, Churg-Strauss syndrome, polyarteritis
10 nodosa, microscopic polyarteritis, and vasculitides associated with viral infection, hypersensitivity reactions, cryoglobulins, and paraproteins; low back pain; Familial Mediterranean fever, Muckle-Wells syndrome, and Familial Hibernian Fever, Kikuchi disease; drug-induced arthralgias, tendonitides, and myopathies;
3. pain and connective tissue remodelling of musculoskeletal disorders due to injury [for
15 example sports injury] or disease: arthritides (for example rheumatoid arthritis, osteoarthritis, gout or crystal arthropathy), other joint disease (such as intervertebral disc degeneration or temporomandibular joint degeneration), bone remodelling disease (such as osteoporosis, Paget's disease or osteonecrosis), polychondritits, scleroderma, mixed connective tissue disorder, spondyloarthropathies or periodontal disease (such as
20 periodontitis);
4. skin: psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatoses, and delayed-type hypersensitivity reactions; phyto- and photodermatitis; seborrhoeic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosus et atrophica, pyoderma gangrenosum, skin sarcoid, discoid lupus erythematosus, pemphigus, pemphigoid,
25 epidermolysis bullosa, urticaria, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-Christian syndrome, erythema multiforme; cellulitis, both infective and non-infective; panniculitis; cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; drug-induced disorders including fixed drug eruptions;
- 30 5. eyes: blepharitis; conjunctivitis, including perennial and vernal allergic conjunctivitis; iritis; anterior and posterior uveitis; choroiditis; autoimmune; degenerative or

- inflammatory disorders affecting the retina; ophthalmitis including sympathetic ophthalmitis; sarcoidosis; infections including viral, fungal, and bacterial;
6. gastrointestinal tract: glossitis, gingivitis, periodontitis; oesophagitis, including reflux; eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, colitis including ulcerative colitis, proctitis, pruritis ani; coeliac disease, irritable bowel syndrome, and food-related allergies which may have effects remote from the gut (for example migraine, rhinitis or eczema);
7. abdominal: hepatitis, including autoimmune, alcoholic and viral; fibrosis and cirrhosis of the liver; cholecystitis; pancreatitis, both acute and chronic;
- 10 8. genitourinary: nephritis including interstitial and glomerulonephritis; nephrotic syndrome; cystitis including acute and chronic (interstitial) cystitis and Hunner's ulcer; acute and chronic urethritis, prostatitis, epididymitis, oophoritis and salpingitis; vulvo-vaginitis; Peyronie's disease; erectile dysfunction (both male and female);
9. allograft rejection: acute and chronic following, for example, transplantation of
- 15 kidney, heart, liver, lung, bone marrow, skin or cornea or following blood transfusion; or chronic graft versus host disease;
10. CNS: Alzheimer's disease and other dementing disorders including CJD and nvCJD; amyloidosis; multiple sclerosis and other demyelinating syndromes; cerebral atherosclerosis and vasculitis; temporal arteritis; myasthenia gravis; acute and chronic pain
- 20 (acute, intermittent or persistent, whether of central or peripheral origin) including visceral pain, headache, migraine, trigeminal neuralgia, atypical facial pain, joint and bone pain, pain arising from cancer and tumor invasion, neuropathic pain syndromes including diabetic, post-herpetic, and HIV-associated neuropathies; neurosarcoidosis; central and peripheral nervous system complications of malignant, infectious or autoimmune
- 25 processes;
11. other auto-immune and allergic disorders including Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome;
12. other disorders with an inflammatory or immunological component; including
- 30 acquired immune deficiency syndrome (AIDS), leprosy, Sezary syndrome, and paraneoplastic syndromes;

13. cardiovascular: atherosclerosis, affecting the coronary and peripheral circulation; pericarditis; myocarditis, inflammatory and auto-immune cardiomyopathies including myocardial sarcoid; ischaemic reperfusion injuries; endocarditis, valvulitis, and aortitis including infective (for example syphilitic); vasculitides; disorders of the proximal and peripheral veins including phlebitis and thrombosis, including deep vein thrombosis and complications of varicose veins;
14. oncology: treatment of common cancers including prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, skin and brain tumors and malignancies affecting the bone marrow (including the leukaemias) and lymphoproliferative systems, such as Hodgkin's and non-Hodgkin's lymphoma; including the prevention and treatment of metastatic disease and tumour recurrences, and paraneoplastic syndromes; and,
15. gastrointestinal tract: Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, microscopic colitis, indeterminant colitis, irritable bowel disorder, irritable bowel syndrome, non-inflammatory diarrhea, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema.

Accordingly, the present invention provides a compound of formula (IC), or a pharmaceutically acceptable salt thereof, for use in therapy,



wherein

n is 1, 2 or 3;

when n is 1, A represents NHC(O) or NHC(S);

when n is 2 or 3, A represents NHC(O), C(O)NH, NHC(S) or C(S)NH;

D represents O, S or NR⁷, wherein R⁷ represents hydrogen, C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl or C₁₋₆ haloalkyl;

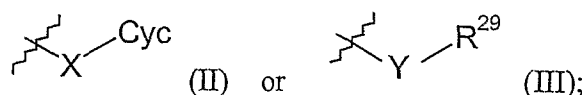
R^1 represents a 6-10 membered aryl, or a 5-10 membered heteroaryl ring, which aryl or heteroaryl ring may be optionally substituted by one or more substituents independently selected from halogen, cyano, C_{1-6} alkyl, C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, NR^8R^9 , $S(O)_{0-2}R^{10}$, $S(O)_2NR^{11}R^{12}$, $C(O)NR^{13}R^{14}$, CO_2R^{15} , $NR^{16}S(O)_2R^{17}$, $C(O)R^{18}$, $NR^{19}C(O)R^{20}$,
 5 $NR^{21}C(O)NR^{22}R^{23}$, $NR^{24}S(O)_2NR^{25}R^{26}$ and OR^{27} ;

within each grouping CR^2R^3 , R^2 and R^3 each independently represent hydrogen, halogen, C_{1-3} alkyl, C_{1-3} hydroxyalkyl or C_{1-3} haloalkyl;

p represents 0, 1, 2 or 3; each R^4 independently represents halogen, cyano, C_{1-6} alkyl, C_{1-6} hydroxyalkyl or C_{1-6} haloalkyl;

10 q represents 0, 1 or 2; each R^5 independently represents halogen, cyano, C_{1-6} alkyl, C_{1-6} hydroxyalkyl or C_{1-6} haloalkyl;

R^6 represents a group



15 wherein X represents a bond, O, S, NR^{30} or a C_{1-4} alkylene which C_{1-4} alkylene may be optionally substituted by one or more substituents independently selected from halogen, hydroxy and C_{1-4} alkoxy;

Cyc represents a 3-8 membered carbocyclic or a 4-8 membered heterocyclic ring, which ring may be optionally substituted by one or more substituents R^{28} , wherein each

20 substituent R^{28} is independently selected from halogen, cyano, $=O$, $S(O)_2R^{31}$, $C(O)R^{32}$, CO_2R^{33} , $C(O)NR^{34}R^{35}$, $NR^{36}C(O)R^{37}$, $S(O)_2NR^{38}R^{39}$, $NR^{40}S(O)_2R^{41}$, OR^{42} , SR^{43} , $NR^{44}R^{45}$, Z^1 or a C_{1-6} alkyl group which C_{1-6} alkyl group may be optionally substituted by one or more substituents independently selected from halogen, hydroxyl, C_{1-6} alkoxy, $NR^{46}R^{47}$, $S(O)_{0-2}R^{48}$, $C(O)R^{49}$, CO_2R^{50} , $C(O)NR^{51}R^{52}$, $NR^{53}C(O)R^{54}$, $S(O)_2NR^{55}R^{56}$, $NR^{57}S(O)_2R^{58}$
 25 and Z^2 ;

Y represents a bond, OC_{1-6} alkylene, $S(O)_{0-2}C_{1-6}$ alkylene, $N(R^{59})C_{1-6}$ alkylene or C_{1-6} alkylene, wherein any alkylene group in Y may be optionally substituted by one or more substituents independently selected from halogen, hydroxy and C_{1-4} alkoxy;

R^{29} represents hydrogen, halogen, hydroxyl, C_{1-6} alkoxy, cyano, $NR^{60}R^{61}$, $S(O)_{0-2}R^{62}$,
 30 $C(O)R^{63}$, CO_2R^{64} , $C(O)NR^{65}R^{66}$, $NR^{67}C(O)R^{68}$, $S(O)_2NR^{69}R^{70}$, $NR^{71}S(O)_2R^{72}$ or Z^3 ;
 with the proviso that when Y is a bond R^{29} is not hydrogen;

R^{42} , R^{43} , R^{44} and R^{45} each independently represent hydrogen or a C_{1-6} alkyl group which C_{1-6} alkyl group may be optionally substituted by one or more substituents independently selected from halogen, hydroxyl, C_{1-6} alkoxy, $NR^{73}R^{74}$, $S(O)_{0-2}R^{75}$, $C(O)R^{76}$, CO_2R^{77} , $C(O)NR^{78}R^{79}$, $NR^{80}C(O)R^{81}$, $S(O)_2NR^{82}R^{83}$, $NR^{84}S(O)_2R^{85}$ or Z^4 , or R^{44} and R^{45} , together
 5 with the nitrogen atom to which they are both attached, may form a 4-8 membered aliphatic heterocyclic ring, which heterocyclic ring may be optionally substituted by one or more substituents independently selected from halogen, hydroxy, C_{1-6} alkyl, C_{1-6} hydroxyalkyl and C_{1-6} haloalkyl;
 Z^1 , Z^2 , Z^3 and Z^4 each independently represent tetrazole, or a 5-6 membered heterocyclic
 10 ring, which heterocyclic ring is substituted by one or more substituents independently selected from hydroxy, amino, $=O$, $=S$, and which heterocyclic ring may further be optionally substituted by one or more substituents independently selected from halogen and C_{1-6} alkyl;
 R^8 , R^9 , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} , R^{30} , R^{32} ,
 15 R^{33} , R^{34} , R^{35} , R^{36} , R^{37} , R^{38} , R^{39} , R^{40} , R^{46} , R^{47} , R^{49} , R^{50} , R^{51} , R^{52} , R^{53} , R^{54} , R^{55} , R^{56} , R^{57} , R^{59} , R^{60} , R^{61} , R^{63} , R^{64} , R^{65} , R^{66} , R^{67} , R^{68} , R^{69} , R^{70} , R^{71} , R^{73} , R^{74} , R^{76} , R^{77} , R^{78} , R^{79} , R^{80} , R^{81} , R^{82} , R^{83} and R^{84} each independently represent hydrogen, C_{1-6} alkyl, C_{1-6} hydroxyalkyl or C_{1-6} haloalkyl; or any of R^8 and R^9 , R^{11} and R^{12} , R^{13} and R^{14} , R^{22} and R^{23} , R^{25} and R^{26} , R^{34} and R^{35} , R^{38} and R^{39} , R^{46} and R^{47} , R^{51} and R^{52} , R^{55} and R^{56} , R^{60} and R^{61} , R^{65} and R^{66} , R^{69} and
 20 R^{70} , R^{73} and R^{74} , R^{78} and R^{79} , and R^{82} and R^{83} , together with the nitrogen atom to which they are both attached, may form a 4-8 membered aliphatic heterocyclic ring, which heterocyclic ring may be optionally substituted by one or more substituents independently selected from halogen, hydroxy, C_{1-6} alkyl, C_{1-6} hydroxyalkyl and C_{1-6} haloalkyl; and
 R^{10} , R^{17} , R^{31} , R^{41} , R^{48} , R^{58} , R^{62} , R^{72} , R^{75} and R^{85} each independently represent C_{1-6} alkyl,
 25 C_{1-6} hydroxyalkyl or C_{1-6} haloalkyl.

For compounds of formula (IC), embodiments of the invention include those wherein each of A, D, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , n, p and q are as defined herein above in embodiments of the invention concerning compounds of formula (I).

In another aspect, the invention provides the use of a compound of formula (IC), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

5 In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

10 In another aspect, the invention provides the use of a compound of formula (IC), or a pharmaceutically acceptable thereof, as hereinbefore defined in the manufacture of a medicament for use in the treatment of rheumatoid arthritis.

15 In another aspect, the invention provides the use of a compound of formula (IC), or a pharmaceutically acceptable thereof, as hereinbefore defined, in the manufacture of a medicament for use in the treatment of osteoarthritis.

20 In another aspect, the invention provides the use of a compound of formula (IC), or a pharmaceutically acceptable thereof, as hereinbefore defined, in the manufacture of a medicament for use in the treatment of asthma or chronic obstructive pulmonary disease.

In another aspect, the invention provides the use of a compound of formula (IC), or a pharmaceutically acceptable thereof, as hereinbefore defined, in the manufacture of a medicament for use in the treatment of atherosclerosis.

25 In another aspect, the invention provides the use of a compound of formula (IC), or a pharmaceutically acceptable thereof, as hereinbefore defined, in the manufacture of a medicament for use in the treatment of inflammatory bowel disease.

30 The invention further provides a method of effecting immunosuppression (e.g. in the treatment of rheumatoid arthritis, osteoarthritis, irritable bowel disease, atherosclerosis or psoriasis) which comprises administering a therapeutically effective amount of a

compound of formula (IC), or a pharmaceutically acceptable salt thereof, as hereinbefore defined to a patient.

The invention also provides a method of treating rheumatoid arthritis which comprises
5 administering to a patient a therapeutically effective amount of a compound of formula (IC), or a pharmaceutically acceptable salt thereof, as hereinbefore defined to a patient.

The invention also provides a method of treating an obstructive airways disease (e.g. asthma or COPD) which comprises administering to a patient a therapeutically effective
10 amount of a compound of formula (IC), or a pharmaceutically acceptable salt thereof, as hereinbefore defined to a patient.

In order to use a compound of the invention, or a pharmaceutically acceptable salt thereof, for the therapeutic treatment of a warm-blooded animal, such as man, said ingredient is
15 normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula (IC), or a pharmaceutically acceptable salt
20 thereof (active ingredient), and a pharmaceutically acceptable adjuvant, diluent or carrier. In a further aspect the present invention provides a process for the preparation of said composition which comprises mixing active ingredient with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will, for example, comprise from 0.05 to 99%w (per cent by weight), such as
25 from 0.05 to 80%w, for example from 0.10 to 70%w, such as from 0.10 to 50%w, of active ingredient, all percentages by weight being based on total composition.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by topical (such as
30 to the lung and/or airways or to the skin), oral, rectal or parenteral administration. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, aerosols, dry powder formulations, tablets, capsules,

syrups, powders, granules, aqueous or oily solutions or suspensions, (lipid) emulsions, dispersible powders, suppositories, ointments, creams, drops and sterile injectable aqueous or oily solutions or suspensions.

- 5 A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 0.1mg and 1g of active ingredient.

- In another aspect a pharmaceutical composition of the invention is one suitable for
10 intravenous, subcutaneous or intramuscular injection. Each patient may receive, for example, an intravenous, subcutaneous or intramuscular dose of 0.01 mgkg^{-1} to 100 mgkg^{-1} of the compound, for example in the range of 0.1 mgkg^{-1} to 20 mgkg^{-1} of this invention, the composition being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively the
15 intravenous dose may be given by continuous infusion over a period of time. Alternatively each patient will receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

- The invention further relates to combination therapies wherein a compound of the
20 invention, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition or formulation comprising a compound of the invention, is administered concurrently or sequentially or as a combined preparation with another therapeutic agent or agents, for the treatment of one or more of the conditions listed.

- 25 In particular, for the treatment of the inflammatory diseases such as (but not restricted to) rheumatoid arthritis, osteoarthritis, asthma, allergic rhinitis, chronic obstructive pulmonary disease (COPD), psoriasis, and inflammatory bowel disease, the compounds of the invention may be combined with agents listed below.

- 30 Non-steroidal anti-inflammatory agents (hereinafter NSAIDs) including non-selective cyclo-oxygenase COX-1 / COX-2 inhibitors whether applied topically or systemically (such as piroxicam, diclofenac, propionic acids such as naproxen, flurbiprofen, fenoprofen,

ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, azapropazone, pyrazolones such as phenylbutazone, salicylates such as aspirin); selective COX-2 inhibitors (such as meloxicam, celecoxib, rofecoxib, valdecoxib, lumarocoxib, parecoxib and etoricoxib); cyclo-oxygenase inhibiting nitric oxide donors (CINODs);
5 glucocorticosteroids (whether administered by topical, oral, intramuscular, intravenous, or intra-articular routes); methotrexate; leflunomide; hydroxychloroquine; d-penicillamine; auranofin or other parenteral or oral gold preparations; analgesics; diacerein; intra-articular therapies such as hyaluronic acid derivatives; and nutritional supplements such as glucosamine.

10

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with a cytokine or agonist or antagonist of cytokine function, (including agents which act on cytokine signalling pathways such as modulators of the SOCS system) including alpha-, beta-, and gamma-
15 interferons; insulin-like growth factor type I (IGF-1); interleukins (IL) including IL1 to 17, and interleukin antagonists or inhibitors such as anakinra; tumour necrosis factor alpha (TNF- α) inhibitors such as anti-TNF monoclonal antibodies (for example infliximab; adalimumab, and CDP-870) and TNF receptor antagonists including immunoglobulin molecules (such as etanercept) and low-molecular-weight agents such as pentoxifylline

20

In addition the invention relates to a combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with a monoclonal antibody targeting B-Lymphocytes (such as CD20 (rituximab), MRA-aIL16R and T-Lymphocytes, CTLA4-Ig, HuMax II-15).

25

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with a modulator of chemokine receptor function such as an antagonist of CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1,
30 CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX₃CR1 for the C-X₃-C family.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with an inhibitor of matrix metalloprotease (MMPs), i.e., the stromelysins, the collagenases, and the gelatinases, as well as aggrecanase; especially collagenase-1 (MMP-1), collagenase-2 (MMP-8), collagenase-3 (MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), and stromelysin-3 (MMP-11) and MMP-9 and MMP-12, including agents such as doxycycline.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist such as; zileuton; ABT-761; fenleuton; tepoxalin; Abbott-79175; Abbott-85761; a *N*-(5-substituted)-thiophene-2-alkylsulfonamide; 2,6-di-tert-butylphenolhydrazones; a methoxytetrahydropyrans such as Zeneca ZD-2138; the compound SB-210661; a pyridinyl-substituted 2-cyanonaphthalene compound such as L-739,010; a 2-cyanoquinoline compound such as L-746,530; or an indole or quinoline compound such as MK-591, MK-886, and BAY x 1005.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a receptor antagonist for leukotrienes (LT) B₄, LTC₄, LTD₄, and LTE₄ selected from the group consisting of the phenothiazin-3-1s such as L-651,392; amidino compounds such as CGS-25019c; benzoxalamines such as ontazolast; benzenecarboximidamides such as BIIL 284/260; and compounds such as zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAY x 7195.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a phosphodiesterase (PDE) inhibitor such as a methylxanthanine including theophylline and aminophylline; a selective PDE isoenzyme inhibitor including a PDE4 inhibitor an inhibitor of the isoform PDE4D, or an inhibitor of PDE5.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a histamine type 1 receptor antagonist such as cetirizine, loratadine, desloratadine, fexofenadine, acrivastine, terfenadine, astemizole, azelastine, levocabastine, chlorpheniramine, promethazine, cyclizine, or mizolastine;
5 applied orally, topically or parenterally.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a proton pump inhibitor (such as omeprazole) or a gastroprotective histamine type 2 receptor antagonist.

10 The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an antagonist of the histamine type 4 receptor.

15 The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an alpha-1/alpha-2 adrenoceptor agonist vasoconstrictor sympathomimetic agent, such as propylhexedrine, phenylephrine, phenylpropanolamine, ephedrine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride,
20 xylometazoline hydrochloride, tramazoline hydrochloride or ethylnorepinephrine hydrochloride.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an anticholinergic agents including
25 muscarinic receptor (M1, M2, and M3) antagonist such as atropine, hyoscine, glycopyrrolate, ipratropium bromide, tiotropium bromide, oxitropium bromide, pirenzepine or telenzepine.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a beta-adrenoceptor agonist
30 (including beta receptor subtypes 1-4) such as isoprenaline, salbutamol, formoterol,

salmeterol, terbutaline, orciprenaline, bitolterol mesylate, or pirbuterol, or a chiral enantiomer thereof.

The present invention further relates to the combination of a compound of the invention, or
5 a pharmaceutically acceptable salt thereof, and a chromone, such as sodium cromoglycate or nedocromil sodium.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with a glucocorticoid, such as
10 flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, ciclesonide or mometasone furoate.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with an agent that modulates a nuclear hormone
15 receptor such as PPARs.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with an immunoglobulin (Ig) or Ig preparation or an antagonist or antibody modulating Ig function such as anti-IgE
20 (for example omalizumab).

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and another systemic or topically-applied anti-inflammatory agent, such as thalidomide or a derivative thereof, a retinoid, dithranol or
25 calcipotriol.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and combinations of aminosaliclates and sulfapyridine such as sulfasalazine, mesalazine, balsalazide, and
30 olsalazine; and immunomodulatory agents such as the thiopurines, and corticosteroids such as budesonide.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with an antibacterial agent such as a penicillin derivative, a tetracycline, a macrolide, a beta-lactam, a fluoroquinolone, metronidazole, an inhaled aminoglycoside; an antiviral agent including acyclovir, famciclovir, valaciclovir, ganciclovir, cidofovir, amantadine, rimantadine, ribavirin, zanamavir and oseltamavir; a protease inhibitor such as indinavir, nelfinavir, ritonavir, and saquinavir; a nucleoside reverse transcriptase inhibitor such as didanosine, lamivudine, stavudine, zalcitabine or zidovudine; or a non-nucleoside reverse transcriptase inhibitor such as nevirapine or efavirenz.

10

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a cardiovascular agent such as a calcium channel blocker, a beta-adrenoceptor blocker, an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin-2 receptor antagonist; a lipid lowering agent such as a statin or a fibrate; a modulator of blood cell morphology such as pentoxifylline; thrombolytic, or an anticoagulant such as a platelet aggregation inhibitor.

15

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a CNS agent such as an antidepressant (such as sertraline), an anti-Parkinsonian drug (such as deprenyl, L-dopa, ropinirole, pramipexole, a MAOB inhibitor such as selegine and rasagiline, a comP inhibitor such as tasmar, an A-2 inhibitor, a dopamine reuptake inhibitor, an NMDA antagonist, a nicotine agonist, a dopamine agonist or an inhibitor of neuronal nitric oxide synthase), or an anti-Alzheimer's drug such as donepezil, rivastigmine, tacrine, a COX-2 inhibitor, propentofylline or metrifonate.

20

25

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an agent for the treatment of acute or chronic pain, such as a centrally or peripherally-acting analgesic (for example an opioid or derivative thereof), carbamazepine, phenytoin, sodium valproate, amitriptyline or other anti-depressant agent-s, paracetamol, or a non-steroidal anti-inflammatory agent.

30

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with a parenterally or topically-applied (including inhaled) local anaesthetic agent such as lignocaine or a derivative thereof.

- 5 A compound of the present invention, or a pharmaceutically acceptable salt thereof, can also be used in combination with an anti-osteoporosis agent including a hormonal agent such as raloxifene, or a biphosphonate such as alendronate.

The present invention still further relates to the combination of a compound of the
10 invention, or a pharmaceutically acceptable salt thereof, together with a: (i) tryptase inhibitor; (ii) platelet activating factor (PAF) antagonist; (iii) interleukin converting enzyme (ICE) inhibitor; (iv) IMPDH inhibitor; (v) adhesion molecule inhibitors including VLA-4 antagonist; (vi) cathepsin; (vii) kinase inhibitor such as an inhibitor of tyrosine
15 kinase (such as Btk, Itk, Jak3 or MAP, for example Gefitinib or Imatinib mesylate), a serine / threonine kinase (such as an inhibitor of a MAP kinase such as p38, JNK, protein kinase A, B or C, or IKK), or a kinase involved in cell cycle regulation (such as a cyclin dependent kinase); (viii) glucose-6 phosphate dehydrogenase inhibitor; (ix) kinin-B1. - or B2. -receptor antagonist; (x) anti-gout agent, for example colchicine; (xi) xanthine oxidase inhibitor, for example allopurinol; (xii) uricosuric agent, for example probenecid,
20 sulfinpyrazone or benzbromarone; (xiii) growth hormone secretagogue; (xiv) transforming growth factor (TGF β); (xv) platelet-derived growth factor (PDGF); (xvi) fibroblast growth factor for example basic fibroblast growth factor (bFGF); (xvii) granulocyte macrophage colony stimulating factor (GM-CSF); (xviii) capsaicin cream; (xix) tachykinin NK1 or NK3 receptor antagonist such as NKP-608C, SB-233412 (talnetant) or D-4418; (xx)
25 elastase inhibitor such as UT-77 or ZD-0892; (xxi) TNF-alpha converting enzyme inhibitor (TACE); (xxii) induced nitric oxide synthase (iNOS) inhibitor; (xxiii) chemoattractant receptor-homologous molecule expressed on TH2 cells, (such as a CRTH2 antagonist); (xxiv) inhibitor of P38; (xxv) agent modulating the function of Toll-like receptors (TLR), or (xxvi) inhibitor of transcription factor activation such as NFkB, API, or STATS.

A compound of the invention, or a pharmaceutically acceptable salt thereof, can also be used in combination with an existing therapeutic agent for the treatment of cancer, for example suitable agents include:

- 5 (i) an antiproliferative/antineoplastic drug or a combination thereof, as used in medical oncology, such as an alkylating agent (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan or a nitrosourea); an antimetabolite (for example an antifolate such as a fluoropyrimidine like 5-fluorouracil or tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine or paclitaxel); an antitumour antibiotic (for example an anthracycline such as 10 adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin or mithramycin); an antimetotic agent (for example a vinca alkaloid such as vincristine, vinblastine, vindesine or vinorelbine, or a taxoid such as taxol or taxotere); or a topoisomerase inhibitor (for example an epipodophyllotoxin such as etoposide, teniposide, amsacrine, topotecan or a camptothecin);
- 15 (ii) a cytostatic agent such as an antioestrogen (for example tamoxifen, toremifene, raloxifene, droloxifene or idoxifene), an oestrogen receptor down regulator (for example fulvestrant), an antiandrogen (for example bicalutamide, flutamide, nilutamide or cyproterone acetate), a LHRH antagonist or LHRH agonist (for example goserelin, leuporelin or buserelin), a progestogen (for example megestrol acetate), an aromatase 20 inhibitor (for example as anastrozole, letrozole, vorazole or exemestane) or an inhibitor of 5α -reductase such as finasteride;
- (iii) an agent which inhibits cancer cell invasion (for example a metalloproteinase inhibitor like marimastat or an inhibitor of urokinase plasminogen activator receptor function);
- (iv) an inhibitor of growth factor function, for example: a growth factor antibody (for 25 example the anti-erbB2 antibody trastuzumab, or the anti-erbB1 antibody cetuximab [C225]), a farnesyl transferase inhibitor, a tyrosine kinase inhibitor or a serine/threonine kinase inhibitor, an inhibitor of the epidermal growth factor family (for example an EGFR family tyrosine kinase inhibitor such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7- 30 bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) or 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), an

inhibitor of the platelet-derived growth factor family, or an inhibitor of the hepatocyte growth factor family;

(v) an antiangiogenic agent such as one which inhibits the effects of vascular endothelial growth factor (for example the anti-vascular endothelial cell growth factor antibody

5 bevacizumab, a compound disclosed in WO 97/22596, WO 97/30035, WO 97/32856 or WO 98/13354), or a compound that works by another mechanism (for example linomide, an inhibitor of integrin $\alpha v \beta 3$ function or an angiostatin);

(vi) a vascular damaging agent such as combretastatin A4, or a compound disclosed in WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 or WO 02/08213;

10 (vii) an agent used in antisense therapy, for example one directed to one of the targets listed above, such as ISIS 2503, an anti-ras antisense;

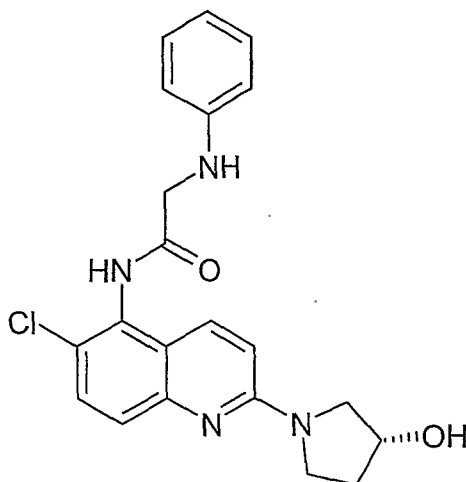
(viii) an agent used in a gene therapy approach, for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or
15 a bacterial nitroreductase enzyme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

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

The invention will now be further explained by reference to the following illustrative
25 examples. In the examples the NMR spectra were measured on a Varian Unity spectrometer at a proton frequency of either 300 or 400 MHz. The MS spectra were measured on either an Agilent 1100 MSD G1946D spectrometer or a Hewlett Packard HP1100 MSD G1946A spectrometer. Preparative HPLC separations were performed using a Waters Symmetry® or Xterra® column using 0.1% aqueous trifluoroacetic acid:
30 acetonitrile, 0.1% aqueous ammonia: acetonitrile or 0.1% ammonium acetate: acetonitrile as the eluant. Microwave reactions were performed in a CEM Discover single mode microwave.

Example 1

***N*-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-2-(phenylamino)-acetamide**

**a) (3*R*)-1-(5-Amino-6-chloro-2-quinolinyl)-3-pyrrolidinol**

A mixture of (3*R*)-3-pyrrolidinol (620 mg), 2,6-dichloro-5-aminoquinoline (WO2005009968) (500 mg) and triethylamine (0.66 mL) in acetonitrile (3 mL) was heated with stirring in a microwave at 120°C for 30 minutes. The products were concentrated *in vacuo* and purified by chromatography (SiO₂, dichloromethane:methanol:7N NH₃ in methanol 97:3:0.2 as eluant) to yield the sub-title compound as a solid (490 mg).

¹H NMR (300 MHz, d₆-DMSO) δ 8.30 (1H, d), 7.26 (1H, d), 6.82-6.69 (2H, m), 5.78 (2H, s), 4.95 (1H, d), 4.44-4.36 (1H, m), 3.65-3.39 (4H, m), 2.10-1.97 (1H, m), 1.95-1.85 (1H, m).

b) 6-Chloro-2-[(3*R*)-3-[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-pyrrolidinyl]-5-quinolinamine

Chloro(1,1-dimethylethyl)dimethyl-silane (2.5 g) was added with stirring to a mixture of (3*R*)-1-(5-amino-6-chloro-2-quinolinyl)-3-pyrrolidinol (Example 1 (a)) (2.9 g) and imidazole (1.1 g) in *N,N*-dimethylformamide (50 mL). The mixture was stirred under nitrogen at room temperature for 24 hours and then water (100 mL) was added, the mixture was stirred for 5 minutes and the resulting precipitate was collected by filtration, washed

with water (2 x 100 mL) and *isohexane* (2 x 100 mL), and dried to yield the sub-title compound as a solid (3.8 g).

¹H NMR (300 MHz, d₆-DMSO) δ 8.32 (1H, d), 7.27 (1H, d), 6.83-6.74 (2H, m), 5.80 (2H, s), 4.58 (1H, s), 3.72-3.49 (3H, m), 3.43-3.26 (1H, m), 2.16-2.02 (1H, m), 1.96-1.84 (1H, m), 0.85 (9H, s), 0.10 (6H, d).

c) 2-Chloro-*N*-[6-chloro-2-[(3*R*)-3-[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-pyrrolidinyl]-5-quinolinyl]-acetamide

Chloroacetyl chloride (1.5 mL) was added dropwise to a stirred mixture of 6-chloro-2-[(3*R*)-3-[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-pyrrolidinyl]-5-quinolinamine (Example 1 (b)) (3.8 g) and potassium carbonate (4.1 g) in acetone (40 mL) under nitrogen at 0°C. The mixture was allowed to warm to room temperature and stirred for 2 hours. Potassium carbonate (2.0 g) and chloroacetyl chloride (0.75 mL) were added and the mixture was stirred for 2 hours. Water was added, the mixture was stirred for 10 minutes and the resulting precipitate was collected by filtration and purified by chromatography (SiO₂, *isohexane*:ethyl acetate 85:15-75:25 as eluant) to yield the sub-title compound as a solid (3.5 g).

¹H NMR (300 MHz, d₆-DMSO) δ 10.23 (1H, s), 7.92 (1H, d), 7.58 (1H, d), 7.51 (1H, d), 6.97 (1H, d), 4.64-4.55 (1H, m), 4.42 (2H, s), 3.76-3.53 (3H, m), 3.46-3.37 (1H, m), 2.20-2.05 (1H, m), 1.98-1.85 (1H, m), 0.86 (9H, s), 0.10 (6H, d).

d) *N*-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-2-(phenylamino)-acetamide

A mixture of 2-chloro-*N*-[6-chloro-2-[(3*R*)-3-[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-pyrrolidinyl]-5-quinolinyl]-acetamide (Example 1 (c)) (100 mg) and aniline (0.2 mL) were heated for 5 minutes with stirring at 120°C in a microwave. The resulting products were purified by chromatography (SiO₂, ethyl acetate:*isohexane*:7N NH₃ in methanol 50:50:0.5 as eluant) to leave a solid which was dissolved in tetrahydrofuran (0.8 mL) and tetrabutylammonium fluoride (1M in tetrahydrofuran, 0.19 mL) was added. The mixture was stirred at room temperature for 3 hours, concentrated *in vacuo* and purified by

chromatography (SiO₂, dichloromethane:methanol:7N NH₃ in methanol 95:5:0.5 as eluant) to give the title compound as a solid (35 mg).

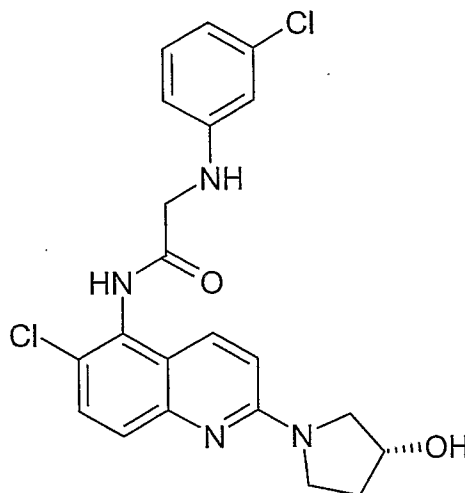
MS: APCI(+ve) 397 (M+H⁺).

5 m.p. 230-232°C.

¹H NMR (300 MHz, d₆-DMSO) δ 9.91 (1H, s), 7.82 (1H, d), 7.54 (1H, d), 7.47 (1H, d), 7.15 (2H, dd), 6.86 (1H, d), 6.70 (2H, d), 6.63 (1H, t), 6.13 (1H, t), 4.98 (1H, d), 4.41 (1H, s), 3.98 (2H, d), 3.69-3.39 (4H, m), 2.11-1.86 (2H, m).

10 Example 2

***N*-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-2-[(3-chlorophenyl)amino]- acetamide monohydrochloride**



2-Chloro-*N*-[6-chloro-2-[(3*R*)-3-[[1,1-dimethylethyl]dimethylsilyl]oxy]-1-pyrrolidinyl]-5-quinolinyl]-acetamide (Example 1 (c)) (150 mg) and 3-chloroaniline (0.35 mL) were heated at 140°C for 30 minutes in a microwave. The resulting products were purified by chromatography (SiO₂, dichloromethane : methanol : 7N NH₃ in methanol 99:0.5:0.5 as eluant) to leave a solid which was dissolved in dichloromethane (0.5 mL) and hydrogen chloride (2M in diethyl ether, 0.1 mL) was added. The mixture was stirred at room temperature for 10 minutes and concentrated *in vacuo* to give the title compound as a solid (35 mg).

MS: APCI(+ve) 431 (M+H⁺).

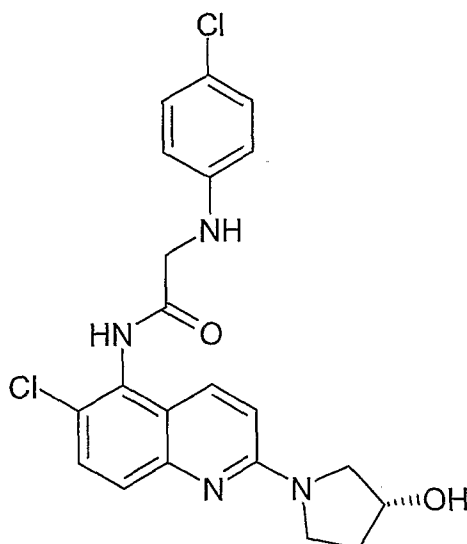
m.p. 180°C dec.

¹H NMR (300 MHz, d₆-DMSO) δ 10.39 (1H, s), 8.26-8.13 (2H, m), 7.91 (1H, d), 7.30 (1H, d), 7.14 (1H, t), 6.71 (1H, t), 6.68-6.60 (2H, m), 4.61-4.46 (1H, m), 4.08 (2H, s), 4.00-3.64 (4H, m), 2.21-1.97 (2H, m).

5

Example 3

***N*-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinoliny]-2-[(4-chlorophenyl)amino]- acetamide monohydrochloride**



10 2-Chloro-*N*-[6-chloro-2-[(3*R*)-3-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-pyrrolidinyl]-5-quinoliny]-acetamide (Example 1 (c)) (150 mg) and 4-chloroaniline (211 mg) were heated at 130°C for 15 minutes in a microwave. The resulting products were purified by chromatography (SiO₂, dichloromethane:methanol:7N NH₃ in methanol 98.5:1.5:0.5 as eluant) to leave a solid which was dissolved in dichloromethane (0.5 mL) and hydrogen
15 chloride (2M in diethyl ether, 0.16 mL) was added. The mixture was stirred at room temperature for 15 minutes and concentrated *in vacuo* to give the title compound as a solid (40 mg).

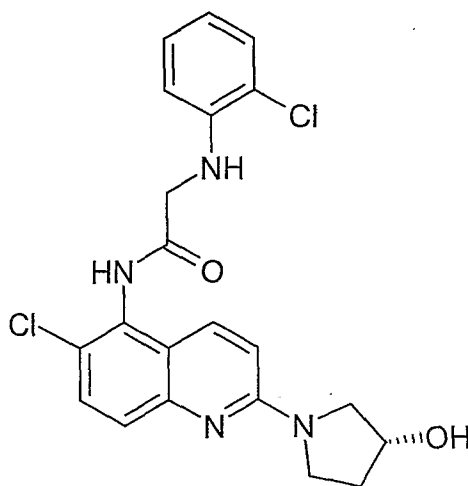
MS: APCI(+ve) 431 (M+H⁺).

20 m.p. 175°C dec.

¹H NMR (300 MHz, d₆-DMSO) δ 10.37 (1H, s), 8.23 (1H, d), 8.15 (1H, d), 7.91 (1H, d), 7.32 (1H, d), 7.18 (2H, d), 6.71 (2H, d), 4.60-4.46 (1H, m), 4.06 (2H, s), 3.99-3.63 (4H, m), 2.22-1.95 (2H, m).

5 **Example 4**

***N*-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinoliny]-2-[(2-chlorophenyl)amino]-acetamide**



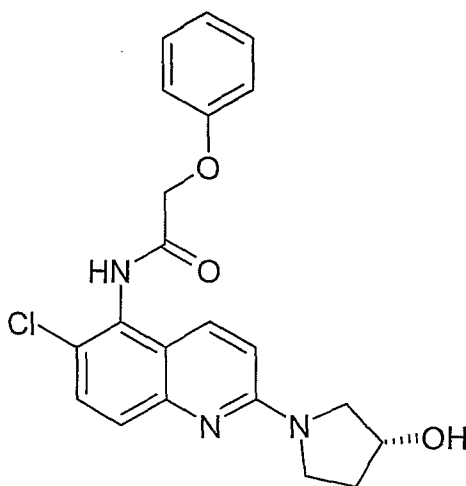
A mixture of 2-chloro-*N*-[6-chloro-2-[(3*R*)-3-[[1,1-dimethylethyl]dimethylsilyl]oxy]-1-pyrrolidinyl]-5-quinoliny]-acetamide (Example 1 (c)) (120 mg) and 2-chloroaniline (0.28 mL) were heated at 140°C for 30 minutes in a microwave. The resulting products were purified by chromatography (SiO₂, ethyl acetate:isohexane 20:80, then ethyl acetate:isohexane:7N NH₃ in methanol 30:70:0.5 as eluant) to leave a solid which was dissolved in tetrahydrofuran (0.8 mL) and tetrabutylammonium fluoride (1M in tetrahydrofuran, 0.22 mL) was added. The mixture was stirred at room temperature for 3 hours, concentrated *in vacuo* and purified by chromatography (SiO₂, dichloromethane:methanol:7N NH₃ in methanol 99.5:0.5:0.5-98.5:1.5:0.5 as eluant) to give the title compound as a solid (20 mg).

20 MS: APCI(+ve) 431 (M+H⁺).
m.p. 215 - 219°C.

¹H NMR (300 MHz, d₆-DMSO) δ 10.03 (1H, s), 7.88 (1H, d), 7.55 (1H, d), 7.48 (1H, d), 7.30 (1H, dd), 7.22 (1H, t), 6.89 (1H, d), 6.74 (1H, d), 6.67 (1H, dd), 5.86 (1H, t), 4.98 (1H, d), 4.41 (1H, s), 4.13 (2H, d), 3.70-3.39 (4H, m), 2.14-1.83 (2H, m).

5 **Example 5**

***N*-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-2-phenoxy-acetamide**



A mixture of 2-chloro-*N*-[6-chloro-2-[(3*R*)-3-[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-pyrrolidinyl]-5-quinolinyl]-acetamide (Example 1 (c)) (150 mg), phenol (310 mg),
10 potassium carbonate (136 mg) and *N*-methylpyrrolidinone (0.75 mL) was heated at 100°C for 10 minutes in a microwave. Water (20 mL) and dichloromethane (20 mL) were added, the layers separated, and the aqueous fraction was extracted with dichloromethane (20 mL). The combined organic layers were concentrated *in vacuo* and the residue was purified by chromatography (SiO₂, ethyl acetate:isohexane 20:80 as eluant) to leave a solid which
15 was dissolved in tetrahydrofuran (0.8 mL) and tetrabutylammonium fluoride (1M in tetrahydrofuran, 0.3 mL) was added. The mixture was stirred at room temperature for 18 hours, concentrated *in vacuo* and purified by chromatography (SiO₂, dichloromethane:methanol 97.5:2.5) to give the title compound as a solid (40 mg).

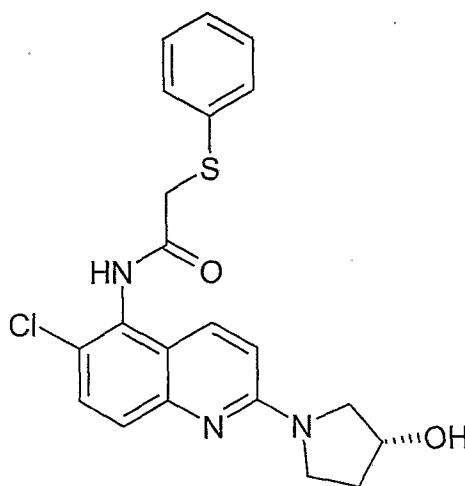
20 MS: APCI(+ve) 398 (M+H⁺).

m.p. 233 - 235°C.

^1H NMR (300 MHz, d_6 -DMSO) δ 10.09 (1H, s), 7.87 (1H, d), 7.57 (1H, d), 7.50 (1H, d), 7.40-7.31 (2H, m), 7.09 (2H, dd), 7.01 (1H, t), 6.90 (1H, d), 4.99 (1H, d), 4.84 (2H, s), 4.41 (1H, s), 3.71-3.40 (4H, m), 2.12-1.87 (2H, m).

5 Example 6

***N*-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-2-(phenylthio)-acetamide**



10 a) *N*-[6-Chloro-2-[(3*R*)-3-[[1,1-dimethylethyl]dimethylsilyl]oxy]-1-pyrrolidinyl]-5-quinolinyl]-2-(phenylthio)-acetamide

A mixture of 2-chloro-*N*-[6-chloro-2-[(3*R*)-3-[[1,1-dimethylethyl]dimethylsilyl]oxy]-1-pyrrolidinyl]-5-quinolinyl]-acetamide (Example 1 (c)) (400 mg), benzenethiol (0.18 mL), triethylamine (0.37 mL) and acetonitrile (4 mL) was heated at 100°C for 5 minutes in a microwave. The products were concentrated *in vacuo* and the residue was purified by
15 chromatography (SiO_2 , ethyl acetate:isohexane 20:80 as eluant) to give the sub-title compound as a solid (440 mg).

^1H NMR (300 MHz, d_6 -DMSO) δ 10.11 (1H, s), 7.70 (1H, d), 7.58-7.44 (4H, m), 7.37 (2H, t), 7.25 (1H, t), 6.86 (1H, d), 4.59 (1H, s), 4.01 (2H, s), 3.74-3.51 (3H, m), 3.40 (1H, d),
20 2.19-2.04 (1H, m), 1.97-1.85 (1H, m), 0.86 (9H, s), 0.10 (6H, d).

b) *N*-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-2-(phenylthio)-acetamide

N-[6-Chloro-2-[(3*R*)-3-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-pyrrolidinyl]-5-quinolinyl]-2-(phenylthio)-acetamide (Example 6 (a)) (40 mg) was dissolved in tetrahydrofuran (0.3 mL) and tetrabutylammonium fluoride (1M in tetrahydrofuran, 0.1 mL) was added. The mixture was stirred at room temperature for 4 hours, concentrated *in vacuo* and purified by chromatography (SiO₂, dichloromethane:methanol 98:2-95:5 as eluant) to give the title compound as a solid (18 mg).

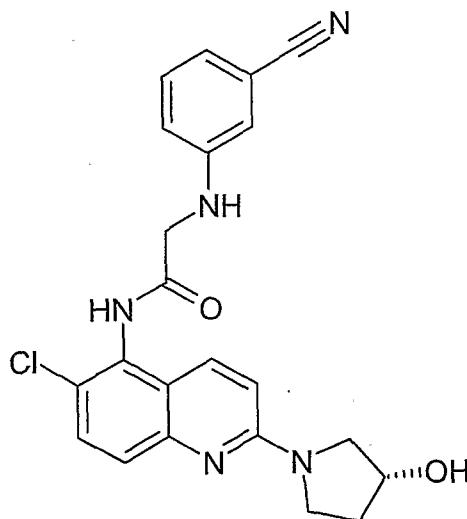
MS: APCI(+ve) 414 (M+H⁺).

m.p. 246 - 249°C.

¹H NMR (300 MHz, d₆-DMSO) δ 10.11 (1H, s), 7.69 (1H, d), 7.58-7.44 (4H, m), 7.37 (2H, t), 7.25 (1H, t), 6.84 (1H, d), 4.98 (1H, d), 4.41 (1H, s), 4.01 (2H, s), 3.67-3.40 (4H, m), 2.13-1.85 (2H, m).

Example 7

N-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-2-[(3-cyanophenyl)amino]-acetamide



Prepared according to the method of Example 1 (d) using 2-chloro-*N*-[6-chloro-2-[(3*R*)-3-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-pyrrolidinyl]-5-quinolinyl]-acetamide (Example 1 (c)) (120 mg) and 3-aminobenzonitrile (310 mg) heating at 120°C for 10 minutes in a microwave, and then tetrabutylammonium fluoride (1M in tetrahydrofuran, 0.2 mL) and tetrahydrofuran (0.8 mL). Purification by chromatography (SiO₂, dichloromethane :

methanol : 7N NH₃ in methanol 97.5:2.5:0.5-96:4:0.5 as eluant) gave the title compound as a solid (30 mg).

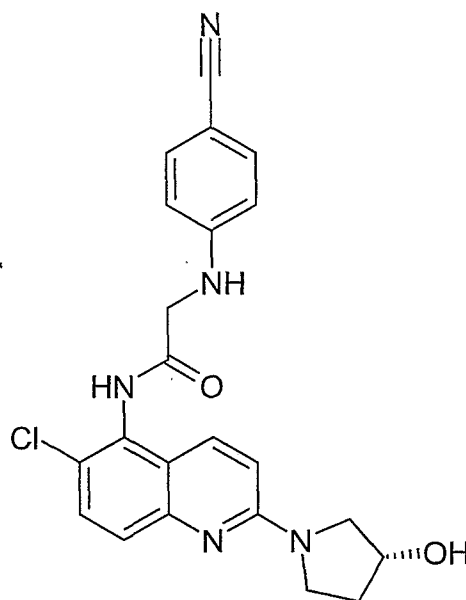
MS: APCI(+ve) 422 (M+H⁺).

5 m.p. 254 - 256°C.

¹H NMR (300 MHz, d₆-DMSO) δ 10.03 (1H, s), 7.88 (1H, d), 7.56 (1H, d), 7.48 (1H, d), 7.37-7.28 (1H, m), 7.05-6.98 (3H, m), 6.88 (1H, d), 6.72 (1H, t), 4.99 (1H, d), 4.41 (1H, s), 4.08 (2H, d), 3.69-3.40 (4H, m), 2.12-1.87 (2H, m).

10 Example 8

N-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinoliny]-2-[(4-cyanophenyl)amino]-acetamide



Prepared according to the method of Example 1 (d) using 2-chloro-*N*-[6-chloro-2-[(3*R*)-3-
15 [[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-pyrrolidinyl]-5-quinoliny]-acetamide (Example 1 (c)) (120 mg) and 4-aminobenzonitrile (310 mg) heating at 110°C for 45 minutes in a microwave, and then tetrabutylammonium fluoride (1M in tetrahydrofuran, 0.2 mL) and tetrahydrofuran (0.8 mL). Purification by chromatography (SiO₂, dichloromethane : methanol : 7N NH₃ in methanol 98:2:0.5-96:4:0.5 as eluant) gave the title compound as a
20 solid (30 mg).

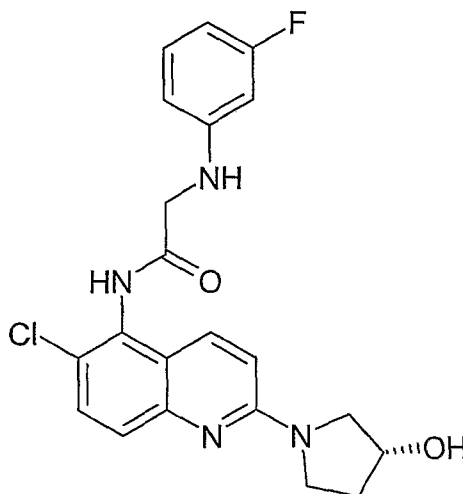
MS: APCI(+ve) 422 ($M+H^+$).

m.p. 230 - 233°C.

^1H NMR (300 MHz, d_6 -DMSO) δ 10.04 (1H, s), 7.88 (1H, d), 7.61-7.45 (4H, m), 7.14 (1H, t), 6.91 (1H, d), 6.77 (2H, d), 4.99 (1H, d), 4.42 (1H, s), 4.12 (2H, d), 3.71-3.41 (4H, m),
5 2.13-1.86 (2H, m).

Example 9

***N*-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-2-[(3-fluorophenyl)amino]-acetamide**



10

Prepared according to the method of Example 1 (d) using 2-chloro-*N*-[6-chloro-2-[(3*R*)-3-
[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-pyrrolidinyl]-5-quinolinyl]-acetamide (Example
1 (c)) (120 mg) and 3-fluoroaniline (0.25 mL) heating at 120°C for 15 minutes in a
microwave, and then tetrabutylammonium fluoride (1M in tetrahydrofuran, 0.25 mL) and
15 tetrahydrofuran (0.8 mL). Purification by chromatography (SiO_2 , dichloromethane :
methanol : 7N NH_3 in methanol 98:2:0.5-96:4:0.5 as eluant) gave the title compound as a
solid (50 mg).

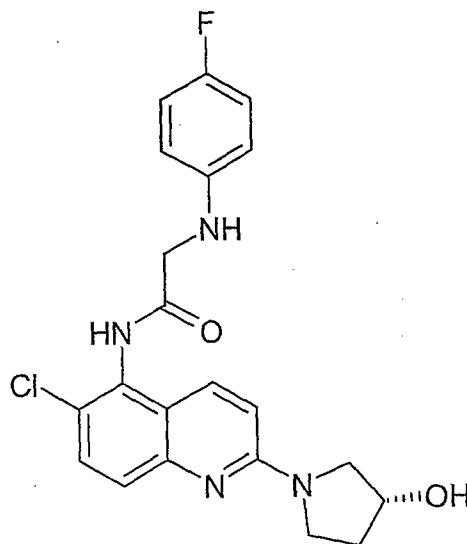
MS: APCI(+ve) 415 ($M+H^+$).

20 m.p. 218 - 220°C.

^1H NMR (300 MHz, d_6 -DMSO) δ 9.97 (1H, s), 7.85 (1H, d), 7.55 (1H, d), 7.48 (1H, d),
7.14 (1H, q), 6.87 (1H, d), 6.55-6.34 (4H, m), 4.98 (1H, d), 4.41 (1H, s), 4.02 (2H, d),
3.67-3.41 (4H, m), 2.12-1.86 (2H, m).

Example 10

***N*-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinoliny]-2-[(4-fluorophenyl)amino]-acetamide**



5

Prepared according to the method of Example 1 (d) using 2-chloro-*N*-[6-chloro-2-[(3*R*)-3-
 [[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-pyrrolidinyl]-5-quinoliny]-acetamide (Example
 1 (c)) (120 mg) and 4-fluoroaniline (0.3 mL) heating at 120°C for 5 minutes in a
 microwave, and then tetrabutylammonium fluoride (1M in tetrahydrofuran, 0.26 mL) and
 10 tetrahydrofuran (0.8 mL). Purification by chromatography (SiO₂, dichloromethane :
 methanol : 7N NH₃ in methanol 98:2:0.5-96:4:0.5 as eluant) gave the title compound as a
 solid (65 mg).

MS: APCI(+ve) 415 (M+H⁺).

15

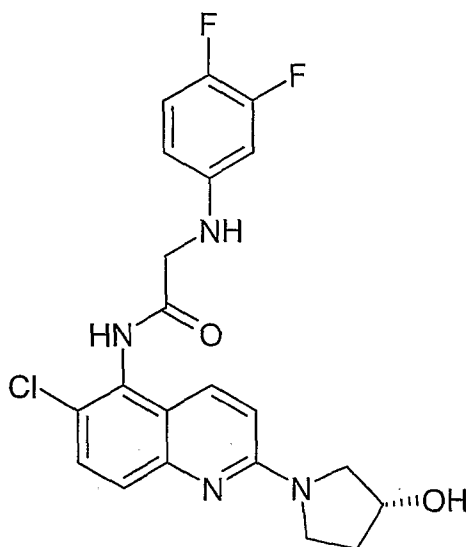
m.p. 242 - 246°C.

¹H NMR (300 MHz, d₆-DMSO) δ 9.92 (1H, s), 7.82 (1H, d), 7.54 (1H, d), 7.47 (1H, d),
 7.00 (2H, t), 6.87 (1H, d), 6.68 (2H, dd), 6.10 (1H, t), 4.98 (1H, d), 4.42 (1H, s), 3.97 (2H,
 d), 3.70-3.41 (4H, m), 2.13-1.85 (2H, m).

20

Example 11

***N*-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinoliny]-2-[(3,4-difluorophenyl)amino]-acetamide**



Prepared according to the method of Example 1 (d) using 2-chloro-*N*-[6-chloro-2-[(3*R*)-3-
 5 [[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-pyrrolidinyl]-5-quinoliny]-acetamide (Example
 1 (c)) (105 mg) and 3,4-difluoroaniline (0.23 mL) heating at 120°C for 10 minutes in a
 microwave, and then tetrabutylammonium fluoride (1M in tetrahydrofuran, 0.2 mL) and
 tetrahydrofuran (0.8 mL). Purification by chromatography (SiO₂, dichloromethane :
 methanol : 7N NH₃ in methanol 99:1:0.5-98:2:0.5 as eluant) gave the title compound as a
 solid (45 mg).

10 MS: APCI(+ve) 433 (M+H⁺).

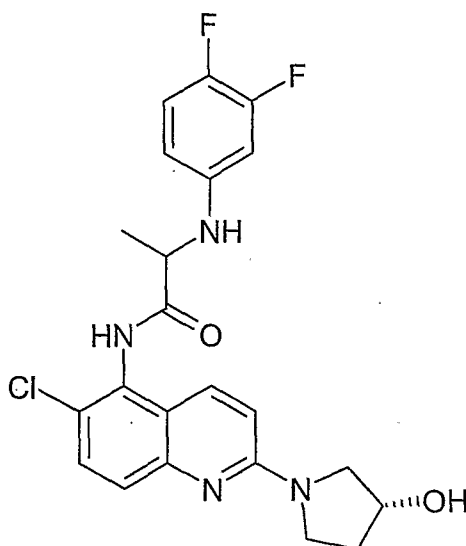
m.p. 238 - 240°C.

¹H NMR (300 MHz, d₆-DMSO) δ 9.97 (1H, s), 7.86 (1H, d), 7.55 (1H, d), 7.48 (1H, d),
 7.19 (1H, dd), 6.88 (1H, d), 6.65 (1H, ddd), 6.50-6.42 (1H, m), 6.37 (1H, t), 4.99 (1H, s),
 4.42 (1H, s), 4.00 (2H, d), 3.69-3.41 (4H, m), 2.14-1.86 (2H, m).

15

Example 12

N-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinoliny]-2-[(3,4-
 difluorophenyl)amino]-propanamide



a) 2-Chloro-N-[6-chloro-2-[(3R)-3-[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-pyrrolidinyl]-5-quinolinyl]-propanamide

2-Chloro-propanoyl chloride (0.15 mL) was added to a stirred solution of 6-chloro-2-[3-
 5 [[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-pyrrolidinyl]-5-quinolinamine (Example 1 (b))
 (520 mg) and triethylamine (0.42 mL) in dichloromethane (20 mL) at 0°C under nitrogen.
 The mixture was allowed to warm to room temperature over 18 hours, dichloromethane
 and water were added and the layers were separated. The aqueous fraction was extracted
 with dichloromethane and the combined organic extracts were dried (MgSO₄), filtered and
 10 concentrated *in vacuo*. Purification by chromatography (SiO₂, *isohexane*:ethyl acetate
 80:20 as eluant) gave the sub-title compound as a foam (350 mg).

¹H NMR (300 MHz, CDCl₃) δ 8.20 (1H, s), 7.77 (1H, d), 7.63 (1H, d), 7.52 (1H, d), 6.76
 (1H, d), 4.69 (1H, q), 4.56 (1H, s), 3.72 (3H, m), 3.52 (1H, m), 2.08 (2H, m), 1.92 (3H, d),
 15 0.89 (9H, s), 0.10 (3H, s), 0.10 (3H, s).

b) N-[6-Chloro-2-[(3R)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-2-[(3,4-difluorophenyl)amino]-propanamide

Prepared according to the method of Example 1 (d) using 2-chloro-N-[6-chloro-2-[(3R)-3-
 20 [[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-pyrrolidinyl]-5-quinolinyl]-propanamide
 (Example 12 (a)) (150 mg) and 3,4-difluoroaniline (500 mg) heating at 120°C for 25
 minutes in a microwave, and then tetrabutylammonium fluoride (1M in tetrahydrofuran,

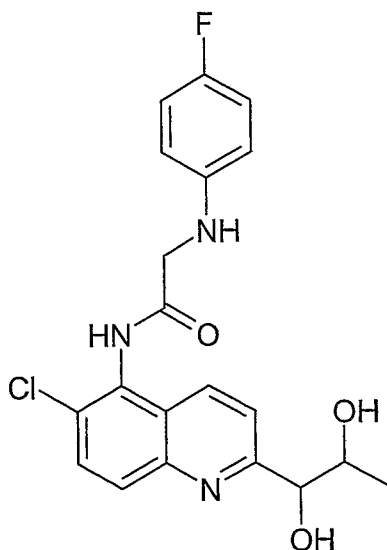
1.0 mL) and tetrahydrofuran (5 mL). Purification by trituration with diethyl ether gave the title compound as a solid (82 mg).

MS: APCI(+ve) 447 ($M+H^+$).

5. ^1H NMR (400 MHz, CD_3OD) δ 7.65 (1H, d), 7.58 (1H, d), 7.51 (1H, d), 7.06 (1H, q), 6.80 (1H, d), 6.63 (1H, m), 6.50 (1H, m), 4.53 (1H, m), 4.05 (1H, q), 3.68 (3H, m), 3.57 (1H, br d), 2.14 (1H, m), 2.06 (1H, m), 1.66 (3H, d).

Example 13

- 10 ***N*-[6-Chloro-2-(1,2-dihydroxypropyl)-5-quinolinyl]-2-[(4-fluorophenyl)amino]-acetamide**



a) (2,6-Dichloro-5-quinolinyl)-[(1,1-dimethylethoxy)carbonyl]-carbamic acid 1,1-dimethylethyl ester

- 15 Di-tert-butyl dicarbonate (3.3 g) was added to a solution of 2,6-dichloro-5-aminoquinoline (WO2005009968) (1.1 g) and 4-dimethylaminopyridine (20 mg) in acetonitrile (25 mL) at room temperature under nitrogen. The reaction was heated to 80°C for 4 hours. The reaction was then concentrated *in vacuo* and the residue partitioned between diethyl ether and water. The phases were separated, the aqueous phase was further extracted with
- 20 diethyl ether and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residual solid was trituated with diethyl ether to give the subtitle compound as a pale brown solid (1.7 g).

¹H NMR (400 MHz, CDCl₃) δ 8.11(1H, d), 7.97 (1H, d), 7.77 (1H, d), 7.48 (1H, d), 1.33 (18H, s).

5 **b) 6-Chloro-2-(2-propenyl)-5-quinolinyl]-[(1,1-dimethylethoxy)carbonyl]-carbamic acid 1,1-dimethylethyl ester**

A solution of (2,6-dichloro-5-quinolinyl)-[(1,1-dimethylethoxy)carbonyl]-carbamic acid 1,1-dimethylethyl ester (Example 13(a)) (1.7 g), 4,4,5,5-tetramethyl-2-(2-propenyl)-1,3,2-dioxaborolane (1.4 g), potassium carbonate (1.2 g) and tetrakis(triphenylphosphine) palladium(0) (490 mg) in tetrahydrofuran (10 mL) and water (10 mL) was heated in a sealed vessel at 60°C for 4 hours. The reaction was concentrated *in vacuo* before re-dissolving in dichloromethane and washing with water. The organic layer was separated, dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by chromatography (SiO₂, iso-hexane:dichloromethane 50:50-10:90 as eluant) gave the sub-title compound as an oil
15 (1.7 g).

¹H NMR (400 MHz, CDCl₃) δ 8.08 (1H, d), 7.98 (1H, d), 7.70 (1H, d), 7.40 (1H, d), 6.15 (1H, m), 5.21 (2H, m), 3.78 (2H, d), 1.31 (18H, s).

20 **c) 2-Chloro-N-[6-chloro-2-(1-propenyl)-5-quinolinyl]-acetamide**

4N HCl in dioxane was added to 6-chloro-2-(2-propenyl)-5-quinolinyl]-[(1,1-dimethylethoxy)carbonyl]-carbamic acid 1,1-dimethylethyl ester (Example 13 (b)) (1.7 g) and the mixture was stirred under nitrogen for 40 minutes, after which time the reaction was concentrated *in vacuo*. The residue was then redissolved in acetone (40 mL), treated
25 with potassium carbonate (2.3 g) and chloroacetyl chloride (0.61 mL). The reaction was stirred for 18 hours under nitrogen before being concentrated *in vacuo* and partitioned between water and ethyl acetate. The phases were separated and the water layer was further extracted with ethyl acetate. The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by chromatography (SiO₂, dichloromethane
30 -dichloromethane:acetonitrile 20:1 as eluant) gave the sub-title compound as a solid (350 mg).

¹H NMR (400 MHz, DMSO) δ 8.21 (1H, d), 7.90 (1H, d), 7.82 (1H, d), 7.78 (1H, d), 6.97 (1H, m), 6.71 (1H, d), 4.45 (2H, s), 1.98 (3H, d).

d) 2-Chloro-*N*-[6-chloro-2-(1,2-dihydroxypropyl)-5-quinoliny]-acetamide

5 A solution of 2-chloro-*N*-[6-chloro-2-(1-propenyl)-5-quinoliny]-acetamide (Example 13(c)) (350 mg) in acetone (3 mL) and water (3 mL) was treated with 4-methylmorpholine *N*-oxide (318 mg) and potassium osmate (20 mg). The reaction was then stirred under nitrogen at room temperature for 18 hours. After this time a solution of saturated sodium metabisulphite was added and stirring continued for 30 minutes. Water was added and the
10 mixture was extracted with dichloromethane and ethyl acetate. The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. Trituration with dichloromethane gave the sub-title compound as a colourless solid (120 mg).

¹H NMR (400 MHz, CD₃OD) δ 8.40 (1H, d), 8.10 (1H, d), 7.91 (1H, d), 7.85 (1H, d), 4.75
15 (1H, d), 4.47 (2H, s), 4.17 (1H, m), 1.24, (3H, d).

e) *N*-[6-Chloro-2-(1,2-dihydroxypropyl)-5-quinoliny]-2-[(4-fluorophenyl)amino]-acetamide

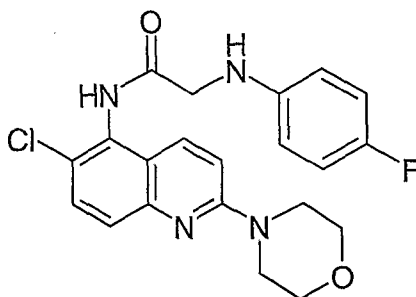
A solution of 2-chloro-*N*-[6-chloro-2-(1,2-dihydroxypropyl)-5-quinoliny]-acetamide
20 (Example 13(d)) (120 mg) in acetonitrile (2.5 mL) was treated with 4-fluoroaniline (200 mg) and diisopropylethylamine (0.3 mL). The reaction was heated in the microwave with stirring at 100°C for 30 mins before being cooled to room temperature and concentrated *in vacuo*. Purification of the residue by trituration with *iso*-hexane and then by HPLC (Waters Symmetry column, aqueous ammonium acetate:acetonitrile) gave the title compound as a
25 colourless solid (25 mg).

MS: APCI(+ve) 404 (M+H⁺).

m.p. 135-138°C.

¹H NMR (400 MHz, CD₃OD) δ 8.21 (1H, d), 8.06 (1H, d), 7.87 (1H, d), 7.76(1H, d), 7.04
30 (2H, t), 6.84 (2H, m), 4.73 (1H, d), 4.17-4.10 (3H, m), 1.23 (3H, d).

Example 14

N-(6-Chloro-2-morpholin-4-yl-quinolin-5-yl)-2-(4-fluoro-phenylamino)-acetamide**a) (6-Chloro-2-morpholin-4-yl-quinolin-5-yl)-carbamic acid tert-butyl ester**

A solution of (2,6-dichloro-5-quinoliny)-[(1,1-dimethylethoxy)carbonyl]-carbamic acid 1,1-dimethylethyl ester (Example 13(a)) (2.07g), morpholine (0.70mL) and triethylamine (1.4mL) were heated in a sealed vessel to 110°C for 4 hours. The reaction was cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between water and ethyl acetate, further extracting with ethyl acetate (2 x 100mL). The combined organic extracts were washed with 10% K₂CO₃ (aq), dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by chromatography (SiO₂, *iso*hexane:ethyl acetate 80:20 as eluant) gave the sub-title compound as a solid (1.9g).

¹H NMR (400 MHz, d₆-DMSO) δ 9.05 (1H, s), 7.96 (1H, d), 7.59 (1H, d), 7.49 (1H, d), 7.33 (1H, d), 3.72 (2H, m), 3.67 (2H, m), 3.52 (2H, m) 3.28 (2H, m), 1.40 (9H, s)

b) 6-Chloro-2-morpholin-4-yl-quinolin-5-ylamine

(6-Chloro-2-morpholin-4-yl-quinolin-5-yl)-carbamic acid tert-butyl ester (Example 14 (a)) (2.2g) in dichloromethane (30mL) was treated with trifluoroacetic acid (10mL) and the reaction was stirred at room temperature overnight. The reaction was concentrated *in vacuo* before dissolving in dichloromethane and washing with saturated sodium hydrogen carbonate. The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo* to give the sub-title compound as a solid (1.0g) which was used in the next step without further purification.

MS: APCI(+ve) 264 (M+H⁺).

c) 2-Chloro-N-(6-chloro-2-morpholin-4-yl-quinolin-5-yl)-acetamide

6-Chloro-2-morpholin-4-yl-quinolin-5-ylamine (Example 14 (b)) (1.0g) in acetone (15mL) was treated with K_2CO_3 (1.57g) and cooled to $0^\circ C$ before the addition of chloroacetyl chloride (0.45mL). The reaction was stirred for 16 hours before being filtered, washing through with acetone. The filtrates were concentrated *in vacuo* and the residue triturated with diethyl ether to give a pale gray solid (0.38g)

MS: APCI(-ve) 388 ($M-H^+$).

d) N-(6-Chloro-2-morpholin-4-yl-quinolin-5-yl)-2-(4-fluoro-phenylamino)-acetamide

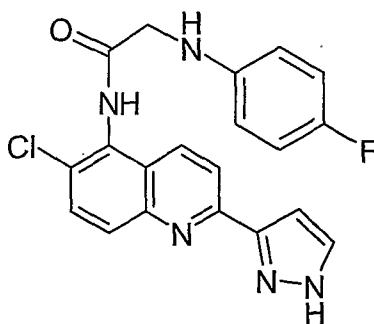
2-Chloro-N-(6-chloro-2-morpholin-4-yl-quinolin-5-yl)-acetamide (Example 14 (c)) (0.2g) in acetonitrile (4mL) was treated with 4-fluoroaniline (0.33g) and diisopropylethylamine (0.53mL) before being heated to $110^\circ C$ for 2 hours. The reaction was cooled to room temperature, concentrated *in vacuo* and triturated with iso-Hexane. The residue was then redissolved in acetonitrile methanol mixture and purified by HPLC (Xterra column, aqueous ammonium acetate:acetonitrile) gave the title compound as a colourless solid (30 mg).

MS: APCI(+ve) 415 ($M+H^+$).

^1H NMR (400 MHz, d_6 -DMSO) δ 9.95 (1H, s), 7.92 (1H, d), 7.59 (1H, d), 7.51 (1H, d), 7.25 (1H, d), 6.99 (2H, m), 6.67 (2H, m), 6.11 (1H, q), 3.97 (2H, d), 3.72-3.65 (8H, complex)

Example 15

N-[6-Chloro-2-(1H-pyrazol-3-yl)-quinolin-5-yl]-2-(4-fluoro-phenylamino)-acetamide.



a) [6-Chloro-2-(1H-pyrazol-3-yl)-quinolin-5-yl]-carbamic acid tert-butyl ester

A solution of (2,6-dichloro-5-quinoliny)-[(1,1-dimethylethoxy)carbonyl]-carbamic acid 1,1-dimethylethyl ester (Example 13(a)) (1.65g), 1H-pyrazole-5-boronic acid (0.9g) cesium carbonate (2.6 g) and tetrakis(triphenylphosphine) palladium(0) (1.2g) were combined and suspended in dioxane (12mL) and water (5mL). The reaction was heated overnight at reflux before being concentrated *in vacuo*. The residue was partitioned between water and dichloromethane, further extracting with dichloromethane (2 x 50mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo* to give the sub-title compound as a solid (1.0g). Progressed to next stage without further purification.

MS: APCI(-ve) 343 (M-H⁺).

b) 6-chloro-2-(1H-pyrazol-3-yl)quinolin-5-amine

[6-Chloro-2-(1H-pyrazol-3-yl)-quinolin-5-yl]-carbamic acid tert-butyl ester (Example 15(a)) (1.0g), was dissolved in 4N HCl in Dioxane (30mL) and stirred for 2 hours. The reaction was concentrated *in vacuo*, partitioned between water and dichloromethane, further extracting with dichloromethane (2 x 50mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by chromatography (SiO₂, isohexane:ethyl acetate 1:1 as eluant) gave the sub-title compound as a solid (0.7g).

MS: APCI(-ve) 245.5 (M-H⁺).

c) 6-Chloro-2-[1-(2-trimethylsilyl-ethoxymethyl)-1H-pyrazol-3-yl]-quinolin-5-ylamine

6-chloro-2-(1H-pyrazol-3-yl)quinolin-5-amine (Example 15(b)) (0.7g) was dissolved in dimethylformamide (10mL) cooled to -10°C and treated with sodium hydride (200mg). The reaction was stirred for 20 minutes before 2-(trimethylsilyl)ethoxymethyl chloride (0.89mL) was added and stirring continued for 18 hours at room temperature. The reaction was partitioned between water and ethyl acetate, further washing the organic layer with water (3 x 50mL). The organic layer was washed with saturated sodium chloride solution, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by chromatography (SiO₂,

isohexane:ethyl acetate 80:20 as eluant) gave the crude sub-title compound as a yellow oil (0.4g) which was used without further purification.

MS: APCI(+ve) 375 ($M+H^+$).

5

d) 2-Chloro-N-{6-chloro-2-[1-(2-trimethylsilyl-ethoxymethyl)-1H-pyrazol-3-yl]-quinolin-5-yl}-acetamide

Chloroacetyl chloride (0.17 mL) was added dropwise to a stirred mixture of 6-Chloro-2-[1-(2-trimethylsilyl-ethoxymethyl)-1H-pyrazol-3-yl]-quinolin-5-ylamine (Example 15 (c)) (0.4 g) and potassium carbonate (0.44 g) in acetone (10 mL) under nitrogen at 0°C. The reaction was concentrated *in vacuo*, partitioned between water and ethyl acetate, further extracting with ethyl acetate (2 x 50mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by chromatography (SiO_2 , isohexane:ethyl acetate 70:30 as eluant) gave the sub-title compound as a yellow oil (0.16g).

15

MS: APCI(-ve) 449 ($M-H^+$).

e) N-{6-Chloro-2-[1-(2-trimethylsilyl-ethoxymethyl)-1H-pyrazol-3-yl]-quinolin-5-yl}-2-(4-fluoro-phenylamino)-acetamide

20

2-Chloro-N-{6-chloro-2-[1-(2-trimethylsilyl-ethoxymethyl)-1H-pyrazol-3-yl]-quinolin-5-yl}-acetamide (Example 15 (d)) (0.16g) was dissolved in acetonitrile (2mL). The solution was treated with 4-fluoroaniline (0.2g) and triethylamine (0.24mL) before being heated to 100°C for 30 minutes. The reaction was cooled to room temperature, concentrated *in vacuo* and triturated with iso-Hexane. The residue was then redissolved in acetonitrile methanol mixture and purified by HPLC (Xterra column, aqueous ammonium acetate:acetonitrile) to give the title compound as a white solid (50 mg).

25

MS: APCI(-ve) 524 ($M-H^+$).

30

f) N-[6-Chloro-2-(1H-pyrazol-3-yl)-quinolin-5-yl]-2-(4-fluoro-phenylamino)-acetamide.

N-{6-Chloro-2-[1-(2-trimethylsilyl-ethoxymethyl)-1H-pyrazol-3-yl]-quinolin-5-yl}-2-(4-fluoro-phenylamino)-acetamide (Example 15 (e)) (40mg) was dissolved in 4N HCl in Dioxane and stirred for 48 hours. The reaction was concentrated *in vacuo*, redissolved in methanol and purified by HPLC (Xterra column, aqueous ammonium acetate:acetonitrile) to give the title compound as a white solid (10 mg).

MS: APCI(-ve) 394 ($M-H^+$).

^1H NMR (400 MHz, CD_3OD) δ 8.17 (2H, d), 8.04 (1H, d), 7.79 (1H, d), 7.76 (1H, broad s), 7.10 (1H, broad s), 6.97 (2H, t), 6.77 (2H, m), 4.07 (2H, s)

Pharmacological Analysis

Certain compounds such as benzoylbenzoyl adenosine triphosphate (bbATP) are known to be agonists of the $P2X_7$ receptor, effecting the formation of pores in the plasma membrane (Drug Development Research (1996), 37(3), p.126). Consequently, when the receptor is activated using bbATP in the presence of ethidium bromide (a fluorescent DNA probe), an increase in the fluorescence of intracellular DNA-bound ethidium bromide is observed. The increase in fluorescence can be used as a measure of $P2X_7$ receptor activation and therefore to quantify the effect of a compound on the $P2X_7$ receptor.

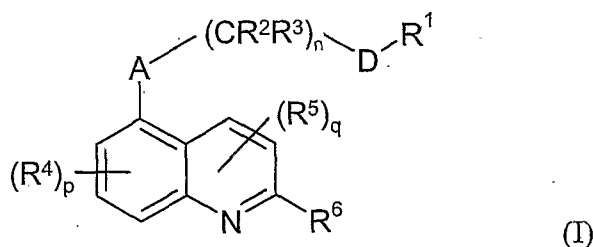
In this manner, each of the title compounds of the Examples was tested for antagonist activity at the $P2X_7$ receptor. Thus, the test was performed in 96-well flat bottomed microtitre plates, the wells being filled with 250 μ l of test solution comprising 200 μ l of a suspension of THP-1 cells (2.5×10^6 cells/ml) containing $10^{-4}M$ ethidium bromide, 25 μ l of a high potassium buffer solution containing $10^{-5}M$ bbATP, and 25 μ l of the high potassium buffer solution containing concentrations of test compound typically from 30 μ M – 0.001 μ M. The plate was covered with a plastics sheet and incubated at 37 °C for one hour. The plate was then read in a Perkin-Elmer fluorescent plate reader, excitation 520 nm, emission 595 nm, slit widths: Ex 15 nm, Em 20 nm. For the purposes of comparison, bbATP (a $P2X_7$ receptor agonist) and pyridoxal 5-phosphate (a $P2X_7$ receptor antagonist) were used separately in the test as controls. From the readings obtained, a pIC_{50} figure was calculated for each test compound, this figure being the negative logarithm of the concentration of test compound necessary to reduce the bbATP agonist

activity by 50%. Each of the compounds of the Examples demonstrated antagonist activity, having a pIC_{50} figure > 5.5 . For example, the following table shows the pIC_{50} figures for a representative selection of compounds:

Compound of Example No.	pIC_{50}
6	6.4
7	7.1

CLAIMS

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof,



wherein

n is 1, 2 or 3;

when n is 1, A represents NHC(O) or NHC(S);

when n is 2 or 3, A represents NHC(O), C(O)NH, NHC(S) or C(S)NH;

D represents O, S or NR⁷, wherein R⁷ represents hydrogen, C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl or C₁₋₆ haloalkyl;

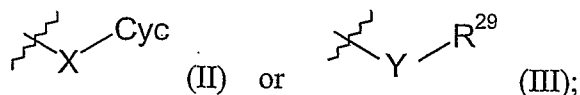
R¹ represents a 6-10 membered aryl, or a 5-10 membered heteroaryl ring, which aryl or heteroaryl ring may be optionally substituted by one or more substituents independently selected from halogen, cyano, C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, NR⁸R⁹, S(O)₀₋₂R¹⁰, S(O)₂NR¹¹R¹², C(O)NR¹³R¹⁴, CO₂R¹⁵, NR¹⁶S(O)₂R¹⁷, C(O)R¹⁸, NR¹⁹C(O)R²⁰, NR²¹C(O)NR²²R²³, NR²⁴S(O)₂NR²⁵R²⁶ and OR²⁷;

within each grouping CR²R³, R² and R³ each independently represent hydrogen, halogen, C₁₋₃ alkyl, C₁₋₃ hydroxyalkyl or C₁₋₃ haloalkyl;

p represents 0, 1, 2 or 3; each R⁴ independently represents halogen, cyano, C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl or C₁₋₆ haloalkyl;

q represents 0, 1 or 2; each R⁵ independently represents halogen, cyano, C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl or C₁₋₆ haloalkyl;

R⁶ represents a group



wherein X represents a bond, O, S, NR³⁰ or a C₁₋₄ alkylene which C₁₋₄ alkylene may be optionally substituted by one or more substituents independently selected from halogen, hydroxy and C₁₋₄ alkoxy;

Cyc represents a 3-8 membered carbocyclic or a 4-8 membered heterocyclic ring, which ring may be optionally substituted by one or more substituents R²⁸, wherein each substituent R²⁸ is independently selected from halogen, cyano, =O, S(O)₂R³¹, C(O)R³², CO₂R³³, C(O)NR³⁴R³⁵, NR³⁶C(O)R³⁷, S(O)₂NR³⁸R³⁹, NR⁴⁰S(O)₂R⁴¹, OR⁴², SR⁴³, NR⁴⁴R⁴⁵, Z¹ or a C₁₋₆ alkyl group which C₁₋₆ alkyl group may be optionally substituted by one or more substituents independently selected from halogen, hydroxyl, C₁₋₆ alkoxy, NR⁴⁶R⁴⁷, S(O)₀₋₂R⁴⁸, C(O)R⁴⁹, CO₂R⁵⁰, C(O)NR⁵¹R⁵², NR⁵³C(O)R⁵⁴, S(O)₂NR⁵⁵R⁵⁶, NR⁵⁷S(O)₂R⁵⁸ and Z²;

Y represents a bond, OC₁₋₆ alkylene, S(O)₀₋₂C₁₋₆alkylene, N(R⁵⁹)C₁₋₆alkylene or C₁₋₆ alkylene, wherein any alkylene group in Y may be optionally substituted by one or more substituents independently selected from halogen, hydroxy and C₁₋₄ alkoxy;

R²⁹ represents hydrogen, halogen, hydroxyl, C₁₋₆alkoxy, cyano, NR⁶⁰R⁶¹, S(O)₀₋₂R⁶², C(O)R⁶³, CO₂R⁶⁴, C(O)NR⁶⁵R⁶⁶, NR⁶⁷C(O)R⁶⁸, S(O)₂NR⁶⁹R⁷⁰, NR⁷¹S(O)₂R⁷² or Z³; with the proviso that when Y is a bond R²⁹ is not hydrogen;

R⁴², R⁴³, R⁴⁴ and R⁴⁵ each independently represent hydrogen or a C₁₋₆ alkyl group which C₁₋₆ alkyl group may be optionally substituted by one or more substituents independently selected from halogen, hydroxyl, C₁₋₆ alkoxy, NR⁷³R⁷⁴, S(O)₀₋₂R⁷⁵, C(O)R⁷⁶, CO₂R⁷⁷, C(O)NR⁷⁸R⁷⁹, NR⁸⁰C(O)R⁸¹, S(O)₂NR⁸²R⁸³, NR⁸⁴S(O)₂R⁸⁵ or Z⁴, or R⁴⁴ and R⁴⁵, together with the nitrogen atom to which they are both attached, may form a 4-8 membered aliphatic heterocyclic ring, which heterocyclic ring may be optionally substituted by one or more substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl and C₁₋₆ haloalkyl;

Z^1, Z^2, Z^3 and Z^4 each independently represent tetrazole, or a 5-6 membered heterocyclic ring, which heterocyclic ring is substituted by one or more substituents independently selected from hydroxy, amino, =O, =S, and which heterocyclic ring may further be
5 optionally substituted by one or more substituents independently selected from halogen and C_{1-6} alkyl;

$R^8, R^9, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{30}, R^{32},$
 $R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{46}, R^{47}, R^{49}, R^{50}, R^{51}, R^{52}, R^{53}, R^{54}, R^{55}, R^{56}, R^{57}, R^{59},$
10 $R^{60}, R^{61}, R^{63}, R^{64}, R^{65}, R^{66}, R^{67}, R^{68}, R^{69}, R^{70}, R^{71}, R^{73}, R^{74}, R^{76}, R^{77}, R^{78}, R^{79}, R^{80}, R^{81}, R^{82},$
 R^{83} and R^{84} each independently represent hydrogen, C_{1-6} alkyl, C_{1-6} hydroxyalkyl or C_{1-6} haloalkyl; or any of R^8 and R^9, R^{11} and R^{12}, R^{13} and R^{14}, R^{22} and R^{23}, R^{25} and R^{26}, R^{34} and
 R^{35}, R^{38} and R^{39}, R^{46} and R^{47}, R^{51} and R^{52}, R^{55} and R^{56}, R^{60} and R^{61}, R^{65} and R^{66}, R^{69} and
 R^{70}, R^{73} and R^{74}, R^{78} and R^{79} , and R^{82} and R^{83} , together with the nitrogen atom to which
15 they are both attached, may form a 4-8 membered aliphatic heterocyclic ring, which
heterocyclic ring may be optionally substituted by one or more substituents independently
selected from halogen, hydroxy, C_{1-6} alkyl, C_{1-6} hydroxyalkyl and C_{1-6} haloalkyl;

$R^{10}, R^{17}, R^{31}, R^{41}, R^{48}, R^{58}, R^{62}, R^{72}, R^{75}$ and R^{85} each independently represent C_{1-6} alkyl,
20 C_{1-6} hydroxyalkyl or C_{1-6} haloalkyl; and

with the proviso that when R^1 is phenyl, D is O, n is 1, R^2 is hydrogen, R^3 is hydrogen, A is
NHC(O), p is 0, q is 0 and R^6 is methyl, then the phenyl group R^1 must be substituted by at
least one substituent other than C_{1-4} alkyl, chlorine and methoxy.

25

2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof,
wherein A represents NHC(O).
3. A compound according to claim 1 or claim 2, or a pharmaceutically acceptable salt
30 thereof, wherein R^1 represents phenyl, which phenyl may be optionally substituted by one
or more substituents independently selected from halogen, cyano, nitro, C_{1-4} alkyl, C_{1-4}

hydroxyalkyl, C₁₋₄ haloalkyl, NR⁸R⁹, S(O)₀₋₂R¹⁰, S(O)₂NR¹¹R¹², C(O)NR¹³R¹⁴, CO₂R¹⁵, NR¹⁶S(O)₂R¹⁷, C(O)R¹⁸, NR¹⁹C(O)R²⁰, NR²¹C(O)NR²²R²³, NR²⁴S(O)₂NR²⁵R²⁶ and OR²⁷.

4. A compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein D represents NR⁷ and R⁷ represents hydrogen, C₁₋₄ alkyl, C₁₋₄ hydroxyalkyl or C₁₋₄ haloalkyl.

5. A compound according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R⁶ represents a group of formula (II)



wherein,

X represents a bond; and

Cyc represents a 4-8 membered heterocyclic ring, which heterocyclic ring may be optionally substituted by one or more substituents R²⁸.

15

6. A compound according to any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein each substituent R²⁸ is independently selected from halogen, OR⁴², NR⁴⁴R⁴⁵ or a C₁₋₄ alkyl group, which C₁₋₄ alkyl group may be optionally substituted by one or more substituents independently selected from halogen, hydroxyl, C₁₋₄ alkoxy, NR⁴⁶R⁴⁷ and C(O)NR⁵¹R⁵²;

20

R⁴², R⁴⁴ and R⁴⁵ each independently represent hydrogen or a C₁₋₄ alkyl group which C₁₋₄ alkyl group may be optionally substituted by one or more substituents independently selected from halogen, hydroxyl, C₁₋₄ alkoxy, NR⁷³R⁷⁴ and C(O)NR⁷⁸R⁷⁹; and R⁴⁶, R⁴⁷, R⁵¹, R⁵², R⁷³, R⁷⁴, R⁷⁸ and R⁷⁹ each independently represent hydrogen or a C₁₋₄ alkyl group which C₁₋₄ alkyl group may be optionally substituted by one or more substituents independently selected from halogen and hydroxyl.

25

7. A compound according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R⁶ represents a group of formula (III),



wherein

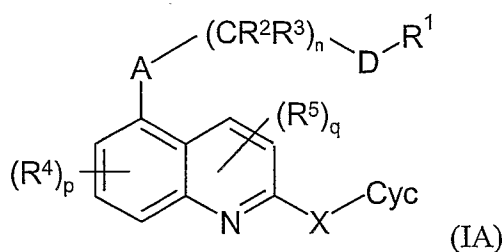
Y represents a bond, OC₁₋₄alkylene, N(R⁵⁹)C₁₋₄alkylene or C₁₋₄ alkylene, wherein any alkylene group in Y may be optionally substituted by one or more substituents independently selected from halogen, hydroxy and C₁₋₄ alkoxy;

5 R⁵⁹ represents hydrogen or C₁₋₄ alkyl;

R²⁹ represents hydrogen, halogen, hydroxyl, C₁₋₄alkoxy, NR⁶⁰R⁶¹ and C(O)NR⁶⁵R⁶⁶; and R⁶⁰, R⁶¹, R⁶⁵ and R⁶⁶ each independently represent hydrogen or a C₁₋₄ alkyl group which C₁₋₄ alkyl group may be optionally substituted by one or more substituents independently selected from halogen and hydroxyl.

10

8. A compound according to claim 1 of formula (IA), or a pharmaceutically acceptable salt thereof,



15 wherein

n is 1;

A represents NHC(O);

D represents O, S or NR⁷, wherein R⁷ represents hydrogen or C₁₋₄ alkyl;

R¹ represents phenyl, which phenyl may be optionally substituted by one or more

20 substituents independently selected from halogen, cyano, nitro, C₁₋₄ alkyl, C₁₋₄ hydroxyalkyl, C₁₋₄ haloalkyl, NR⁸R⁹, S(O)₀₋₂R¹⁰, S(O)₂NR¹¹R¹², C(O)NR¹³R¹⁴, CO₂R¹⁵, NR¹⁶S(O)₂R¹⁷, C(O)R¹⁸, NR¹⁹C(O)R²⁰, NR²¹C(O)NR²²R²³, NR²⁴S(O)₂NR²⁵R²⁶ and OR²⁷;

R² and R³ each independently represent hydrogen or C₁₋₃ alkyl;

p represents 0 or 1; R⁴ represents halogen or C₁₋₄ alkyl;

25 q represents 0 or 1; R⁵ represents halogen or C₁₋₄ alkyl;

X represents a bond,

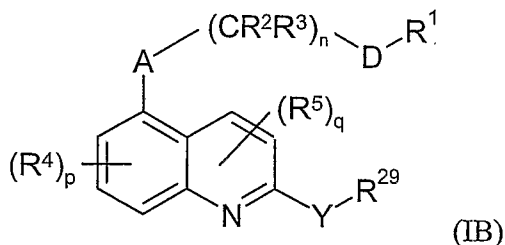
Cyc represents a 4-8 membered heterocyclic ring, which heterocyclic ring may be optionally substituted by one or more substituents R²⁸;

each substituent R^{28} is independently selected from halogen, OR^{42} , $NR^{44}R^{45}$ or a C_{1-4} alkyl group, which C_{1-4} alkyl group may be optionally substituted by one or more substituents independently selected from halogen, hydroxyl, C_{1-4} alkoxy, $NR^{46}R^{47}$ and $C(O)NR^{51}R^{52}$; R^{42} , R^{44} and R^{45} each independently represent hydrogen or a C_{1-4} alkyl group which C_{1-4} alkyl group may be optionally substituted by one or more substituents independently selected from halogen, hydroxyl, C_{1-4} alkoxy, $NR^{73}R^{74}$ and $C(O)NR^{78}R^{79}$; R^{46} , R^{47} , R^{51} , R^{52} , R^{73} , R^{74} , R^{78} and R^{79} each independently represent hydrogen or a C_{1-4} alkyl group which C_{1-4} alkyl group may be optionally substituted by one or more substituents independently selected from halogen and hydroxyl;

R^8 , R^9 , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} and R^{27} each independently represent hydrogen or C_{1-4} alkyl; and

R^{10} and R^{17} each independently represent C_{1-4} alkyl.

9. A compound according to claim 1 of formula (IB), or a pharmaceutically acceptable salt thereof,



wherein

n is 1;

A represents $NHC(O)$;

D represents O, S or NR^7 , wherein R^7 represents hydrogen or C_{1-4} alkyl;

R^1 represents phenyl, which phenyl may be optionally substituted by one or more substituents independently selected from halogen, cyano, nitro, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} haloalkyl, NR^8R^9 , $S(O)_{0-2}R^{10}$, $S(O)_2NR^{11}R^{12}$, $C(O)NR^{13}R^{14}$, CO_2R^{15} , $NR^{16}S(O)_2R^{17}$, $C(O)R^{18}$, $NR^{19}C(O)R^{20}$, $NR^{21}C(O)NR^{22}R^{23}$, $NR^{24}S(O)_2NR^{25}R^{26}$ and OR^{27} ;

R^2 and R^3 each independently represent hydrogen or C_{1-3} alkyl;

p represents 0 or 1; R^4 represents halogen or C_{1-4} alkyl;

q represents 0 or 1; R^5 represents halogen or C_{1-4} alkyl;

Y represents a bond, OC₁₋₄alkylene, N(R⁵⁹)C₁₋₄alkylene or C₁₋₄ alkylene, wherein any alkylene group in Y may be optionally substituted by one or more substituents independently selected from halogen, hydroxy and C₁₋₄ alkoxy;

R⁵⁹ represents hydrogen or C₁₋₄ alkyl;

5 R²⁹ represents hydrogen, halogen, hydroxyl, C₁₋₄alkoxy, NR⁶⁰R⁶¹ and C(O)NR⁶⁵R⁶⁶;

with the proviso that when Y is a bond R²⁹ is not hydrogen; and

R⁶⁰, R⁶¹, R⁶⁵ and R⁶⁶ each independently represent hydrogen or a C₁₋₄ alkyl group which C₁₋₄ alkyl group may be optionally substituted by one or more substituents independently selected from halogen and hydroxyl;

10 R⁸, R⁹, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶ and R²⁷ each independently represent hydrogen or C₁₋₄ alkyl;

R¹⁰ and R¹⁷ each independently represent C₁₋₄ alkyl and

with the proviso that when R¹ is phenyl, D is O, n is 1, R² is hydrogen, R³ is hydrogen, A is NHC(O), p is 0, q is 0 and YR²⁹ represents methyl, then the phenyl group R¹ must be

15 substituted by at least one substituent other than C₁₋₄ alkyl, chlorine and methoxy.

10. A compound according to claim 1, which is selected from:

N-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-2-(phenylamino)- acetamide,

20 *N*-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-2-[(3-chlorophenyl)amino]-acetamide,

N-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-2-[(4-chlorophenyl)amino]-acetamide,

N-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-2-[(2-chlorophenyl)amino]-acetamide,

25 *N*-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-2-phenoxy-acetamide,

N-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-2-(phenylthio)-acetamide ,

N-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-2-[(3-cyanophenyl)amino]-acetamide,

30 *N*-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-2-[(4-cyanophenyl)amino]-acetamide,

N-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-2-[(3-fluorophenyl)amino]-acetamide,

N-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinoliny]-2-[(4-fluorophenyl)amino]-acetamide,

N-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinoliny]-2-[(3,4-difluorophenyl)amino]-acetamide,

5 *N*-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinoliny]-2-[(3,4-difluorophenyl)amino]-propanamide,

N-[6-Chloro-2-(1,2-dihydroxypropyl)-5-quinoliny]-2-[(4-fluorophenyl)amino]-acetamide,

N-(6-Chloro-2-morpholin-4-yl-quinolin-5-yl)-2-(4-fluoro-phenylamino)-acetamide,

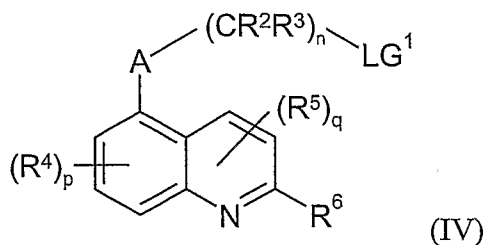
N-[6-Chloro-2-(1*H*-pyrazol-3-yl)-quinolin-5-yl]-2-(4-fluoro-phenylamino)-acetamide

10 or a pharmaceutically acceptable salt thereof.

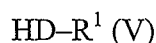
11. A process for the preparation of a compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, which comprises either

(a) reacting a compound of formula (IV)

15



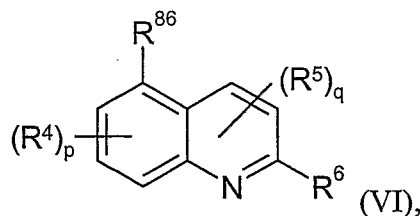
with a compound of formula



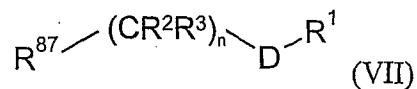
wherein LG¹ represents a leaving group such as a halogeno or sulphonyloxy group and A,

20 D, R¹, R², R³, R⁴, R⁵, R⁶, n, p and q are as defined in formula (I); or

(b) reacting a compound of formula

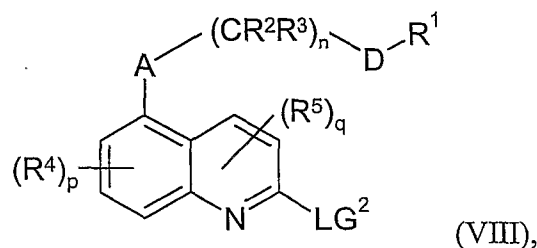


25 with a compound of formula

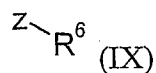


wherein one of R^{86} and R^{87} represents NH_2 and the other of R^{86} and R^{87} represents CO_2H , COF , $COBr$ or $COCl$, and D , X , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , n , p and q are as defined in formula (I); or

(c) reacting a compound of formula



with a compound of formula

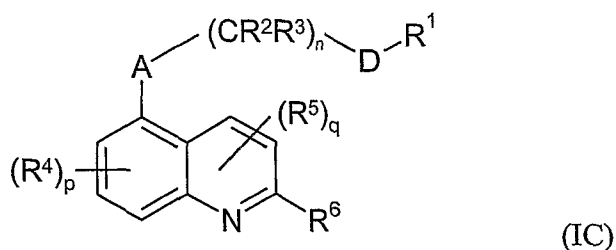


wherein LG^2 represents a leaving group such as a halogeno or sulphonyloxy group, A , D , R^1 , R^2 , R^3 , R^4 , R^5 , n , p and q are as defined in formula (I), z either represents hydrogen when R^6 is attached to z at a heteroatom, otherwise when R^6 is attached to z at a carbon atom, z represents a metallic, organometallic or organosilicon group,

and optionally after (a), (b) or (c), carrying out one or more of the following:

- converting the compound to a further compound of the invention
- forming a pharmaceutically acceptable salt of the compound.

12. A compound of formula (IC), or a pharmaceutically acceptable salt thereof, for use in therapy.



wherein

n is 1, 2 or 3;

when n is 1, A represents NHC(O) or NHC(S);

when n is 2 or 3, A represents NHC(O), C(O)NH, NHC(S) or C(S)NH;

D represents O, S or NR⁷, wherein R⁷ represents hydrogen, C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl or C₁₋₆ haloalkyl;

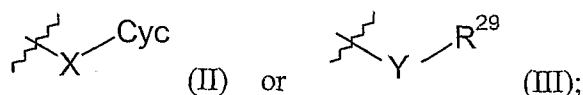
R¹ represents a 6-10 membered aryl, or a 5-10 membered heteroaryl ring, which aryl or heteroaryl ring may be optionally substituted by one or more substituents independently selected from halogen, cyano, C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, NR⁸R⁹, S(O)₀₋₂R¹⁰, S(O)₂NR¹¹R¹², C(O)NR¹³R¹⁴, CO₂R¹⁵, NR¹⁶S(O)₂R¹⁷, C(O)R¹⁸, NR¹⁹C(O)R²⁰, NR²¹C(O)NR²²R²³, NR²⁴S(O)₂NR²⁵R²⁶ and OR²⁷;

within each grouping CR²R³, R² and R³ each independently represent hydrogen, halogen, C₁₋₃ alkyl, C₁₋₃ hydroxyalkyl or C₁₋₃ haloalkyl;

p represents 0, 1, 2 or 3; each R⁴ independently represents halogen, cyano, C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl or C₁₋₆ haloalkyl;

q represents 0, 1 or 2; each R⁵ independently represents halogen, cyano, C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl or C₁₋₆ haloalkyl;

R⁶ represents a group



wherein X represents a bond, O, S, NR³⁰ or a C₁₋₄ alkylene which C₁₋₄ alkylene may be optionally substituted by one or more substituents independently selected from halogen, hydroxy and C₁₋₄ alkoxy;

Cyc represents a 3-8 membered carbocyclic or a 4-8 membered heterocyclic ring, which ring may be optionally substituted by one or more substituents R²⁸, wherein each

substituent R²⁸ is independently selected from halogen, cyano, =O, S(O)₂R³¹, C(O)R³², CO₂R³³, C(O)NR³⁴R³⁵, NR³⁶C(O)R³⁷, S(O)₂NR³⁸R³⁹, NR⁴⁰S(O)₂R⁴¹, OR⁴², SR⁴³, NR⁴⁴R⁴⁵, Z¹ or a C₁₋₆ alkyl group which C₁₋₆ alkyl group may be optionally substituted by one or more substituents independently selected from halogen, hydroxyl, C₁₋₆ alkoxy, NR⁴⁶R⁴⁷, S(O)₀₋₂R⁴⁸, C(O)R⁴⁹, CO₂R⁵⁰, C(O)NR⁵¹R⁵², NR⁵³C(O)R⁵⁴, S(O)₂NR⁵⁵R⁵⁶, NR⁵⁷S(O)₂R⁵⁸ and Z²;

Y represents a bond, OC₁₋₆ alkylene, S(O)₀₋₂C₁₋₆alkylene, N(R⁵⁹)C₁₋₆alkylene or C₁₋₆ alkylene, wherein any alkylene group in Y may be optionally substituted by one or more substituents independently selected from halogen, hydroxy and C₁₋₄ alkoxy;

R²⁹ represents hydrogen, halogen, hydroxyl, C₁₋₆alkoxy, cyano, NR⁶⁰R⁶¹, S(O)₀₋₂R⁶²,
 5 C(O)R⁶³, CO₂R⁶⁴, C(O)NR⁶⁵R⁶⁶, NR⁶⁷C(O)R⁶⁸, S(O)₂NR⁶⁹R⁷⁰, NR⁷¹S(O)₂R⁷² or Z³;
 with the proviso that when Y is a bond R²⁹ is not hydrogen;

R⁴², R⁴³, R⁴⁴ and R⁴⁵ each independently represent hydrogen or a C₁₋₆ alkyl group which
 C₁₋₆ alkyl group may be optionally substituted by one or more substituents independently
 selected from halogen, hydroxyl, C₁₋₆ alkoxy, NR⁷³R⁷⁴, S(O)₀₋₂R⁷⁵, C(O)R⁷⁶, CO₂R⁷⁷,
 10 C(O)NR⁷⁸R⁷⁹, NR⁸⁰C(O)R⁸¹, S(O)₂NR⁸²R⁸³, NR⁸⁴S(O)₂R⁸⁵ or Z⁴, or R⁴⁴ and R⁴⁵, together
 with the nitrogen atom to which they are both attached, may form a 4-8 membered
 aliphatic heterocyclic ring, which heterocyclic ring may be optionally substituted by one or
 more substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, C₁₋₆
 hydroxyalkyl and C₁₋₆ haloalkyl;

15 Z¹, Z², Z³ and Z⁴ each independently represent tetrazole, or a 5-6 membered heterocyclic
 ring, which heterocyclic ring is substituted by one or more substituents independently
 selected from hydroxy, amino, =O, =S, and which heterocyclic ring may further be
 optionally substituted by one or more substituents independently selected from halogen
 and C₁₋₆ alkyl;

20 R⁸, R⁹, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R³⁰, R³²,
 R³³, R³⁴, R³⁵, R³⁶, R³⁷, R³⁸, R³⁹, R⁴⁰, R⁴⁶, R⁴⁷, R⁴⁹, R⁵⁰, R⁵¹, R⁵², R⁵³, R⁵⁴, R⁵⁵, R⁵⁶, R⁵⁷, R⁵⁹,
 R⁶⁰, R⁶¹, R⁶³, R⁶⁴, R⁶⁵, R⁶⁶, R⁶⁷, R⁶⁸, R⁶⁹, R⁷⁰, R⁷¹, R⁷³, R⁷⁴, R⁷⁶, R⁷⁷, R⁷⁸, R⁷⁹, R⁸⁰, R⁸¹, R⁸²,
 R⁸³ and R⁸⁴ each independently represent hydrogen, C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl or C₁₋₆
 haloalkyl; or any of R⁸ and R⁹, R¹¹ and R¹², R¹³ and R¹⁴, R²² and R²³, R²⁵ and R²⁶, R³⁴ and
 25 R³⁵, R³⁸ and R³⁹, R⁴⁶ and R⁴⁷, R⁵¹ and R⁵², R⁵⁵ and R⁵⁶, R⁶⁰ and R⁶¹, R⁶⁵ and R⁶⁶, R⁶⁹ and
 R⁷⁰, R⁷³ and R⁷⁴, R⁷⁸ and R⁷⁹, and R⁸² and R⁸³, together with the nitrogen atom to which
 they are both attached, may form a 4-8 membered aliphatic heterocyclic ring, which
 heterocyclic ring may be optionally substituted by one or more substituents independently
 selected from halogen, hydroxy, C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl and C₁₋₆ haloalkyl; and
 30 R¹⁰, R¹⁷, R³¹, R⁴¹, R⁴⁸, R⁵⁸, R⁶², R⁷², R⁷⁵ and R⁸⁵ each independently represent C₁₋₆ alkyl,
 C₁₋₆ hydroxyalkyl or C₁₋₆ haloalkyl.

13. A pharmaceutical composition comprising a compound of formula (IC), or a pharmaceutically acceptable salt thereof, as defined in claim 12 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

5 14. A process for the preparation of a pharmaceutical composition as claimed in claim 13 which comprises mixing a compound of formula (IC), or a pharmaceutically acceptable salt thereof, as defined in claim 12 with a pharmaceutically acceptable adjuvant, diluent or carrier.

10 15. Use of a compound of formula (IC), or a pharmaceutically acceptable salt thereof, as defined in claim 12, in the manufacture of a medicament for use in the treatment of rheumatoid arthritis.

15 16. Use of a compound of formula (IC), or a pharmaceutically acceptable salt thereof, as defined in claim 12, in the manufacture of a medicament for use in the treatment of osteoarthritis.

17. Use of a compound of formula (IC), or a pharmaceutically acceptable salt thereof, as defined in claim 12, in the manufacture of a medicament for use in the treatment of asthma
20 or chronic obstructive pulmonary disease.

18. Use of a compound of formula (IC), or a pharmaceutically acceptable salt thereof, as defined in claim 12, in the manufacture of a medicament for use in the treatment of inflammatory bowel disease.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE2007/000699

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D, A61K

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

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEM ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN International, File REGISTRY, Registry Copyright 14 July 2006 ACS on STN RN: 892733-99-2 --	1-3,7,9
P,X	STN International, File REGISTRY, Registry Copyright 08 August 2006 ACS on STN RN: 899526-58-0 --	1-3,7,9
X	WO 2005009968 A1 (ASTRAZENECA AB), 3 February 2005 (03.02.2005) --	1-18
A	WO 2004106305 A1 (ASTRAZENECA AB), 9 December 2004 (09.12.2004) --	1-18

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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

"E" earlier application or patent 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

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Date of mailing of the international search report

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Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE2007/000699**C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2006059945 A1 (ASTRAZENECA AB), 8 June 2006 (08.06.2006) --	1-18
A	WO 03045313 A2 (MERCK & CO. INC.), 5 June 2003 (05.06.2003) -- -----	1-18

International patent classification (IPC)**C07D 401/04** (2006.01)**A61K 31/47** (2006.01)**A61K 31/4709** (2006.01)**A61P 19/02** (2006.01)**C07D 215/38** (2006.01)**Download your patent documents at www.prv.se**

The cited patent documents can be downloaded at www.prv.se by following the links:

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- e-tjänster/anförda dokument(service in Swedish).

Use the application number as username.

The password is **GUPZPUWEVT**.

Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

INTERNATIONAL SEARCH REPORT
Information on patent family members

01/09/2007

International application No.
PCT/SE2007/000699

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Information on patent family members

01/09/2007

International application No.

PCT/SE2007/000699

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