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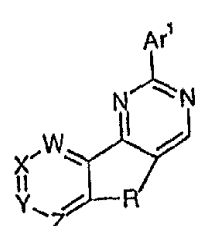
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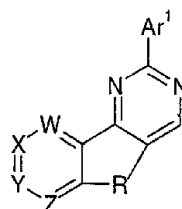
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(21) International Application Number: PCT/SE97/01219 (22) International Filing Date: 4 July 1997 (04.07.97) (30) Priority Data: 9614360.7 9 July 1996 (09.07.96) GB 9626884.2 24 December 1996 (24.12.96) GB (71) Applicant (for all designated States except MG US): ASTRA PHARMACEUTICALS LTD. [GB/GB]; Home Park, Kings Langley, Herts WD4 8DH (GB). (71) Applicant (for MG only): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): BANTICK, John [GB/GB]; 78 Melton Road, Burton-on-the-Wolds, Leics LE12 5HG (GB). PERRY, Matthew [GB/GB]; 11 Kenilworth Avenue, Loughborough, Leics LE11 4SL (GB). THORNE, Philip [GB/GB]; 20 Bainbridge Road, Loughborough, Leics LE11 2LE (GB). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: NOVEL COMPOUNDS (57) Abstract The invention relates to pharmaceutically useful pyrimidine compounds of formula (I), methods for their preparation, their use as medicaments, and pharmaceutical formulations including them.  (I)		

NOVEL COMPOUNDS

This invention relates to pharmaceutically useful compounds, methods for their preparation, their use as medicaments, and pharmaceutical formulations including them.

Certain pyridinocyclohexano-1,3-pyrimidines are known from Heterocycles, **43**, 391 (1996) and European Patent Application 0 260 642 A2. 2-Aryl substituents are not mentioned. It has now surprisingly been found that a series of structurally distinct quinazoline and pyrimidine derivatives exhibit anti-allergic and anti-inflammatory activity.

In a first aspect the invention therefore provides a compound of formula I:



(I)

wherein

R represents $(CH_2)_n$, $CH=CH$, BCH_2 or CH_2B where B is O or S;

n is 1 to 3;

Ar^1 represents thiazolyl, phenyl, pyridyl, pyrimidinyl, 2-benzothiazolyl, 2- or 3-quinolyl or 2-quinoxaliny, all of which are optionally substituted by one or more substituents selected from halo, nitro, cyano, phenyl, phenylsulfonyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, $COOH$, $COO(C_{1-6} \text{ alkyl})$, $CONH_2$, C_{1-6} alkyl substituted by phenyl, or phenyl, in which any alkyl, alkoxy, alkylthio and alkylsulfinyl groups may optionally be substituted by one or more fluorine atoms;

W represents CH, CA or N;

X represents CH, CA, N or N^+-O^- ;

Y represents CH, CA, N or N^+-O^- ;

Z represents CH, CA, N or N^+-O^- ;

A represents hydroxy, halogen, nitro, cyano, phenyl, C_{1-6} thioalkyl, CO_2R^1 , NR^2R^3 ,

$NR^4C(O)R^5$, methoxy (optionally substituted by CO_2R^6), C_{1-6} alkyl or C_{2-6} alkoxy (which

latter two groups are optionally substituted by one or more substituents selected from NH_2 , hydroxy or CO_2R^7 ;

R^2 represents H or C_{1-6} alkyl and R^3 represents H, C_{1-6} alkyl or CH_2Ar^2 or R^2 and R^3 together with the nitrogen atom to which they are attached form a pyrrolidiny or piperidiny ring;

5 R^5 represents H, C_{1-5} alkyl or Ar^3 ;

R^1 , R^4 , R^6 and R^7 independently represent H or C_{1-6} alkyl;

Ar^2 and Ar^3 independently represent phenyl optionally substituted by one or more substituents selected from halogen, hydroxy, methoxy (optionally substituted by fluorine), phenoxy, C_{2-6} alkoxy and C_{1-6} alkyl (which latter three groups are optionally substituted by one or more substituents selected from halogen, hydroxy or C_{1-6} alkyl);

10 provided that:

(a) when one of X, Y and Z represent N^+-O^- , W and the other two groups all represent CH;

(b) W may only represent N when Y represents N and X and Z both represent CH;

(c) X may only represent N when Z represents CH or N, W represents CH and Y represents CH or CA;

15 (d) Y may only represent N when W represents N or CH and X and Z both represent CH;

(e) Z may only represent N when X represents N or CH, W represents CH and Y represents CH or CA;

(f) when only one of X or Z represent N then Y represents CH;

20 (g) when A represents C_{2-6} alkoxy substituted by hydroxy, halogen (other than fluorine) or NH_2 , or when Ar^1 , Ar^2 or Ar^3 are substituted by C_{2-6} alkoxy substituted by halogen (other than fluorine) or hydroxy, then the hydroxy, halogen or NH_2 substituent as appropriate is not attached to the same carbon atom as the oxygen is; and

(h) when W, X, Y and Z are all CH, R is $(\text{CH}_2)_2$ or OCH_2 then Ar^1 is not unsubstituted phenyl,

25 or a pharmaceutically acceptable derivative thereof.

Pharmaceutically acceptable derivatives includes solvates, salts and N-oxides. For example the compounds of the formula (I) can form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, 30 hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric and methanesulfonic acids.

The compounds of the invention may exhibit tautomerism. All tautomeric forms and mixtures thereof are included within the scope of the invention.

35

The compounds of the invention may also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism. All diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various optical isomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation, or by derivatisation or salt formation, for example with a homochiral acid followed by separation of the diastereomeric derivatives by conventional means (e.g. HPLC, chromatography over silica, or, in the case of salts, crystallisation). All stereoisomers are included within the scope of the invention.

Alkyl groups, whether alone or as part of another group, may be linear or branched.

Preferably R represents $\text{CH}=\text{CH}$, OCH_2 or $(\text{CH}_2)_n$ where n is 1, 2 or 3. Most preferably R represents $(\text{CH}_2)_n$ where n is 2 or R represents $\text{CH}=\text{CH}$.

Preferably Ar^1 represents thiazolyl optionally substituted by methyl, phenyl optionally substituted by chloro, CF_3 , CONH_2 , or methyl or Ar^1 represents pyridyl or pyridyl N-oxide optionally substituted by chloro, CF_3 , methyl or methoxy. When present, substituents on phenyl or pyridyl groups are preferably para with respect to the linkage to the remainder of the molecule. Preferred substituents are halo and C_{1-6} alkyl. Most preferably Ar^1 represents pyridyl substituted by chloro or methyl, particularly 3-pyridyl substituted by methyl.

Preferably W, X, Y and Z form an optionally substituted phenyl, pyridyl or pyrimidine ring. More preferably W, X, Y and Z are all CH; W is CH, X is N, Y is CH or CA and Z is N; W and Y are both N and X and Z are both CH or one of X, Y or Z is N or N^+-O^- , and the others together with W are all CH. Preferred groups A include C_{1-6} alkyl, C_{1-6} alkoxy and amino, particularly methyl, methoxy or amino groups.

Most preferably W and Y are both CH, X is CH or N and Z is N.

Preferred compounds of the invention include:

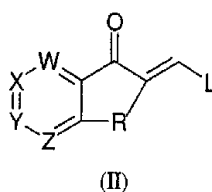
2-(4-Chlorophenyl)-5,6-dihydro-8-methylpyrimido[4,5-f]quinazoline,
2-(4-Chlorophenyl)-5,6-dihydro-8-methoxypyrimido[4,5-f]quinazoline,
2-(4-Chlorophenyl)-5,6-dihydropyrimido[5,4-h]quinazoline,

- 2-(4-Chlorophenyl)-5,6-dihydropyrido[3,4-h]quinazoline,
2-(4-Chlorophenyl)-5,6-dihydro-8-methylthiopyrimido[4,5-f]quinazoline,
2-(4-Chlorophenyl)-5,6-dihydropyrimido[4,5-f]quinazoline,
2-(4-Chlorophenyl)-5,6-dihydropyrido[3,4-h]quinazoline-8-oxide,
5 2-(4-Chlorophenyl)-5,6-dihydropyrimido[4,5-f]quinazoline-8-amine,
5,6-Dihydro-2-(pyridin-3-yl)pyrimido[4,5-f]quinazoline,
5,6-Dihydro-2-(pyridin-2-yl)pyrimido[4,5-f]quinazoline,
5,6-Dihydro-2-(6-methylpyridin-3-yl)pyrimido[4,5-f]quinazoline,
5,6-Dihydro-2-(6-methylpyridin-3-yl-N-oxide)-pyrimido[4,5-f]quinazolin-8-amine,
10 2-(4-Chlorophenyl)-6,7-dihydro-5H-pyrido[2,3-i]cycloheptapyrimidine,
2-(4-Chlorophenyl)-5,6-dihydropyrido[2,3-h]quinazoline,
2-(Pyridin-3-yl)-5,6-dihydropyrido[2,3-h]quinazoline,
2-(6-Methylpyridin-3-yl)-5,6-dihydropyrido[2,3-h]quinazoline,
2-(4-Chlorophenyl)-5,6-dihydropyrido[2,3-h]quinazoline, 7-oxide,
15 2-(4-Chlorophenyl)-5,6-dihydropyrido[4,3-h]quinazoline,
5,6-Dihydro-2-(pyridin-3-yl)-pyrido[4,3-h]quinazoline,
2-(Pyridin-3-yl)-pyrido[4,3-h]quinazoline,
2-(4-Chlorophenyl)-5,6-dihydropyrido[4,3-h]quinazoline, 9-oxide,
5,6-Dihydro-2-(6-methoxypyridin-3-yl)pyrimido[4,5-f]quinazoline,
20 2-(6-Chloropyridin-3-yl)-5,6-dihydropyrimido[4,5-f]quinazoline,
2-(6-Methylpyridin-3-yl)-pyrimido[4,5-f]quinazoline,
2-(4-Chlorophenyl)-5H-[1]benzopyrano[4,3-d]pyrimidine,
2-(4-Chlorophenyl)-5H-indeno[1,2-d]pyrimidine,
2-Phenyl-5H-[1]benzopyrano[4,3-d]pyrimidine,
25 2-Pyridin-4-yl-5H-[1]benzopyrano[4,3-d]pyrimidine,
2-(Pyridin-4-yl)-N-oxide-5H-[1]benzopyrano[4,3-d]pyrimidine,
2-Pyridin-2-yl-5H-[1]benzopyrano[4,3-d]pyrimidine,
2-Pyridin-3-yl-5H-[1]benzopyrano[4,3-d]pyrimidine,
2-(6-Methylpyridin-3-yl)-5H-[1]benzopyrano[4,3-d]pyrimidine,
30 2-(6-Chloropyridin-3-yl)-5H-[1]benzopyrano[4,3-d]pyrimidine,
2-Pyrazin-2-yl-5H-[1]benzopyrano[4,3-d]pyrimidine,
2-(6-Trifluoromethylpyridin-2-yl)-5H-[1]benzopyrano[4,3-d]pyrimidine,
2-(2-Methylthiazol-4-yl)-5H-[1]benzopyrano[4,3-d]pyrimidine,
4-(5H-[1]benzopyrano[4,3-d]pyrimidin-2-yl)benzenecarboxamide,
35 2-(6-methylpyridin-3-yl)-5,6-dihydropyrido[4,3-h]quinazoline,

and pharmaceutically acceptable derivatives thereof.

According to the invention there is also provided a process for the preparation of the compounds of the invention which comprises:

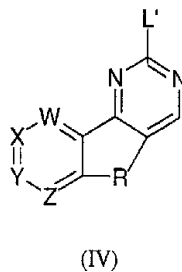
- 5 (a) reaction of a compound of formula (II):



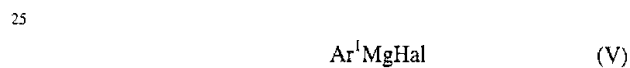
- 10 in which W, X, Y, Z and R are as defined in formula (I) and L is a leaving group with a compound of formula (III) or a salt thereof:



- 15 in which Ar^1 is as defined in formula (I); or
 (b) for compounds of formula (I) where Y is N or CA and A is H, NH_2 , C_{1-6} alkyl or C_{1-6} alkoxy, reaction of a compound of formula (IV):



20 in which W, X, Y, Z and R are as defined in formula (I) and L' is a leaving group with a compound of formula (V):



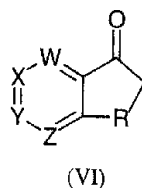
25 wherein Hal represents Cl or Br and Ar^1 is as defined in formula (I).
 and optionally thereafter (a) or (b):

- converting the compound of formula (I) into a further compound of formula (I)
- forming a pharmaceutically acceptable derivative.

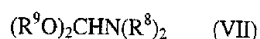
5 In compounds of formula (II) L is a suitable leaving group such as OR^8 or $N(R^8)_2$ where R^8 is C_{1-6} alkyl such as methyl or ethyl. Preferably L is NMe_2 . Reaction of compounds of formulae (II) and (III) is suitably carried out in the presence of a base, for example sodium methoxide, in an organic solvent such as methanol or ethanol. The reaction can be carried out at elevated temperature, for example at reflux temperature.

10 For compounds of formula (IV) L' is a leaving group, preferably thioalkyl, in particular thiomethyl. Compounds of formula (IV) and (V) can be reacted together in the presence of a suitable catalyst (e.g. 1,3-bis(disphenylphosphino)propane nickel dichloride) and an appropriate organic solvent (e.g. tetrahydrofuran) at ambient temperature.

15 Compounds of formula (II) may be prepared by reaction of a compound of formula VI:



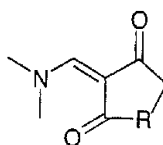
20 wherein W, X, Y, Z and R are as defined in formula (I) with a compound of formula (VII):



25 in which R^8 groups are as defined in above and R^9 groups are C_{1-6} alkyl. Preferably R^8 groups are both methyl and R^9 groups are both methyl or ethyl. Preferred compounds of formula (VII) include *N,N*-dimethylformamide dimethyl acetal. Preferably the compound of formula (VII) is used in excess in the absence of additional solvent and the reaction is carried out at elevated temperature such as reflux temperature.

30 Compounds of formula (II) where L is OR^8 can be prepared analogously to the methods described by Nasipuri et al in *Indian J. Chem.* **10**, 897, (1972).

Compounds of formula (VI) are known in the literature (see e.g. East German Patent 62 062; Chem. Pharm. Bull., (1983) **31**, 4554; J. Pharm. Soc. Jpn. (1956) **76**, 1308; J. Chem. Soc., Perkin Trans. 1 (1984) 2297; and Arch. Pharm., (1961), **294**, 759) or are available using known techniques. For example compounds of formula VI wherein X and Z both
5 represent N may be prepared by reaction of a compound of formula VIII:



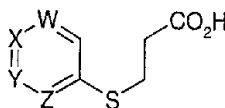
(VIII)

10

wherein R is as defined in formula (I), with a compound of formula IX:



15 wherein A is as hereinbefore defined for example at reflux in the presence of a suitable organic solvent (e.g. ethanol). Compounds of formula (VI) where R is SCH₂ and W, X, Y and Z are CA/CA can be prepared by dehydrative cyclisation of a compound of formula (X):



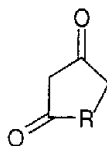
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(X)

in the presence of a suitable dehydrating agent such as polyphosphoric acid at elevated temperature.

25

Compounds of formula (VIII) may be prepared by reaction of a compound of formula XI:



(XI)

wherein R is as defined in formula (I) with *N,N*-dimethylformamide dimethyl acetal, for example under reflux.

Compounds of formula (III) are either commercially available or are readily available using known techniques. For example compounds of formula (III) may be prepared by reaction of a compound of formula XII:



wherein Ar^1 is as hereinbefore defined with ammonium chloride, for example at about 90°C in the presence of trimethylaluminium and an appropriate organic solvent (e.g. toluene).

Compounds of formula (IV) may be prepared by reaction of a corresponding compound of formula II wherein Y represents N or CR^{3a} and R^{3a} is as hereinbefore defined with 2-methyl-2-thiopseudourea or a hydrohalide salt thereof, for example at reflux in the presence of a suitable base (e.g. sodium ethoxide) and an appropriate organic solvent (e.g. ethanol).

Compounds of formula (I) can be converted into further compounds of formula (I) using procedures known in the art. For example:

(a) Preparation of a compound of formula (I) wherein R represents $\text{CH}=\text{CH}$ can be carried out by heating the corresponding compound of formula (I) wherein R is CH_2CH_2 to, for example, about 170°C in an inert solvent (e.g. dimethyl acetamide) in the presence of an appropriate catalyst (e.g. palladium on carbon or platinum on carbon)

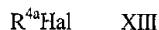
(b) Preparation of a compound of formula (I) wherein Y represents CH and R represents $(\text{CH}_2)_n$ by hydrogenolysis of a corresponding compound of formula (I) wherein Y represents CA where A represents C_{1-6} thioalkyl, for example at about 100°C in the presence of a suitable catalyst (e.g. Raney nickel) and an appropriate organic solvent (e.g. dimethylacetamide).

(c) Preparation of a compound of formula (I) wherein one of X, Y or Z represent N^+-O^- and when n represents 1 and R^1 and R^2 both represent H by oxidation of a corresponding

compound of formula (I) wherein one of X, Y or Z as appropriate represent N, in the presence of a suitable oxidizing agent (e.g. 3-chloroperbenzoic acid) and an appropriate organic solvent (e.g. dichloromethane).

- 5 (d) Preparation of a compound of formula (I) wherein Y represents CA and A represents NH_2 , X and Z both represent N and R represents $(\text{CH}_2)_n$ by reaction of a corresponding compound of formula (I) where A is $\text{R}^{10}\text{SO}_2^-$ wherein R^{10} represents C_{1-6} alkyl with ammonia at elevated temperature for example at about 180°C in dioxan in a bomb.

- 10 (e) preparation of a compound of formula (I), wherein A represents $\text{NR}^4\text{C}(\text{O})\text{R}^5$, R^4 represents C_{1-6} alkyl and R^5 is as hereinbefore defined, by reaction of a corresponding compound of formula (I), wherein R^4 represents H with a compound of formula XIII:



- wherein R^{4a} represents C_{1-6} alkyl and Hal represents Cl, Br or I, for example at room
15 temperature in the presence of a suitable base (e.g. potassium carbonate) and an appropriate organic solvent (e.g. dimethylformamide);

- (f) preparation of a compound of formula (I), wherein A represents $\text{NR}^4\text{C}(\text{O})\text{R}^5$ and R^4 and R^5 are as hereinbefore defined, by reaction of a corresponding compound of formula (I),
20 wherein A represents NR^{2a}H wherein R^{2a} represents H or C_{1-6} alkyl and corresponds with R^4 , with a compound of formula XIV:



- wherein R^5 is as hereinbefore defined, for example at room temperature in the presence of an appropriate peptide synthesis agent (e.g. dicyclohexylcarbodiimide and catalytic
25 4-dimethylaminopyridine) and a suitable organic solvent (e.g. dichloromethane or dimethylformamide);

- (g) preparation of a compound of formula (I), wherein A represents NR^2R^3 , R^2 represents H or C_{1-6} alkyl and R^3 represents C_{1-6} alkyl or CH_2Ar^2 , by reduction of a corresponding
30 compound of formula (I), wherein A represents $\text{NR}^4\text{C}(\text{O})\text{R}^5$, wherein R^4 is as hereinbefore defined and corresponds with R^2 , and R^5 is as hereinbefore defined and corresponds with Ar^2 when it represents Ar^3 , for example at room temperature in the presence of a suitable reducing agent (e.g. borane) and an appropriate organic solvent (e.g. tetrahydrofuran);

- 35 (h) preparation of a compound of formula (I), wherein A represents NR^2H and R^2 represents H or C_{1-6} alkyl, by hydrolysis of a corresponding compound of formula (I), wherein A

represents $\text{NR}^4\text{C}(\text{O})\text{CH}_3$ and R^4 is as hereinbefore defined and corresponds with R^2 , for example at reflux in the presence of aqueous acid (e.g. hydrochloric acid);

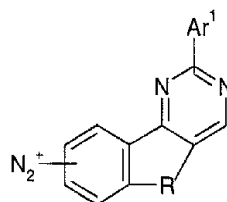
- (i) preparation of a compound of formula (I), wherein A represents NR^2R^3 and R^2 and R^3 represent C_{1-6} alkyl or, together with the nitrogen atom to which they are attached form a pyrrolidiny1 or piperidiny1 ring, by reaction of a corresponding compound of formula (I), wherein A represents NH_2 , with a compound of formula XV:



- wherein R^x represents C_{1-5} alkyl or $\text{HC}(\text{O})\text{Z}^1$, wherein Z^1 represents C_{2-3} alkylene, and a suitable reducing agent (e.g. sodium cyanoborohydride) for example at room temperature in the presence of zinc chloride and appropriate organic solvent (e.g. methanol);

- (j) preparation of a compound of formula (I) wherein A represents cyano by reaction of a corresponding compound of formula (I) wherein A represents bromine with copper (I) cyanide, for example at reflux in the presence of *N*-methylpyrrolidone;

- (k) when W, X, Y and Z are all CH preparation of a compound of formula (I) wherein A represents fluorine by reaction of a compound of formula XVI:



(XVI)

- wherein R and Ar^1 are as hereinbefore defined, with sodium tetrafluoroborate, for example by heating to 170°C in the presence of a suitable organic solvent (e.g. 1,2-dichlorobenzene); or, alternatively, when the counter-ion is tetrafluoroborate, preparation of such a compound of formula I by heating the diazonium salt to 170°C , in the presence of a suitable organic solvent (e.g. 1,2-dichlorobenzene);

- (l) when W, X, Y and Z are all CH preparation of a compound of formula (I) wherein A represents nitro by reaction of a diazonium salt of formula (XVI) as hereinbefore defined with

sodium nitrite, for example at room temperature in the presence of copper powder and an appropriate solvent (e.g. water);

(m) when W, X, Y and Z are all CH preparation of a compound of formula (I) wherein A represents chlorine by reaction of a diazonium salt of formula (XVI) as hereinbefore defined with copper (I) chloride, for example by warming in a suitable solvent (e.g. aqueous ethanol);

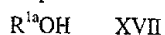
(n) when W, X, Y and Z are all CH preparation of a compound of formula (I) wherein A represents bromine by reaction of a diazonium salt of formula (XVI) as hereinbefore defined with copper (I) bromide, for example by warming in a suitable solvent (e.g. aqueous ethanol);

(o) when W, X, Y and Z are all CH preparation of a compound of formula (I) wherein A represents iodine by reaction of a diazonium salt of formula (XVI) as hereinbefore defined with potassium iodide, for example by warming in a suitable solvent (e.g. aqueous ethanol);

(p) preparation of a compound of formula (I) wherein A represents NH_2 by reduction of a corresponding compound of formula (I) wherein A represents nitro in the presence of a suitable reducing agent (e.g. iron and ammonium chloride) for example by heating to reflux in the presence of a suitable solvent (e.g. aqueous ethanol);

(q) preparation of a compound of formula (I) wherein A represents CO_2H by hydrolysis of a corresponding compound of formula (I), wherein A represents cyano under appropriate conditions for example by refluxing in the presence of 50% sulphuric acid;

(r) preparation of a compound of formula (I) wherein A represents CO_2R^1 and R^1 represents C_{1-6} alkyl, by esterification of a corresponding compound of formula (I), wherein A represents CO_2H , in the presence of a compound of formula XVII:



wherein R^1a represents C_{1-6} alkyl, and a suitable acid or base catalyst or activating agent (e.g. thionyl chloride);

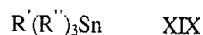
(s) preparation of a compound of formula (I) wherein A represents hydroxy by hydrolysis of a corresponding compound of formula (I) wherein A represents C_{1-6} alkoxy, for example between 0 and -78°C in the presence of a suitable Lewis acid (e.g. boron tribromide or aluminium tribromide) and an appropriate organic solvent (e.g. dichloromethane or ethanethiol);

(t) preparation of a compound of formula (I) wherein A represents C₁₋₆ alkoxy, by reaction of a corresponding compound of formula (I) wherein A represents hydroxy with a compound of formula XVIII:



wherein R' represents C₁₋₆ alkyl and Hal is as hereinbefore defined, for example at room temperature in the presence of base (e.g. sodium hydride) and an appropriate organic solvent (e.g. dimethylformamide);

(u) preparation of a compound of formula (I) wherein A represents C₁₋₆ alkyl, by reaction of a corresponding compound of formula (I) wherein A represents hydroxy with a compound of formula XIX:



wherein R'' represents C₁₋₄ alkyl and R' is as hereinbefore defined, for example by heating up to reflux temperature in the presence of a suitable catalyst system (e.g. palladium on activated carbon and triphenylphosphine or dichloro(triphenylphosphine)palladium, lithium chloride and 2,6-di-*tert*-butyl-4-methylphenol) and an appropriate organic solvent (e.g. dimethylformamide or dioxane); or alternatively activating the OH group with the use of an appropriate activating agent (e.g. trifluoromethanesulphonic anhydride);

(v) preparation of a compound of formula (I) wherein A represents phenyl, by reaction of a corresponding compound of formula (I) wherein A represents bromine with phenylboric acid, for example by refluxing in the presence of cesium fluoride and tetrakis(triphenylphosphine)palladium(0) and an appropriate organic solvent (e.g. dimethoxyethane);

(w) preparation of a compound of formula (I) wherein A represents methoxy substituted by CO₂R⁶ or C₂₋₆ alkoxy substituted by CO₂R⁷ and R⁶ and/or R⁷ as appropriate represent C₁₋₆ alkyl, by reaction of a corresponding compound of formula (I) wherein A represents hydroxy with a compound of formula XX:



wherein Z² represents C₁₋₆ alkylene, R^y represents C₁₋₆ alkyl and Hal is as hereinbefore defined, for example at room temperature in the presence of a suitable base (e.g. potassium carbonate) and an appropriate organic solvent (e.g. dimethylformamide); alkylene groups which Z² may represent being linear or branched;

(x) preparation of a compound of formula (I) wherein A represents C₁₋₆ alkoxy substituted by CO₂H, by hydrolysis of a corresponding compound of formula (I) wherein A represents methoxy substituted by CO₂R⁶ or C₂₋₆ alkoxy substituted by CO₂R⁷ and R⁶ and/or R⁷ as appropriate represent C₁₋₆ alkyl, for example at room temperature in the presence of a
5 suitable hydrolytic agent (e.g. lithium hydroxide) and an appropriate organic/aqueous solvent system (e.g. tetrahydrofuran/water).

Other starting compounds referred to above are either commercially available, are well known in the literature, or are available using known techniques. Novel intermediate
10 compounds disclosed above form a further aspect of the invention.

The compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

15 It will be appreciated by those skilled in the art that in the process steps described above the functional groups of intermediate compounds may need to be protected by protecting groups. The protection of functional groups may take place before any the process steps hereinbefore described. Protecting groups may be removed following a reaction step or at the end of the reaction process using techniques which are well known to those skilled in the art. The use
20 of protecting groups is fully described in "Protective Groups in Organic Chemistry", edited by J W F McOmie, Plenum Press (1973), and "Protective Groups in Organic Synthesis", 2nd edition, T W Greene & P G M Wutz, Wiley-Interscience (1991).

The compounds of the invention are useful because they possess pharmacological activity.
25 The invention therefore provides a compound of formula (I) for use in therapy.

In particular the compounds of the invention possess antiallergic and antiinflammatory activity, for example as shown in the tests described below.

30 The compounds of the invention are thus indicated for use in the treatment of allergic and inflammatory diseases of the airways such as asthma (e.g. bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma and dust asthma), particularly chronic or inveterate asthma (e.g. late asthma and airway hyper-responsiveness), bronchitis and the like.

35

Further, the compounds of the invention are indicated in the treatment of diseases including inflammations/allergies such as rhinitis, including all conditions characterised by inflammation of the nasal mucus membrane, such as acute rhinitis, allergic rhinitis, atrophic rhinitis, chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta and rhinitis sicca, rhinitis medicamentosa, membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis, scrofulous rhinitis, seasonal rhinitis including rhinitis nervosa (hay fever) and vasomotor rhinitis.

The compounds of the invention are also indicated for use in the treatment of chronic allergic disorders, atopic dermatitis, cutaneous eosinophilias, eosinophilic fascitis, hyper IgE syndrome, vernal conjunctivitis, systemic lupus erythematosus, thyroiditis, lepromatous leprosy, sezary syndrome, chronic graft versus host disease, myasthenia gravis, idiopathic thrombocytopenia pupura and the like.

The compounds of the invention may also have activity in both the prophylactic and therapeutic treatment of acquired immunodeficiency syndrome (AIDS), the prevention of chronic rejection of allografts mediated by humoral immunity, and in the treatment of autoimmune diseases such as multiple sclerosis and rheumatoid arthritis.

Of particular interest amongst the above indications are the use of the compounds of the invention in asthma, especially the prophylaxis of asthma, and in rhinitis, most particularly allergic rhinitis and seasonal rhinitis including rhinitis nervosa (hay fever).

According to a further aspect of the present invention, there is provided a method of treatment or prophylaxis of an allergic or an inflammatory disorder, which method comprises administration of a therapeutically effective amount of a compound of formula I as defined above, or a pharmaceutically acceptable derivative thereof, to a person suffering from, or susceptible to such a disorder.

In a still further aspect the invention provides use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the treatment or prophylaxis of the above disorders, especially asthma, and in rhinitis, most particularly allergic rhinitis and seasonal rhinitis including rhinitis nervosa (hay fever).

Administration of the compounds of the invention may be topical (for example by inhalation to the lung). The compounds of the invention may be inhaled as a dry powder which may be pressurized or non-pressurized.

- 5 In non-pressurized powder compositions, the active ingredient in finely divided form may be used in admixture with a larger sized pharmaceutically acceptable inert carrier

The composition may alternatively be pressurized and contain a compressed gas, e.g. nitrogen, or a liquefied gas propellant. In such pressurized compositions, the active
10 ingredient is preferably finely divided. The pressurized composition may also contain a surface active agent. The pressurized compositions may be made by conventional methods.

The compounds of the invention may be administered systemically (for example by oral administration to the gastrointestinal tract). The active ingredient may be formulated
15 together with known adjuvants, diluents or carriers using conventional techniques to produce tablets or capsules for oral administration to the gastrointestinal tract.

Examples of suitable adjuvants, diluents or carriers for oral administration in the form of tablets, capsules and dragees include microcrystalline cellulose, calcium phosphate,
20 diatomaceous earth, a sugar such as lactose, dextrose or mannitol, talc, stearic acid, starch, sodium bicarbonate and/or gelatine.

According to a further aspect of the invention there is provided a pharmaceutical composition including a compound of formula I as hereinbefore defined, or a
25 pharmaceutically acceptable derivative thereof, in association with a pharmaceutically acceptable adjuvant diluent or carrier.

Suitable doses for administration topical or orally are in the range 0.01 to $30\text{mgkg}^{-1}\text{day}^{-1}$,
30 for example $0.3\text{mgkg}^{-1}\text{day}^{-1}$.

It will be understood by those skilled in the art that certain functional groups in the compounds of the invention may be protected using appropriate protecting groups to form "protected derivatives" of the compounds of the invention. It will also be appreciated that, although such protected derivatives may not possess pharmacological activity as such, they
35 may be administered and thereafter metabolised in the body to form the compound of the invention which is pharmacologically active. Such derivatives may therefore be described

as "prodrugs". All protected derivatives and prodrugs of compounds of formula I are included within the scope of the invention.

The invention is illustrated by the following examples:

5

Example 1**2-(4-Chlorophenyl)-5,6-dihydro-8-methylpyrimido[4,5-f]quinazoline**

6,7-Dihydro-2-methylquinazoline-5(8H)-one (East German Patent 62 062; 530mg) and dimethylformamide dimethylacetal (1ml) were heated to reflux for 35 minutes. The
10 reaction was allowed to cool to ambient temperature and the volatiles were evaporated. The residue was dissolved in ethanol (2ml) then 4-chlorophenylbenzamidinium hydriodide (130mg) and sodium methoxide (25mg) were added and the solution was heated to reflux for 75 minutes. The solvent was evaporated and the residue was dissolved in ethyl acetate (25ml). The ethyl acetate solution was washed with water (twice) and brine, then dried,
15 filtered and evaporated. Chromatography eluting with ethyl acetate gave the title compound (48mg).

MS(EI) 308/310 (M⁺)

mp 186-187°C

¹H NMR (DMSO) δ 2.69(3H,s), 3.10(4H,s), 7.61(2H,d), 8.52(2H,d), 8.84(1H,s),
20 9.49(1H,s).

Example 2**2-(4-Chlorophenyl)-5,6-dihydro-8-methoxypyrimido[4,5-f]quinazoline**

Prepared following the method of Example 1 above using 6,7-dihydro-2-methoxyquinazoline-5(8H)-one (East German Patent 62 062; 1.0g) and
25 dimethylformamide dimethylacetal (2ml), followed by 4-chlorophenylbenzamidinium hydriodide (1.6g) and sodium methoxide (300mg) to give the title compound (550mg).

MS(EI) 324/326 (M⁺)

mp 192°C

¹H NMR (DMSO) δ 3.07(4H,s), 4.00(3H,s), 7.59(2H,d), 8.50(2H,d), 8.78(1H,s),
30 9.42(1H,s).

Example 3**2-(4-Chlorophenyl)-5,6-dihydropyrimido[5,4-h]quinazoline**

Prepared following the method of Example 1 above from 5,6-dihydroquinazolin-8(7H)-one (Chem. Pharm. Bull., (1983) 31, 4554; 180mg) and dimethylformamide dimethylacetal (1ml), followed by 4-chlorophenylbenzamidinium hydride (350mg) and sodium methoxide (70mg) to give the title compound (24mg).

MS(APCI) 294/296 ((M - H))

mp 190°C

¹H NMR (DMSO) δ 3.07(4H,s), 7.64(2H,d), 8.50(2H,d), 8.91(1H,s), 8.98(1H,s), 9.32(1H,s).

Example 4**2-(4-Chlorophenyl)-5,6-dihydropyrido[3,4-h]quinazoline**

Prepared following the method of Example 1 above from 6,7-dihydroisoquinolin-5(8H)-one (J. Pharm. Soc. Jpn. (1956) 76, 1308; 900mg) and dimethylformamide dimethylacetal (2ml), followed by 4-chlorophenylbenzamidinium hydride (1.75g) and sodium methoxide (340mg) to give the title compound (700mg).

MS(APCI) 294/296 ((M + H)⁺)

mp 160-162°C

¹H NMR (DMSO) δ 3.02(4H,s), 7.62(2H,d), 8.25(1H,d), 8.51(2H,d), 8.66(1H,d), 8.69(1H,s), 8.89(1H,s).

Example 5**2-(4-Chlorophenyl)-5,6-dihydro-8-methylthiopyrimido[4,5-f]quinazoline**

Prepared following the method of Example 1 above using 6,7-dihydro-2-methylthioquinazoline-5(8H)-one (East German Patent 62 062; 1.0g) and dimethylformamide dimethylacetal (2ml), followed by 4-chlorophenylbenzamidinium hydride (1.45g) and sodium methoxide (278mg) to give the title compound (526mg).

MS (APCI) 341/343 ((M + H)⁺)

mp >200°C dec.

¹H NMR (DMSO) δ 2.59(3H,s), 3.08(4H,s), 7.58(2H,d), 8.49(2H,d), 8.79(1H,s), 9.40(1H,s).

Example 6**2-(4-Chlorophenyl)-5,6-dihydropyrimido[4,5-f]quinazoline**

2-(4-Chlorophenyl)-5,6-dihydro-8-methylthiopyrimido[4,5-f]quinazoline (see Example 5 above; 200mg) and Raney Nickel (10g) in dimethylacetamide (30ml) were heated for 2
5 hours at 100°C. The reaction mixture was allowed to cool and filtered. The nickel was washed with dimethylacetamide and the filtrate was concentrated. The residue was purified by chromatography eluting with dichloromethane:ethyl acetate (1:1), then reverse-phase HPLC eluting with aqueous ammonium acetate:methanol mixtures, and finally recrystallised from aqueous methanol to give the title compound (57mg).
10 MS(EI) 294/296 (M⁺)
mp 157-158°C
¹H NMR (DMSO) δ 3.15(4H,s), 7.60(2H,d), 8.53(2H,d), 8.88(1H,s), 9.21(1H,s), 9.61(1H,s).

Example 7**2-(4-Chlorophenyl)-5,6-dihydropyrido[3,4-h]quinazoline-8-oxide**

2-(4-Chlorophenyl)-5,6-dihydropyrido[3,4-h]quinazoline (see Example 4 above; 220mg) was dissolved in dichloromethane (20ml). 3-Chloroperbenzoic acid (230mg) was added and the reaction was stirred overnight. The reaction was quenched with sodium
20 metabisulfite solution and then diluted with more dichloromethane. The reaction mixture was washed with sodium bicarbonate solution and was then dried, filtered and evaporated. The residue was recrystallised from THF:isohexane and then recrystallised from toluene to give the title compound (93mg).
MS(APCI) 310/312 ((M + H)⁺)
25 mp 245°C
¹H NMR (DMSO) δ 2.98(4H,m), 7.60(2H,d), 8.26(1H,dd), 8.30(1H,d), 8.36(1H,d), 8.49(2H,d), 8.82(1H,s).

Example 8**2-(4-Chlorophenyl)-5,6-dihydropyrimido[4,5-f]quinazoline-8-amine****(a) 2-(4-Chlorophenyl)-5,6-dihydro-8-methylsulfonylpyrimido[4,5-f]quinazoline**

2-(4-Chlorophenyl)-5,6-dihydro-8-methylthiopyrimido[4,5-f]quinazoline (see Example 5 above; 260mg) was dissolved in chloroform (20ml) and *m*-chloroperbenzoic acid (430mg)
35 was added. The reaction was stirred overnight and then quenched with sodium metabisulfite solution. The organic layer was evaporated and the residue was partitioned

between ethyl acetate and sodium bicarbonate solution. The ethyl acetate phase was washed with aqueous sodium bicarbonate and then brine, dried, filtered and evaporated to give the sub-title compound (200mg).

MS(APCI) 373/375 ((M + H)⁺), MS(ESI) 373/375 ((M + H)⁺)

5 mp 225°C

¹H NMR (DMSO) δ 3.19(2H,t), 3.37(2H,t), 3.43(3H,s), 7.50(2H,d), 8.47(2H,d), 8.78(1H,s), 9.77(1H,s).

(b) 2-(4-Chlorophenyl)-5,6-dihydropyrimido[4,5-f]quinazoline-8-amine

10 2-(4-Chlorophenyl)-5,6-dihydro-8-methylsulfonylpyrimido[4,5-f]quinazoline (from step (a) above; 80mg) was dissolved in dioxan (15ml) and ammonia solution (density 0.88; 10ml) was added. The mixture was heated to 100°C for 2 hours in a bomb. The volatiles were evaporated and the residue was purified by chromatography eluting with dioxan:isohexane mixtures, and then reverse-phase HPLC eluting with aqueous ammonium acetate:methanol mixtures. Freeze-drying of appropriate fractions gave the title compound
15 (15mg).

MS(APCI) 310/312 ((M + H)⁺)

mp 273-275°C

20 ¹H NMR (DMSO) δ 2.86(2H,t), 2.99(2H,t), 7.33(2H,br s), 7.57(2H,d), 8.47(2H,d), 8.65(1H,s), 9.13(1H,s).

Example 9

5,6-Dihydro-2-(pyridin-3-yl)pyrimido[4,5-f]quinazoline

25 **(a) 5,6-Dihydro-8-methylthio-2-(pyridin-3-yl)pyrimido[4,5-f]quinazoline**

Prepared following the method of Example 1 above using 6,7-dihydro-2-methylthioquinazoline-5(8H)-one (East German Patent, 62 062; 1.0g) and dimethylformamide dimethylacetal (2ml), followed by 3-pyridylamidine hydrochloride (1.0g) and sodium methoxide (460mg) to give the sub-title compound (800mg).

30 MS(APCI) 308 ((M + H)⁺)

¹H NMR (DMSO) δ 2.60 (3H, s), 3.08 (4H, brs), 7.55 (1H, dd), 8.71 (1H, dd), 8.77 (1H, ddd), 8.83 (1H, s), 9.45 (1H, s), 9.61 (1H, d)

(b) 5,6-Dihydro-2-(pyridin-3-yl)pyrimido[4,5-f]quinazoline

Prepared following the method of Example 6 above using 5,6-dihydro-8-methylthio-2-(pyridin-3-yl)pyrimido[4,5-f]quinazoline (from step (a) above; 800mg) and Raney Nickel (10g) to give the title compound (110mg).

5 MS(APCI) 262 ((M + H)⁺)

mp 187-188°C

¹H NMR (DMSO) δ 3.16(4H,s), 7.59(1H,dd), 8.74(1H,dt), 8.83(1H,dt), 8.92(1H,s), 9.22(1H,s), 9.65(1H,d), 9.67(1H,s).

10 **Example 10**

5,6-Dihydro-2-(pyridin-2-yl)pyrimido[4,5-f]quinazoline**(a) 5,6-Dihydro-8-methylthio-2-(pyridin-2-yl)pyrimido[4,5-f]quinazoline**

Prepared following the method of Example 1 above using 6,7-dihydro-2-methylthioquinazoline-5(8H)-one (East German Patent, 62 062; 1.0g) and dimethylformamide dimethylacetal (3.5ml), followed by 2-pyridylamine hydrochloride (0.81g) and sodium methoxide (460mg) to give the sub-title compound (1.0g).

MS(APCI) 308 ((M + H)⁺)

15 ¹H NMR (DMSO) δ 2.60 (3H, s), 3.11 (4H, m), 7.54 (1H, td), 8.00 (1H, td), 8.51 (1H, d), 8.78 (1H, dd), 8.88 (1H, s), 9.36 (1H, s)

(b) 5,6-Dihydro-2-(pyridin-2-yl)pyrimido[4,5-f]quinazoline

Prepared following the method of Example 6 above using 5,6-dihydro-8-methylthio-2-(pyridin-2-yl)pyrimido[4,5-f]quinazoline (from step (a) above; 1.0g) and Raney Nickel (13g) to give the title compound (260mg).

MS(APCI) 262 (M + H)

mp 177-179°C

25 ¹H NMR (DMSO) δ 3.18(4H,s), 7.55(1H,br dd), 8.00(1H,td), 8.53(1H,d), 8.79(1H,br d), 8.94(1H,s), 9.21(1H,s), 9.55(1H,s).

30

Example 11**5,6-Dihydro-2-(pyridin-3-yl-N-oxide)-pyrimido[4,5-f]quinazoline**

5,6-Dihydro-2-(pyridin-3-yl)pyrimido[4,5-f]quinazoline (see Example 9 above; 60mg) was dissolved in dichloromethane (10ml) and *m*-chloroperbenzoic acid (100mg) added. The reaction was stirred for 130 minutes and was then quenched with sodium metabisulfite solution. The organic phase was washed with aqueous sodium bicarbonate solution, dried

35

and evaporated. The residue was purified by chromatography and then HPLC eluting with dichloromethane:methanol mixtures to give the title compound (20mg).

MS(APCI) 278 ((M + H)⁺)

¹H NMR (DMSO) δ 3.17 (4H, s), 7.60 (1H, t), 8.38 (2H, t), 8.94 (1H, s), 9.12 (1H, br s),
5 9.22 (1H, s), 9.69 (1H, s).

Example 12

5,6-Dihydro-2-(6-methylpyridin-3-yl)pyrimido[4,5-f]quinazoline

10 (a) 6-Methyl-3-pyridylamidine hydrochloride

Trimethylaluminium (2M in hexanes; 15ml) was added to a vigorously stirred suspension of ammonium chloride (1.65g) in toluene (25ml) cooled in an ice bath. The cooling bath was removed and the reaction allowed to attain room temperature. 6-Methyl-pyridine-3-carbonitrile (1.18g) was added and the reaction was heated to 90°C overnight. The reaction
15 was allowed to cool to room temperature then methanol was added dropwise. The mixture was poured onto a slurry of alumina (25g) in chloroform (225ml). Methanol (100ml) was added and the slurry was stirred for 30 minutes. The mixture was filtered, the solid was washed with methanol and the combined filtrates were concentrated to give the sub-title compound (2.78g) contaminated with ammonium chloride.

20 MS(APCI) 136 ((M + H)⁺)

¹H NMR (DMSO) δ 2.57 (3H, s), 7.35 (4H, brs), 7.50 (1H, d), 8.19 (1H, dd), 8.89 (1H, d)

(b) 5,6-Dihydro-8-methylthio-2-(6-methylpyridin-3-yl)pyrimido[4,5-f]quinazoline

Prepared following the method of Example 1 above using 6,7-dihydro-2-methylthioquinazoline-5(8H)-one (East German Patent 62 062; 1.0g) and
25 dimethylformamide dimethylacetal (3ml), followed by 6-methyl-3-pyridylamidine (freed the hydrochloride salt (from step (a) above) as follows: the hydrochloride was added to saturated sodium bicarbonate solution (excess), the solution was evaporated, the resultant residue was extracted with ethanol and the ethanol was filtered and then evaporated to give
30 the free base (0.60g)) and sodium methoxide (230mg) to give the sub-title compound (1.10g).

MS(APCI) 322 ((M + H)⁺)

¹H NMR (DMSO) δ 2.55 (3H, s), 2.58 (3H, s), 3.08 (4H, s), 7.41 (1H, d), 8.66 (1H, dd),
8.80 (1H, s), 9.43 (1H, s), 9.47 (1H, d).

(c) **5,6-Dihydro-2-(6-methylpyridin-3-yl)pyrimido[4,5-f]quinazoline**

Prepared following the method of Example 6 above using 5,6-dihydro-8-methylthio-2-(6-methylpyridin-3-yl)pyrimido[4,5-f]quinazoline (from step (b) above; 1.10g) and Raney Nickel (11.7g) to give the title compound (110mg).

5 MS(APCI) 276 ((M + H)⁺)

mp 157-158°C

¹H NMR (DMSO) δ 2.57(3H,s), 3.15(4H,s), 7.43(1H,d), 8.70(1H,dd), 8.88(1H,s), 9.21(1H,s), 9.51(1H,sd), 9.63(1H,s).

10 **Example 13**

5,6-Dihydro-2-(6-methylpyridin-3-yl-N-oxide)-pyrimido[4,5-f]quinazolin-8-amine

(a) **5,6-Dihydro 2-(6-methylpyridin-3-yl-N-oxide)-8-methylsulfonylpyrimido[4,5-f]quinazoline**

15 5,6-Dihydro-8-methylthio-2-(6-methylpyridin-3-yl)pyrimido[4,5-f]quinazoline (see Example 12(b) above; 500mg) and 3-chloroperbenzoic acid (900mg) were dissolved in dichloromethane (30ml) and stirred for 2 hours at room temperature. The reaction was quenched with sodium metabisulfite solution. The reaction mixture was partitioned between dichloromethane and aqueous sodium bicarbonate, the aqueous layer was
20 extracted with dichloromethane, and then the organic phases were combined, dried, filtered and evaporated to give the sub-title compound (270mg).

MS(APCI) 370 ((M + H)⁺)

¹H NMR (CDCl₃) δ 2.63 (3H, s), 3.22 (2H, t), 3.38 (2H, t), 3.45 (3H, s), 7.43 (1H, d), 8.28 (1H,dd), 8.81 (1H, s), 9.42 (1H, d), 9.75 (1H, s)

25

(b) **5,6-Dihydro-2-(6-methylpyridin-3-yl-N-oxide)-pyrimido[4,5-f]quinazolin-8-amine**

Prepared following the method of Example 8 above using 5,6-dihydro 2-(6-methylpyridin-3-yl-N-oxide)-8-methylsulfonylpyrimido[4,5-f]quinazoline (from step (a) above; 210mg) and 0.88 density ammonia solution (6ml) to give the title compound (75mg)

30 MS(APCI) 307 ((M + H)⁺)

mp >250°C

¹H NMR (DMSO) δ 2.44 (3H s), 2.86(2H,t), 3.02(2H,t), 7.37(2H,br s), 7.65(1H,d), 8.22(1H,dd), 8.68(1H,s), 9.09(1H,d), 9.16(1H,s).

Example 14**2-(4-Chlorophenyl)-6,7-dihydro-5H-pyrido[2,3-i]cycloheptapyrimidine**

Prepared following the method of Example 1 above using 6,7,8,9-tetrahydrocyclohepta-
pyridin-5(5H)-one (J. Chem. Soc., Perkin Trans. 1 (1984) 2297; 600mg) and

5 dimethylformamide dimethylacetal (5ml), followed by 4-chlorophenylbenzamidine
hydriodide (640mg) and sodium methoxide (180mg) to give the title compound (526mg).

MS(APCI) 308/310 ((M + H)⁺)

mp 143-145°C

¹H NMR (DMSO) δ 2.37 (2H, quin), 2.57 (2H, t), 2.75 (2H, t), 7.54 (1H, dd), 7.60 (2H, d),
10 8.22 (1H, dd), 8.47 (2H, d), 8.65 (1H, dd), 8.87 (1H, s)

Example 15**2-(4-Chlorophenyl)-5,6-dihydropyrido[2,3-h]quinazoline**

Prepared following the method of Example 1 above from 6,7-dihydroquinoline-5-(8H)-one
15 (Arch. Pharm. (1961) 294, 759; 150mg) and dimethylformamide dimethylacetal (0.5ml),
followed by 4-chlorophenylbenzamidine hydrochloride (152mg) and sodium methoxide
(43mg) to give the title compound (82mg).

MS(APCI) 294/6 ((M + H)⁺)

mp 133-134°C

20 ¹H NMR (d6-DMSO) δ 3.15 (m, 4H), 7.50 (dd, 1H), 7.60 (d, 2H), 8.50 (d, 2H), 8.65 (dd,
1H), 8.75 (dd, 1H), 8.85 (s, 1H)

Example 16**2-(Pyridin-3-yl)-5,6-dihydropyrido[2,3-h]quinazoline**

25 Prepared following the method of Example 1 above from 6,7-dihydroquinoline-5-(8H)-one
(Arch. Pharm. (1961) 294, 759; 150mg) and dimethylformamide dimethylacetal (0.5ml),
followed by 3-amidinopyridine hydrochloride (125mg) and sodium methoxide (43mg) to
give the title compound (47mg).

MS(APCI) 261 ((M + H)⁺)

30 mp 101-102°C

¹H NMR (d6-DMSO) δ 3.15 (m, 4H), 7.50 (dd, 1H), 7.60 (dd, 1H), 8.65 (dd, 1H), 8.75 (d,
1H), 8.80 (m, 2H), 8.90 (s, 1H), 9.65 (s, 1H)

Example 17**2-(6-Methylpyridin-3-yl)-5,6-dihydropyrido[2,3-h]quinazoline**

Prepared following the method of Example 1 above from 6,7-dihydroquinoline-5-(8H)-one (Arch. Pharm. (1961) **294**, 759; 400mg) and dimethylformamide dimethylacetal (2ml),

5 followed by 6-methyl-3-pyridylamidine hydrochloride (see Example 12(a) above; 300mg) and sodium methoxide (120mg) to give the title compound (225mg).

MS(APCI) 275 ((M + H)⁺)

mp 114-145°C

¹H NMR (d6-DMSO) δ 2.60 (s, 3H), 3.15 (m, 4H), 7.40 (d, 1H), 7.50 (dd, 1H), 8.60-8.70
10 (m, 2H), 8.75 (dd, 1H), 8.85 (s, 1H), 9.50 (s, 1H)

Example 18**2-(4-Chlorophenyl)-5,6-dihydropyrido[2,3-h]quinazoline, 7-oxide**

2-(4-Chlorophenyl)-5,6-dihydropyrido[2,3-h]quinazoline (see Example 15 above; 60mg)
15 was oxidised with 3-chloroperbenzoic acid (85mg) following the method of Example 11 above to give the title compound (29mg).

MS(APCI) 310/2 ((M + H)⁺)

mp 208-209°C

¹H NMR (d6-DMSO) δ 3.10 (t, 2H), 3.25 (t, 2H), 7.50 (t, 1H), 7.60 (d, 2H), 8.35 (d, 1H),
20 8.45 (d, 1H), 8.50 (d, 2H), 8.90 (s, 1H)

Example 19**2-(4-Chlorophenyl)-5,6-dihydropyrido[4,3-h]quinazoline**

Prepared following the method of Example 1 above using 6,7-dihydroisoquinoline-8-(5H)-
25 one (J. Pharm. Soc. Jpn., (1956) **76**, 1308; 400mg) dimethylformamide dimethylacetal (2ml), 4-chlorobenzamidine hydrochloride (475mg) and sodium methoxide (135mg) to give the title compound (175mg).

MS(APCI) 294/6 ((M + H)⁺)

mp 152-153°C

¹H NMR (d6-DMSO) δ 3.02 (s, 4H), 7.43 (d, 1H), 7.61 (d, 2H), 8.53 (d, 2H), 8.63 (d, 2H),
30 8.83 (s, 1H), 9.51 (s, 1H)

Example 20**5,6-Dihydro-2-(pyridin-3-yl)-pyrido[4,3-h]quinazoline**

35 Prepared following the method of Example 1 above using 6,7-dihydroisoquinoline-8-(5H)-one (J. Pharm. Soc. Jpn., (1956) **76**, 1308; 400mg) dimethylformamide dimethylacetal

(2ml), 3-amidinopyridine hydrochloride (390mg) and sodium methoxide (135mg) to give, after chromatography, the title compound (124mg).

MS(APCI) 261 ((M + H)⁺)

mp 151-152°C

¹H NMR (d6-DMSO) δ 3.04 (s, 4H), 7.43 (d, 1H), 7.57-7.62 (m, 1H), 8.63 (d, 1H), 8.73 (dd, 1H), 8.80 (dt, 1H), 8.86 (s, 1H), 9.54 (s, 1H), 9.63 (d, 1H)

Example 21

2-(Pyridin-3-yl)-pyrido[4,3-h]quinazoline

The title compound (11mg) also was isolated from the previous Example.

MS(APCI) 259 ((M + H)⁺)

mp 243-244°C

¹H NMR (d6-DMSO) δ 7.59-7.63 (dd, 1H), 7.98 (d, 1H), 8.04 (d, 1H), 8.23 (d, 1H), 8.7 (dd, 1H), 8.92 (d, 1H), 9.01-9.05 (m, 1H), 9.72 (s, 1H), 9.87 (d, 1H), 10.59 (s, 1H)

Example 22

2-(4-Chlorophenyl)-5,6-dihydropyrido[4,3-h]quinazoline, 9-oxide

2-(4-Chlorophenyl)-5,6-dihydropyrido[4,3-h]quinazoline (see Example 19 above; 290mg) was oxidised with 3-chloroperbenzoic acid (285mg) following the method of Example 7 above to give the title compound (107mg).

MS(APCI) 310/2 ((M + H)⁺)

mp 228-230°C

¹H NMR (d6-DMSO) δ 3.01 (bs, 4H), 7.48 (d, 1H), 7.60 (d, 2H), 8.30 (dd, 1H), 8.51 (d, 2H), 8.89 (s, 1H), 8.99 (s, 1H)

Example 23

5,6-Dihydro-2-(6-methoxypyridin-3-yl)pyrimido[4,5-f]quinazoline

(a) 6-Methoxypyridin-3-ylamidine hydrochloride

Prepared following the method of Example 12(a) above using trimethylaluminium (9.5ml of a 2M solution), ammonium chloride (1.10g) and 6-methoxypyridin-3-carbonitrile (1.218g) to give the sub-title compound (2.02g; containing ammonium chloride).

MS(APCI) 152 ((M + H)⁺)

¹H NMR (DMSO) δ 3.95 (3H, s), 7.06 (1H, d), 8.14 (1H, dd), and 8.69 (1H, d).

(b) 5,6-Dihydro-2-(6-methoxypyridin-3-yl)pyrimido[4,5-f]quinazoline

Prepared following the method of Example 1 above using 6,7-dihydroquinazoline-5(8H)-one (East German Patent 62 062; 151mg), dimethylformamide dimethylacetal (0.75ml), 6-methoxypyridin-3-ylamidine (liberated from the hydrochloride (430mg; from step (a) above) by dissolution in excess aqueous sodium bicarbonate solution, then evaporation to give a solid which was triturated with ethanol, which was filtered and evaporated) and sodium methoxide (54mg) to give the title compound (89mg).

mp 212-213.5°C

MS(APCI) 292 ((M + H)⁺)

¹H NMR (DMSO) δ 3.15 (4H, s), 3.96 (3H, s), 6.99 (1H, d), 8.74 (1H, dd), 8.86 (1H, s), 9.21 (1H, s), 9.30 (1H, d) and 9.65 (1H, s).

Example 24**2-(6-Chloropyridin-3-yl)-5,6-dihydropyrimido[4,5-f]quinazoline****(a) 6-Chloropyridin-3-ylamidine hydrochloride**

Prepared following the method of Example 12(a) above using trimethylaluminium (4.5ml of a 2M solution), ammonium chloride (0.54g) and 6-chloropyridin-3-carbonitrile (0.75g) to give the sub-title compound (0.85g; containing ammonium chloride).

MS(APCI) 156/158 ((M + H)⁺)

¹H NMR (DMSO) δ 7.84 (1H, d), 8.26 (1H, dd), and 8.83 (1H, d)

(b) 5,6-Dihydro-2-(6-chloropyridin-3-yl)pyrimido[4,5-f]quinazoline

Prepared following the method of Example 1 above using 6,7-dihydroquinazoline-5(8H)-one (East German Patent 62 062; 145mg), dimethylformamide dimethylacetal (1.5ml) and 6-chloropyridin-3-ylamidine (liberated from the hydrochloride (290mg) from step (a) above by dissolution in excess aqueous sodium bicarbonate solution, then evaporation to give a solid, extraction of the solid with ethanol, filtration and evaporation) to give the title compound (62mg).

mp 186-187°C

MS(APCI) 296/298 ((M + H)⁺)

¹H NMR (DMSO) δ 3.17 (4H, s), 7.71 (1H, d), 8.87 (1H, dd), 8.93 (1H, s), 9.22 (1H, s), 9.46 (1H, d) and 9.68 (1H, s)

Example 25**2-(6-Methylpyridin-3-yl)-pyrimido[4,5-f]quinazoline**

A mixture of 5,6-dihydro-2-(6-methylpyridin-3-yl)pyrimido[4,5-f]quinazoline (50mg; see Example 12 above) and 5% palladium on carbon (5mg) in *N,N*-dimethylacetamide (5ml) and cyclohexene (5ml) was heated at 170°C for 18 hours. The mixture was allowed to cool and was then filtered and evaporated. Chromatography of the residue eluting with 9:1 ethyl acetate:methanol and RP-HPLC eluting with ammonium acetate:methanol mixtures followed by freeze drying the fractions gave the title compound (18mg).

mp 187-190°C

MS(APCI) 274 ((M+H)⁺)

¹H NMR (DMSO) δ 2.62 (3H,s), 7.53 (1H,d), 8.12 (1H,d), 8.57 (1H,d), 8.97 (1H,dd), 9.66 (1H,s), 9.76 (1H,d), 9.86 (1H,s), 10.74 (1H,s).

Example 26**2-(4-Chlorophenyl)-5H-[1]benzopyrano[4,3-d]pyrimidine****(a) 2,3-Dihydro-3-(*N,N*-dimethylaminomethylene)-4H-1-benzopyran-4-one**

N,N-Dimethylformamide dimethyl acetal (2 ml) was added to 4-chromanone (1 g) and heated at 110 °C for 105 minutes. On cooling the residue was concentrated to give the subtitle compound (1.3 g).

MS(EI) 203 (M⁺)

¹H NMR (CDCl₃) 3.13 (6H,s), 5.25 (2H,s), 6.90 (1H,d), 7.00 (1H,t), 7.40 (1H,t), 7.60 (1H,s), 7.97 (1H,d).

(b) 2-(4-Chlorophenyl)-5H-[1]benzopyrano[4,3-d]pyrimidine

Sodium methoxide (143 mg) and 4-chlorobenzamidine hydroiodide (730 mg) were added to a suspension of 2,3-dihydro-3-(*N,N*-dimethylaminomethylene)[1]benzopyran-4-one (510 mg; from step (a) above) in ethanol (10 ml). The resultant mixture was heated at 100 °C for 8 hours under nitrogen. On cooling the product crystallised from the reaction mixture and was collected by filtration. Purification by chromatography eluting with 8:1:1 isohexane:dichloromethane:ethyl acetate gave the title compound (200 mg).

mp 149 °C

MS(EI) 294,296 (M⁺)

¹H NMR (DMSO) 5.39 (2H,s), 7.07 (1H,d), 7.21 (1H,t), 7.51 (1H,t), 7.62 (2H,d), 8.34 (1H,d), 8.51 (2H,d), 8.78 (1H,s).

Example 27**2-(4-Chlorophenyl)-5H-indeno[1,2-d]pyrimidine****(a) 2-(*N,N*-Dimethylaminomethylene)indanone**

- 5 The subtitle compound was prepared analogously to method described in Example 26(a) from indan-1-one.

MS(APCI) 188 ((M+H)⁺)

¹H NMR (CDCl₃) 3.19 (6H, s), 3.89 (2H, s), 7.38 (1H, t), 7.44-7.50 (2H, m), 7.54 (1H, s) and 7.85 (1H, d).

10

(b) 2-(4-Chlorophenyl)-5H-indeno[1,2-d]pyrimidine

The title compound was prepared according to the method described in Example 26(b) from 2-(*N,N*-dimethylaminomethylene)indanone (from step (a) above).

mp 187-192 °C

15 MS(ESI) 279/281 ((M+H)⁺)

¹H NMR (DMSO) 4.09 (2H, s), 7.56-7.67 (4H, m), 7.78 (1H, d), 8.19 (1H, d), 8.54 (2H, d), 9.07 (1H, s).

Example 28 – 38

- 20 The following examples were prepared following the methods used for examples 26 and 27 (see table):

Ex.	name	m.p.	MS	NMR (DMSO-d ₆) δ
28	2-Phenyl-5H-[1]benzopyrano-[4,3- <i>d</i>]pyrimidine	113	260 M ⁺	5.38 (2H, s), 7.07 (1H, d), 7.23 (1H, t), 7.49 (1H, t), 7.53 (3H, m), 8.34 (1H, d), 8.50 (2H, d), 8.77 (1H, s)
29	2-Pyridin-4-yl-5H-[1]benzo- pyrano[4,3- <i>d</i>]pyrimidine	145-6	262 (M+H) ⁺	5.42 (2H, s), 7.07 (1H, d), 7.22 (1H, t), 7.53 (1H, t), 8.36 (3H, d), 8.80 (2H, d), 8.85 (1H, s)
30	2-(Pyridin-4-yl)- <i>N</i> -oxide-5H- -[1]benzopyrano[4,3- <i>d</i>]- pyrimidine	225-8	278 (M+H) ⁺	5.40 (2H, s), 7.07 (1H, d), 7.21 (1H, t), 7.52 (1H, t), 8.36 (5H, m), 8.81 (1H, s)
31	2-Pyridin-2-yl-5H-[1]benzo- pyrano[4,3- <i>d</i>]pyrimidine	124-5	262 (M+H) ⁺	5.40 (2H, s), 7.07 (1H, d), 7.22 (1H, t), 7.5-7.6 (2H, m),

Ex.	name	m.p.	MS	NMR (DMSO-d ₆) δ
				8.00 (1H, t), 8.30 (1H, d), 8.50 (1H, d), 8.80 (1H, d), 8.84 (1H, s)
32	2-Pyridin-3-yl-5H-[1]benzopyrano[4,3-d]pyrimidine	130	262 (M+H) ⁺	5.41 (2H, s), 7.07 (1H, d), 7.23 (1H, t), 7.52 (1H, t), 7.59 (1H, dd), 8.35 (1H, d), 8.74 (1H, d), 8.74 (1H, d), 8.77 (1H, d), 8.82 (1H, s)
33	2-(6-Methylpyridin-3-yl)-5H-[1]benzopyrano[4,3-d]pyrimidine	132	276 (M+H) ⁺	2.57 (3H, s), 5.39 (2H, s), 7.07 (1H, d), 7.21 (1H, t), 7.44 (1H, d), 7.52 (1H, t), 8.35 (1H, d), 8.67 (1H, d), 8.78 (1H, s), 9.49 (1H, s)
34	2-(6-Chloropyridin-3-yl)-5H-[1]benzopyrano[4,3-d]pyrimidine	193-5	296/298 (M+H) ⁺	5.40 (2H, s), 7.06 (1H, d), 7.20 (1H, t), 7.52 (1H, t), 7.71 (1H, d), 8.34 (1H, d), 8.81 (2H, m), 9.41 (1H, s)
35	2-Pyrazin-2-yl-5H-[1]benzopyrano[4,3-d]pyrimidine	138-147	262 M ⁺	5.43 (2H, s), 7.06 (1H, d), 7.20 (1H, t), 7.52 (1H, t), 8.30 (1H, d), 8.82 (1H, s), 8.86 (2H, s), 9.65 (1H, s)
36	2-(6-Trifluoromethylpyridin-2-yl)-5H-[1]benzopyrano[4,3-d]pyrimidine	124-5	330 (M+H) ⁺	5.45 (2H, s), 7.08 (1H, d), 7.22 (1H, t), 7.53 (1H, t), 8.31 (1H, d), 8.43 (1H, dd), 8.70 (1H, d), 8.89 (1H, s), 9.19 (1H, d)
37	2-(2-Methylthiazol-4-yl)-5H-[1]benzopyrano[4,3-d]pyrimidine	140	282 (M+H) ⁺	2.77 (3H, s), 5.37 (2H, s), 7.06 (1H, d), 7.20 (1H, t), 7.50 (1H, t), 8.27 (1H, d), 8.46 (1H, s), 8.73 (1H, s)
38	4-(5H-[1]benzopyrano[4,3-d]pyrimidin-2-yl)benzenecarboxamide	283	304 (M+H) ⁺	5.40 (2H, s), 7.07 (1H, d), 7.22 (1H, t), 7.53 (2H, br t), 8.04 (2H, d), 8.13 (1H, br s), 8.37 (1H, d), 8.56 (2H, d)

Ex.	name	m.p.	MS	NMR (DMSO-d ₆) δ
				8.81 (1H, s)

Example 39**2-(6-methylpyridin-3-yl)-5,6-dihydropyrido[4,3-b]quinazoline**

Prepared following the method of Example 1 above using 6,7-dihydroisoquinoline-8-(5H)-one (J. Pharm. Soc., **76**, 1308; 500mg) and dimethylformamide dimethylacetal (3ml) followed by 6-methyl-3-pyridylamine (450mg) and sodium methoxide (160mg) to give, after chromatography, the title compound (160mg).

MS(APCI) 275 ((M+H)⁺)

mp 176-8°C

¹H NMR (d₆-DMSO) δ 2.57 (s, 3H), 3.02 (m, 4H), 7.42 (s, 1H), 7.44 (d, 1H), 8.63 (d, 1H), 8.69 (dd, 1H), 8.83 (s, 1H), 9.50 (d, 1H), 9.52 (s, 1H)

Pharmacological Data**Test A****Chronic graft-versus-host test**

Pharmacological activity of the compounds of the invention may be demonstrated using the method of J M Doutrelepon *et al* ([Clin. Exp. Immunol., 1991, vol. 83, 133-6; Inhibition of chronic graft-versus-host (c-GVH) disease in the mouse]. Test compound was administered to mice subcutaneously as a suspension in saline with TWEEN-80 every day for 21 days.

Test B**Inhibition of Eosinophilia**

The effects of the compounds of the invention on inflammatory cells in mouse lungs was assessed by the following method, adapted from Brusselle *et al*, Clin. Exp. Allergy 1994, 24, 73-80. The measurement of eosinophil peroxidase as a marker for eosinophil numbers was adapted from Cheng *et al*, J. Pharmacol. Exp. Ther., 1993, 264, 922-929.

Male Balb/c mice were sensitised to ovalbumin/Al(OH)₃ mixture.

14 days after sensitisation dosing with compound commenced. Compound was administered daily either orally or subcutaneously as a suspension or solution (depending on dose and compound solubility) in 5% Tween 80.

17 days after sensitisation and one hour after the fourth dose of compound, the mice were placed in perspex chambers into which a solution of ovalbumin (2%w/v) was nebulised. The mice were allowed to inhale the ovalbumin for a period of 30-40 min. This challenge was repeated daily at the same time for a further 3 or 7 days.

In the case of the 4 day challenge, on the final day of dosing an additional challenge with ovalbumin was given 4 hours after the first.

The following day the animals were killed and inhibition of the following parameters was measured by comparison to control animals:

- (1) Increase in the numbers of inflammatory cells in the bronchioalveolar lavage, in particular eosinophils (after the 4 day dosing).
- (2) Accumulation of eosinophils within lung tissue, as measured by the

increase in eosinophil peroxidase activity in homogenised lung tissue (after the 8 day dosing).

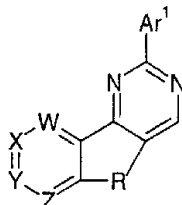
(3) Increase in antibody titres (IgE, IgG1 and IgG2a) present in the serum obtained from whole blood (after the 8 day dosing).

5

Certain compounds of the invention show activities in the chronic graft versus host test and the inhibition of eosinophilia test with ED₅₀'s in the range of 0.1 - 10 mg/kg.

Claims

1. A compound of formula I:



(I)

wherein

R represents $(\text{CH}_2)_n$, $\text{CH}=\text{CH}$, BCH_2 or CH_2B where B is O or S;

n is 1 to 3;

Ar¹ represents thiazolyl, phenyl, pyridyl, pyrimidinyl, 2-benzothiazolyl, 2- or 3-quinolyl or 2-quinoxalyl, all of which are optionally substituted by one or more substituents selected from halo, nitro, cyano, phenyl, phenylsulfonyl, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulfinyl, COOH, COO(C₁₋₆ alkyl), CONH₂, C₁₋₆ alkyl substituted by phenyl, or phenyl, in which any alkyl, alkoxy, alkylthio and alkylsulfinyl groups may optionally be substituted by one or more fluorine atoms;

W represents CH, CA or N;

X represents CH, CA, N or N⁺-O⁻;

Y represents CH, CA, N or N⁺-O⁻;

Z represents CH, CA, N or N⁺-O⁻;

A represents hydroxy, halogen, nitro, cyano, phenyl, C₁₋₆ thioalkyl, CO₂R¹, NR²R³, NR⁴C(O)R⁵, methoxy (optionally substituted by CO₂R⁶), C₁₋₆ alkyl or C₂₋₆ alkoxy (which latter two groups are optionally substituted by one or more substituents selected from NH₂, hydroxy or CO₂R⁷);

R² represents H or C₁₋₆ alkyl and R³ represents H, C₁₋₆ alkyl or CH₂Ar² or R² and R³ together with the nitrogen atom to which they are attached form a pyrrolidinyl or piperidinyl ring;

R⁵ represents H, C₁₋₅ alkyl or Ar³;

R¹, R⁴, R⁶ and R⁷ independently represent H or C₁₋₆ alkyl;

Ar² and Ar³ independently represent phenyl optionally substituted by one or more substituents selected from halogen, hydroxy, methoxy (optionally substituted by fluorine),

phenoxy, C₂₋₆ alkoxy and C₁₋₆ alkyl (which latter three groups are optionally substituted by one or more substituents selected from halogen, hydroxy or C₁₋₆ alkyl);

provided that:

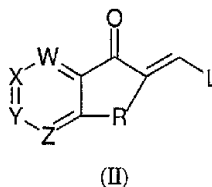
- (a) when one of X, Y and Z represent N^+-O^- , W and the other two groups all represent CH;
(b) W may only represent N when Y represents N and X and Z both represent CH;
(c) X may only represent N when Z represents CH or N, W represents CH and Y represents
5 CH or CA;
(d) Y may only represent N when W represents N or CH and X and Z both represent CH;
(e) Z may only represent N when X represents N or CH, W represents CH and Y represents
CH or CA;
(f) when only one of X or Z represent N then Y represents CH;
10 (g) when A represents C_{2-6} alkoxy substituted by hydroxy, halogen (other than fluorine) or
 NH_2 , or when Ar^1 , Ar^2 or Ar^3 are substituted by C_{2-6} alkoxy substituted by halogen (other
than fluorine) or hydroxy, then the hydroxy, halogen or NH_2 substituent as appropriate is not
attached to the same carbon atom as the oxygen is; and
(h) when W, X, Y and Z are all CH, R is $(CH_2)_2$ or OCH_2 then Ar^1 is not unsubstituted
15 phenyl,
or a pharmaceutically acceptable derivative thereof.
2. A compound according to claim 1 in which R is $CH=CH$, OCH_2 or $(CH_2)_n$ where n is 1,
2 or 3.
20
3. A compound according to claim 1 or 2 in which Ar^1 represents thiazolyl optionally
substituted by methyl, phenyl optionally substituted by chloro, CF_3 , $CONH_2$, or methyl or
 Ar^1 represents pyridyl or pyridyl N-oxide optionally substituted by CF_3 , methyl or methoxy
25
4. A compound according to any one of claims 1 to 3 in which W, X, Y and Z are all CH.
5. A compound according to any one of claims 1 to 3 in which W is CH, X is N, Y is CH
or CA and Z is N.
- 30 6. A compound according to any one of claims 1 to 3 in which W and Y are both N and X
and Z are both CH.
7. A compound according to any one of claims 1 to 3 in which one of X, Y or Z is N or
 N^+-O^- , and the others together with W are all CH.
35
8. A compound according to claim 5 in which A is C_{1-6} alkyl, C_{1-6} alkoxy and amino.

9. A compound according to claim 1 which is:

- 2-(4-Chlorophenyl)-5,6-dihydro-8-methylpyrimido[4,5-f]quinazoline,
2-(4-Chlorophenyl)-5,6-dihydro-8-methoxypyrimido[4,5-f]quinazoline,
5 2-(4-Chlorophenyl)-5,6-dihydropyrimido[5,4-h]quinazoline,
2-(4-Chlorophenyl)-5,6-dihydropyrido[3,4-h]quinazoline,
2-(4-Chlorophenyl)-5,6-dihydro-8-methylthiopyrimido[4,5-f]quinazoline,
2-(4-Chlorophenyl)-5,6-dihydropyrimido[4,5-f]quinazoline,
2-(4-Chlorophenyl)-5,6-dihydropyrido[3,4-h]quinazoline-8-oxide,
10 2-(4-Chlorophenyl)-5,6-dihydropyrimido[4,5-f]quinazoline-8-amine,
5,6-Dihydro-2-(pyridin-3-yl)pyrimido[4,5-f]quinazoline,
5,6-Dihydro-2-(pyridin-2-yl)pyrimido[4,5-f]quinazoline,
5,6-Dihydro-2-(6-methylpyridin-3-yl)pyrimido[4,5-f]quinazoline,
5,6-Dihydro-2-(6-methylpyridin-3-yl-N-oxide)-pyrimido[4,5-f]quinazolin-8-amine,
15 2-(4-Chlorophenyl)-6,7-dihydro-5H-pyrido[2,3-i]cycloheptapyrimidine,
2-(4-Chlorophenyl)-5,6-dihydropyrido[2,3-h]quinazoline,
2-(Pyridin-3-yl)-5,6-dihydropyrido[2,3-h]quinazoline,
2-(6-Methylpyridin-3-yl)-5,6-dihydropyrido[2,3-h]quinazoline,
2-(4-Chlorophenyl)-5,6-dihydropyrido[2,3-h]quinazoline, 7-oxide,
20 2-(4-Chlorophenyl)-5,6-dihydropyrido[4,3-h]quinazoline,
5,6-Dihydro-2-(pyridin-3-yl)-pyrido[4,3-h]quinazoline,
2-(Pyridin-3-yl)-pyrido[4,3-h]quinazoline,
2-(4-Chlorophenyl)-5,6-dihydropyrido[4,3-h]quinazoline, 9-oxide,
5,6-Dihydro-2-(6-methoxypyridin-3-yl)pyrimido[4,5-f]quinazoline,
25 2-(6-Chloropyridin-3-yl)-5,6-dihydropyrimido[4,5-f]quinazoline,
2-(6-Methylpyridin-3-yl)-pyrimido[4,5-f]quinazoline,
2-(4-Chlorophenyl)-5H-[1]benzopyrano[4,3-d]pyrimidine,
2-(4-Chlorophenyl)-5H-indeno[1,2-d]pyrimidine,
2-Phenyl-5H-[1]benzopyrano[4,3-d]pyrimidine,
30 2-Pyridin-4-yl-5H-[1]benzopyrano[4,3-d]pyrimidine,
2-(Pyridin-4-yl)-N-oxide-5H-[1]benzopyrano[4,3-d]pyrimidine,
2-Pyridin-2-yl-5H-[1]benzopyrano[4,3-d]pyrimidine,
2-Pyridin-3-yl-5H-[1]benzopyrano[4,3-d]pyrimidine,
2-(6-Methylpyridin-3-yl)-5H-[1]benzopyrano[4,3-d]pyrimidine,
35 2-(6-Chloropyridin-3-yl)-5H-[1]benzopyrano[4,3-d]pyrimidine,

- 2-Pyrazin-2-yl-5*H*-[1]benzopyrano[4,3-*d*]pyrimidine,
 2-(6-Trifluoromethylpyridin-2-yl)-5*H*-[1]benzopyrano[4,3-*d*]pyrimidine,
 2-(2-Methylthiazol-4-yl)-5*H*-[1]benzopyrano[4,3-*d*]pyrimidine,
 4-(5*H*-[1]benzopyrano[4,3-*d*]pyrimidin-2-yl)benzenecarboxamide,
 2-(6-methylpyridin-3-yl)-5,6-dihydropyrido[4,3-*h*]quinazoline,
 and pharmaceutically acceptable derivatives thereof.

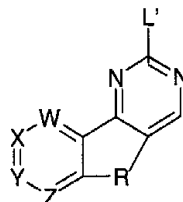
10. A compound according to any one of claims 1 to 9, or a pharmaceutically acceptable derivative thereof, for use as a pharmaceutical.
11. A pharmaceutical formulation comprising a compound according to any one of claims 1 to 9, or a pharmaceutically-acceptable derivative thereof, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.
12. A compound according to any one of claims 1 to 9, or a pharmaceutically-acceptable derivative thereof, for use in the treatment of an allergic or an inflammatory disorder.
13. A process for the preparation of a compound of formula (I) which comprises:
 (a) reaction of a compound of formula (II):



- in which W, X, Y, Z and R are as defined in formula (I) and L is a leaving group with a compound of formula (III) or a salt thereof:



- in which Ar^1 is as defined in formula (I); or
- (b) for compounds of formula (I) where Y is N or CA and A is H, NH_2 , C_{1-6} alkyl or C_{1-6} alkoxy, reaction of a compound of formula (IV):



(IV)

- 5 in which W, X, Y, Z and R are as defined in formula (I) and L' is a leaving group with a compound of formula (V):



- 10 wherein Hal represents Cl or Br and Ar¹ is as defined in formula (I).
and optionally thereafter (a) or (b):
- converting the compound of formula (I) into a further compound of formula (I)
 - forming a pharmaceutically acceptable derivative.
- 15 14. A compound of formula (II) as defined in claim 13, with the proviso that when W, X and Y each represent CH, Z represents N and R represents (CH₂)_n, then L is not a group N(CH₃)₂.



AMENDED SHEET