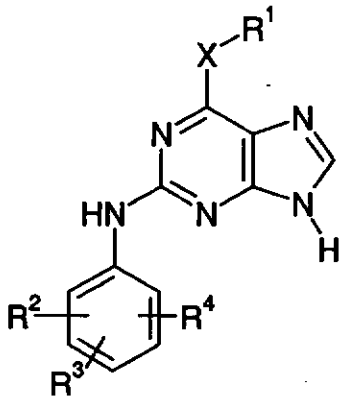
PURINE DERIVATIVES INHIBITORS OF TYROSINE PROTEIN KINASE SYK

This invention relates to organic compounds, their preparation and their use as pharmaceuticals.

More particularly, the present invention relates to:

(a) compounds of formula

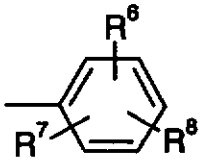


I

in free or salt form, where

X is an oxygen or sulfur atom or a group NR^5,

R^1 is an alkyl, alkenyl, cycloalkyl, benzocycloalkyl, cycloalkylalkyl or aralkyl group which optionally may be substituted by hydroxy, alkoxy, carboxy or alkoxycarbonyl or, when X is NR^5, R^1 may alternatively be a heterocyclyl group or a group of formula



II

R^2, R^3, R^4, R^6, R^7 and R^8 are each independently hydrogen, halogen, alkyl, haloalkyl, alkoxy, carboxy, alkoxycarbonyl, carboxyalkyl, alkoxycarbonylalkyl, $-N(R^9)R^{10}$, $-SO_2N(R^{11})R^{12}$, C_1-C_4-alkylene-$SO_2N(R^{11})R^{12}$ or $-CON(R^{13})R^{14}$ or, when two of R^2, R^3 and R^4, or two of R^6, R^7 and R^8, are attached to adjacent carbon atoms on the indicated benzene rings, they denote, together with the carbon atoms to which they are attached, a carbocyclic group having 5 to 10 ring atoms or a heterocyclic group having 5 to 10 ring atoms of which one, two or three are hetero atoms selected from nitrogen, oxygen and sulfur,

R^5 is hydrogen or alkyl,
R^9 is hydrogen or alkyl and R^{10} is hydrogen, alkyl or -COR^{15} where R^{15} is alkyl, haloalkyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, carboxyalkyl or alkoxycarbonylalkyl, or R^9 and R^{10}, together with the nitrogen atom to which they are attached, denote a heterocyclic group having 5 or 6 ring atoms of which one or two are hetero atoms selected from nitrogen, oxygen and sulfur,
R^{11} is hydrogen or alkyl and R^{12} is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, carboxyalkyl or alkoxycarbonylalkyl, or R^{11} and R^{12} together with the nitrogen atom to which they are attached denote a heterocyclic group having 5 or 6 ring atoms of which one or two are hetero atoms selected from nitrogen, oxygen and sulfur, and
R^{13} and R^{14} are each independently hydrogen or alkyl; particularly to compounds of formula I in free or pharmaceutically acceptable salt form for use as pharmaceuticals; and

(b) compounds of formula I as hereinbefore defined in free or pharmaceutically acceptable salt form for use in the manufacture of medicaments for the treatment of conditions mediated by syk kinase.

In formula I, R^9, R^{10}, R^{11}, R^{12}, R^{13} or R^{14} in R^2, R^3 or R^4 may be the same as, or may differ from, the respective group in R^6, R^7 or R^8.

In another aspect, the present invention provides compounds of formula I as hereinbefore defined in free or salt form, with the exception of 2-(p-n-butylanilino)-6-methoxypurine, 2-(p-n-butylanilino)-6-(methylthio)purine, 2,6-di(phenylamino)purine, 2,6-di(p-tolylamino)purine, and 2-(p-tolylamino)-6-(phenylamino)purine.

In a further aspect, the present invention provides compounds of formula I as hereinbefore defined in free or salt form, with the exception of compounds of formula I where (i) X is oxygen or sulfur, R^1 is alkyl, two of R^2, R^3 and R^4 are hydrogen and one of R^2, R^3 and R^4 is alkyl and (ii) X is NH, R^1 is a group of formula II in which two of R^6, R^7 and R^8 are hydrogen and the remaining one is hydrogen or alkyl, one of R^2, R^3, and R^4 is hydrogen and the remaining two are each hydrogen or alkyl.

In a further aspect, the present invention provides a compound of formula I as hereinbefore described in free or salt form in which

(a) X is NR^5 and R^1, R^2, R^3, R^4 and R^5 are as hereinbefore defined, with the proviso that when R^1 is a group of formula II, R^6, R^7 and R^8 are each independently halogen, haloalkyl, alkoxy, carboxy, alkoxycarbonyl, carboxyalkyl, alkoxycarbonylalkyl, $-N(R^9)R^{10}$, $-SO_2N(R^{11})R^{12}$, C_1-C_4-alkylene-$SO_2N(R^{11})R^{12}$ or $-CON(R^{13})R^{14}$ or, when two of R^6, R^7 and R^8 are attached to adjacent carbon atoms on the indicated benzene ring, they denote, together with the carbon atoms to which they are attached, a carbocyclic group having 5 to 10 ring atoms or a heterocyclic group having 5 to 10 ring atoms of which one, two or three are hetero atoms selected from nitrogen, oxygen and sulfur, or one or two of R^6, R^7 and R^8 are hydrogen; or

(b) X is oxygen or sulfur and R^1, R^2, R^3 and R^4 are as hereinbefore defined, with the proviso that when R^1 is alkyl, R^2, $R^3$and R^4 are each independently hydrogen, halogen, alkoxy, carboxy, alkoxycarbonyl, carboxyalkyl, alkoxycarbonylalkyl, $-N(R^9)R^{10}$, $-SO_2N(R^{11})R^{12}$, C_1-C_4-alkylene-$SO_2N(R^{11})R^{12}$ or $-CON(R^{13})R^{14}$ or, when two of R^2, R^3 and R^4 are attached to adjacent carbon atoms on the indicated benzene rings, they denote, together with the carbon atoms to which they are attached, a carbocyclic group having 5 to 10 ring atoms or a heterocyclic group having 5 to 10 ring atoms of which one, two or three are hetero atoms selected from nitrogen, oxygen and sulfur.

Terms used in this specification have the following meanings:

"Alkyl" denotes straight chain or branched alkyl, which may be, for example, C_1 to C_{10}-alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, straight or branched pentyl, straight or branched hexyl, straight or branched heptyl, straight or branched nonyl or straight or branched decyl. Preferably alkyl is C_1 to C_4-alkyl.

"Alkoxy" denotes straight chain or branched alkoxy and may be, for example, C_1 to C_{10} alkoxy such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, or straight or branched pentoxy, hexyloxy, heptyloxy, octyloxy, nonyloxy or decyloxy. Preferably alkoxy is C_1 to C_4-alkoxy.

"Alkenyl" means straight chain or branched alkenyl, which may be, for example, C_2 to C_{10}-alkenyl such as vinyl, 1-propenyl, 2-propenyl, 1-butenyl, isobutenyl, or straight or branched pentenyl, hexenyl, heptenyl, octenyl, nonenyl or decenyl. Preferred alkenyl is C_2 to C_4-alkenyl.

"Cycloalkyl" means C_3 to C_{10}-cycloalkyl having 3 to 8 ring carbon atoms and may be, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cycloheptyl, any of which can be substituted by one, two or more C_1-C_4 alkyl groups, particularly methyl groups. Preferably, cycloalkyl is C_3-C_6-cycloalkyl.

"Benzocycloalkyl" means cycloalkyl, e.g. one of the C_3 to C_{10} cycloalkyl groups mentioned hereinbefore, attached at two adjacent carbon atoms to a benzene ring. Preferably, benzocycloalkyl is benzo-C_5-C_6-cycloalkyl, especially benzocyclohexyl (tetrahydronaphthyl).

"Cycloalkylalkyl" means C_3 to C_{10}-cycloalkyl -C_1-C_{10} alkyl where the C_3 to C_{10}-cycloalkyl group has 3 to 8 ring carbon atoms and may be, for example, one of the C_1-C_{10}-alkyl groups mentioned hereinbefore, particularly one of the C_1-C_4-alkyl groups, substituted by one of the C_3-C_{10}-cycloalkyl groups mentioned hereinbefore. Preferably cycloalkylalkyl is C_3-C_6-cycloalkyl-C_1-C_4-alkyl.

"Aralkyl" means C_6-C_{10}-aryl-C_1-C_{10} alkyl and may be, for example, one of the C_1-C_{10}-alkyl groups mentioned hereinbefore, particularly one of the C_1-C_4-alkyl groups, substituted by phenyl, tolyl, xylyl or naphthyl. Preferably, aralkyl is phenyl-C_1-C_4-alkyl, particularly benzyl or 2-phenylethyl.

"Heterocyclyl" means a monovalent heterocyclic radical having up to 20 carbon atoms and one, two, three or four heteroatoms selected from nitrogen, oxygen and sulfur, the radical optionally having an alkyl, alkylcarbonyl, hydroxyalkyl, alkoxyalkyl or aralkyl group attached to a ring carbon or nitrogen atom and being linked to the remainder of the molecule through a ring carbon atom, and may be, for example, a radical, preferably a monocyclic radical, with one nitrogen, oxygen or sulfur atom such as pyrryl, pyridyl, piperidyl, furyl, tetrahydrofuryl or thienyl, or a radical, preferably a monocyclic radical, with two hetero atoms selected from nitrogen, oxygen and sulfur, such as imidazolyl, pyrimidinyl, piperazinyl, oxazolyl, isoxazolyl, thiazolyl, morpholinyl or thiomorpholinyl. Preferably, heterocyclyl is a monocyclic radical having 5 or 6 ring atoms and one or two nitrogen atoms, or one nitrogen atom and one oxygen atom, in the ring and optionally substituted on a ring nitrogen atom by C_1-C_4-alkyl, hydroxy-C_1-C_4-alkyl, C_1-C_4-alkylcarbonyl or phenyl-C_1-C_4-alkyl.

"Alkoxyalkyl" means straight chain or branched alkyl substituted by one or more alkoxy groups and may be, for example, a C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl group, such as one of the C_1-C_{10}-alkyl groups, particularly one of the C_1-C_4-alkyl groups, mentioned hereinbefore substituted by one of the C_1-C_{10}-alkoxy groups, preferably one of the C_1-C_4-alkoxy groups, mentioned hereinbefore. Preferably alkoxyalkyl is C_1-C_4-alkoxy-C_1-C_4 alkyl.

"Carboxyalkyl" means straight chain or branched alkyl, for example C_1-C_{10}-alkyl such as one of the C_1-C_{10}-alkyl groups mentioned hereinbefore, substituted, preferably on a primary carbon atom, by a carboxyl group. Preferably carboxyalkyl is carboxy-C_1-C_4-alkyl.

"Alkylcarbonyl" means a group $R^{16}CO$ where R^{16} is alkyl, for example C_1-C_{10}-alkyl such as one of the C_1-C_{10}-, preferably C_1-C_4-, alkyl groups mentioned hereinbefore. Preferably, alkylcarbonyl is C_1-C_4-alkylcarbonyl, i.e. $R^{16}CO$ where R^{16} is C_1-C_4-alkyl.

"Alkoxycarbonyl" means a group $R^{17}CO$ where R^{17} is an alkoxy group, for example a C_1-C_{10} alkoxy group such as one of the C_1-C_{10}, preferably C_1-C_4, alkoxy groups mentioned hereinbefore. Preferably, alkoxycarbonyl is C_1-C_4-alkoxycarbonyl, i.e. $R^{17}CO$ where R^{17} is C_1-C_4-alkoxy.

"Alkoxycarbonylalkyl" means straight or branched chain alkyl, for example a C_1-C_{10} alkyl group such as one of the C_1-C_{10}-, preferably C_1-C_4-, alkyl groups mentioned hereinbefore, substituted by an alkoxycarbonyl group as hereinbefore defined. Preferably, alkoxycarbonylalkyl is C_1-C_4-alkoxy-carbonyl-C_1-C_4-alkyl.

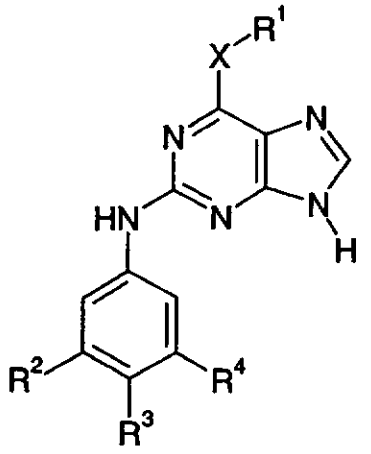
"Haloalkyl" means straight chain or branched alkyl, for example C_1-C_{10}-alkyl such as one of the C_1-C_{10}- alkyl groups mentioned hereinbefore, substituted by one or more, for example one, two or three, halogen atoms, preferably fluorine or chlorine atoms. Preferably haloalkyl is C_1-C_4-alkyl substituted by one, two or three fluorine or chlorine atoms.

"Hydroxyalkyl" means straight chain or branched alkyl, for example C_1-C_{10}-alkyl such as one of the C_1-C_{10}-alkyl groups mentioned hereinbefore, substituted by one, two or three hydroxyl groups. Preferably, hydroxyalkyl is C_1-C_4-alkyl substituted by one hydroxyl group.

Where one of R^2, R^3 and R^4, or one of R^6, R^7 and R^8, is hydrogen and the second and third of R^2, R^3 and R^4, or the second and third of R^6, R^7 and R^8, are attached to adjacent carbon atoms in the respective benzene ring and together with said adjacent carbon atoms denote a carbocyclic group or heterocyclic group, the second and third of R^2, R^3 and R^4, or the second and third of R^6, R^7 and R^8, may denote, together with the benzene ring to which they are attached, a C_9-C_{15}-carbocyclic group such as indenyl or naphthyl, optionally substituted by one or more C_1-C_4-alkyl or C_1-C_4-alkoxy groups, dihydronaphthyl, tetrahydronaphthyl, fluorenyl, anthryl or phenanthryl, preferably a C_{10}-C_{15}-carbocyclic aromatic group or tetrahydronaphthyl; or the second and third of R^2, R^3 and R^4, or the second and third of R^6, R^7 and R^8, may denote, together with the benzene ring to which they are attached, a heterocyclic group having 9 to 14 ring atoms, of which one, two or three are heteroatoms selected from nitrogen, oxygen and sulfur, for example an indolyl, benzimidazolyl, indazolyl or carbazolyl group (which is optionally substituted on a nitrogen atom by C_1-C_4-alkyl, hydroxy-C_1-C_4-alkyl or phenyl-C_1-C_4-alkyl), or benzofuranyl, benzothiophenyl, quinolinyl, isoquinolinyl, naphthyridinyl, dioxanapthyl (benzodioxanyl), benzoxazolyl, benzothiazolyl, benzofuranonyl or benzofurazanyl, preferably a heterocyclic group having 9 to 13 ring atoms, of which one or two are hetero atoms selected from nitrogen, oxygen and sulfur.

Where R^9 and R^{10}, or R^{11} and R^{12}, together with the nitrogen atom to which they are attached, denote a heterocyclic group, the heterocyclic group may be, for example, a group having one or two nitrogen atoms in the ring such as a pyrrolidinyl, imidazolyl, imidazolidinyl, piperidyl or piperazinyl group, the group having two nitrogen atoms in the ring being optionally substituted on the second nitrogen atom by a C_1-C_4-alkyl, hydroxy-C_1-C_4-alkyl, C_1-C_4-alkylcarbonyl, a C_1-C_4-alkoxycarbonyl or phenyl-C_1-C_4-alkyl group, or the heterocyclic group may be a group having one nitrogen atom and one oxygen atom in the ring, such as a tetrahydro-oxazolyl, tetrahydro-isoxazolyl or mopholino group, which may be substituted on one or more ring carbon atoms by a C_1-C_4-alkyl group.

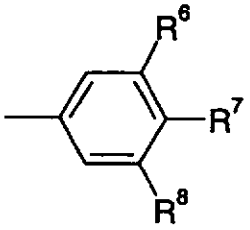
Preferred compounds of formula I and their salts are compounds of formula



III

in free or salt form, where

R^1 is as hereinbefore and, when it is a group of formula II, it is a group of formula



IV

and R^2, R^3, R^4, R^6, R^7 and R^8 are as hereinbefore defined.

Preferably, in formula I and formula III, R^1 is a C_1-C_{10}-alkyl, especially C_1-C_4-alkyl, C_2-C_{10}-alkenyl, especially C_2-C_4-alkenyl, C_3-C_{10}-cycloalkyl, especially C_3-C_6-cycloalkyl, benzo-C_3-C_{10}-cycloalkyl, especially benzo-C_5-C_6-cycloalkyl, phenyl-C_1-C_{10}-alkyl, especially phenyl-C_1-C_4-alkyl, or C_3-C_{10}-cycloalkyl-C_1-C_4-alkyl, especially C_3-C_6-cycloalkyl-C_1-C_4-alkyl, group which is optionally substituted by a hydroxy, carboxy or C_1-C_4-alkoxycarbonyl group, or R^1 is a heterocyclyl radical having 5 or 6 ring atoms and one or two nitrogen atoms, or one nitrogen atom and one oxygen atom, in the ring and optionally substituted on a ring nitrogen atom by C_1-C_4-alkyl, hydroxy-C_1-C_4-alkyl, C_1-C_4-alkylcarbonyl or phenyl-C_1-C_4-alkyl, or

R^1 is a group of formula II or formula IV respectively in which one of R^6, R^7 and R^8 is hydrogen, C_1-C_4-alkyl or C_1-C_4-alkoxy, and (i) the second and third of R^6, R^7 and R^8 are each independently hydrogen, C_1-C_4-alkyl or C_1-C_4-alkoxy or (ii) the second of R^6, R^7 and R^8 is hydrogen and the third of R^6, R^7 and R^8 is carboxy, C_1-C_{10}-, preferably C_1-C_4-alkoxycarbonyl, carboxy C_1-C_{10}-, preferably carboxy-C_1-C_4-alkyl, C_1-C_{10}-alkoxycarbonyl-C_1-C_{10}-alkyl, preferably C_1-C_4-alkoxycarbonyl-C_1-C_4-alkyl, $-N(R^9)R^{10}$, $-SO_2N(R^{11})R^{12}$, C_1-C_4-

alkylene-$SO_2N(R^{11})R^{12}$ or -$CON(R^{13})R^{14}$, or (iii) the second and third of R^6, R^7 and R^8 are attached to adjacent carbon atoms in the indicated benzene ring and, together with said adjacent carbon atoms, denote a carbocyclic group having 5 or 6 ring atoms or a monocyclic heterocyclic group having 5 or 6 ring atoms and one or two nitrogen atoms in the ring,

one of R^2, R^3 and R^4 is hydrogen, C_1-C_4-alkyl or C_1-C_4-alkoxy and (a) the second and third of R^2, R^3 and R^4 are each independently hydrogen, C_1-C_4-alkyl or C_1-C_4-alkoxy, or (b) the second of R^2, R^3 and R^4 is hydrogen and the third of R^2, R^3 and R^4 is carboxy, C_1-C_{10}, preferably C_1-C_4-, alkoxycarbonyl, carboxy-C_1-C_{10}-alkyl, preferably carboxy-C_1-C_4-alkyl, C_1-C_{10}-alkoxycarbonyl-C_1-C_{10}-alkyl, preferably C_1-C_4-alkoxycarbonyl-C_1-C_4-alkyl, -$N(R^9)R^{10}$, -$SO_2N(R^{11})R^{12}$, C_1-C_4-alkylene-$SO_2N(R^{11})R^{12}$ or -$CON(R^{13})R^{14}$, or (c) the second and third of R^2, R^3 and R^4 are attached to adjacent carbon atoms in the indicated benzene ring and, together with said adjacent carbon atoms, denote a carbocyclic group having 5 or 6 ring atoms or a heterocyclic group having 5 to 10 ring atoms, of which one or two are hetero atoms selected from nitrogen, oxygen and sulfur,

R^9 is hydrogen or C_1-C_{10}-, preferably C_1-C_4-, alkyl and R^{10} is hydrogen, C_1-C_{10}-, preferably C_1-C_4-, alkyl, or -COR^{15} where R^{15} is C_1-C_{10}-, preferably C_1-C_4-, alkyl, C_1-C_{10}-haloalkyl, preferably C_1-C_4-haloalkyl, C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl, preferably C_1-C_4-alkoxy- C_1-C_4-alkyl, C_1-C_{10}-alkoxycarbonyl, preferably C_1-C_4-alkoxycarbonyl, carboxy-C_1-C_{10}-alkyl, preferably carboxy-C_1-C_4-alkyl, or C_1-C_{10}-alkoxycarbonyl-C_1-C_{10} alkyl, preferably C_1-C_4-alkoxycarbonyl-C_1-C_4-alkyl, or R^9 and R^{10} together with the nitrogen atom to which they are attached, denote a heterocyclic group having 5 or 6 ring atoms and one or two nitrogen atoms, or one nitrogen atom and one oxygen atom, in the ring,

R^{11} is hydrogen or C_1-C_{10}-, preferably C_1-C_4-, alkyl and R^{12} is hydrogen, C_1-C_{10}-, preferably C_1-C_4-, alkyl, hydroxy-C_1-C_{10}-alkyl, preferably hydroxy-C_1-C_4-alkyl, C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl, preferably C_1-C_4-alkoxy-C_1-C_4-alkyl, carboxy-C_1-C_{10}-alkyl, preferably carboxy- C_1-C_4-alkyl, or C_1-C_{10}-alkoxycarbonyl-C_1-C_{10}-alkyl, preferably C_1-C_4-alkoxycarbonyl-C_1-C_4-alkyl, or R^{11} and R^{12} together with the nitrogen atom to which they are attached denote a heterocyclic group having 5 or 6 ring atoms and one or two nitrogen atoms, or one nitrogen atom and one oxygen atom, in the ring,

and R^{13} and R^{14} are each independently hydrogen or C_1-C_{10}-, preferably C_1-C_4-, alkyl.

Preferred compounds of formula I or III and their salts include those in which:

X is a group NR^5,

R^1 is a C_1-C_4-alkyl, C_2-C_4-alkenyl, C_3-C_5 cycloalkyl, benzo-C_5-C_6-cycloalkyl, phenyl-C_1-C_4-alkyl or C_3-C_5 cycloalkyl-C_1-C_4-alkyl group, which is optionally substituted by a hydroxy,

carboxy or C_1-C_4-alkoxycarbonyl group, or R^1 is a heterocyclyl radical having 5 or 6 ring atoms and one or two nitrogen atoms, or one nitrogen atom and one oxygen atom, in the ring and optionally substituted on a ring nitrogen atom by C_1-C_4 alkyl, C_1-C_4-hydroxyalkyl, C_1-C_4-alkylcarbonyl or phenyl-C_1-C_4-alkyl, or R^1 is a group of formula IV in which one of R^6, R^7 and R^8 is hydrogen, C_1-C_4-alkyl or alkoxy, and (i) the second and third of R^6, R^7 and R^8 are each independently hydrogen, C_1-C_4-alkyl or C_1-C_4-alkoxy or (ii) the second of R^6, R^7 and R^8 is hydrogen and the third of R^6, R^7 and R^8 is $-N(R^9)R^{10}$, $-SO_2N(R^{11})R^{12}$ or $-CON(R^{13})R^{14}$, or (iii) the second and third of R^6, R^7 and R^8 are attached to adjacent carbon atoms in the indicated benzene ring and together with said adjacent carbon atoms denote a carbocyclic group having 5 or 6 ring atoms or a heterocyclic group having 5 or 6 ring atoms, of which one or two are nitrogen atoms, one of R^2, R^3 and R^4 is hydrogen, C_1-C_4-alkyl or C_1-C_4-alkoxy and (a) the second and third of R^2, R^3 and R^4 are each independently hydrogen, C_1-C_4-alkyl or C_1-C_4-alkoxy or (b) the second of R^2, R^3 and R^4 is hydrogen and the third of R^2, R^3 and R^4 is carboxy, C_1-C_4-alkoxycarbonyl, carboxy-C_1-C_4-alkyl, C_1-C_4-alkoxycarbonyl-C_1-C_4-alkyl, $-N(R^9)R^{10}$, $-SO_2N(R^{11})R^{12}$, C_1-C_4-alkylene-$SO_2N(R^{11})R^{12}$ or $-CON(R^{13})R^{14}$, or (c) the second and third of R^2, R^3 and R^4 are attached to adjacent carbon atoms in the indicated benzene ring and denote, together with said adjacent carbon atoms, a heterocyclic group having 5 to 10 ring atoms, of which one or two are hetero atoms selected from nitrogen, oxygen and sulfur,

R^5 is hydrogen or C_1-C_4-alkyl,

R^9 is hydrogen or C_1-C_4 alkyl and R^{10} is hydrogen, C_1-C_4 alkyl, or $-COR^{15}$ where R^{15} is C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-alkoxy-C_1-C_4 alkyl, C_1-C_4-alkoxycarbonyl, or C_1-C_4-alkoxycarbonyl-C_1-C_4-alkyl, or R^9 and R^{10} together with the nitrogen atom to which they are attached denote a heterocyclic group having 5 or 6 ring atoms including one or two ring nitrogen atoms, or one nitrogen ring atom and one oxygen ring atom,

R^{11} is hydrogen or C_1-C_4-alkyl and R^{12} is hydrogen, C_1-C_4-alkyl, hydroxy-C_1-C_4-alkyl, C_1-C_4-alkoxy- C_1-C_4-alkyl or C_1-C_4-alkoxycarbonyl- C_1-C_4-alkyl, or R^{11} and R^{12} together with the nitrogen atom to which they are attached denote a heterocyclic group having 5 or 6 ring atoms including one or two ring nitrogen atoms, or one nitrogen ring atom and one oxygen ring atom, and

R^{13} and R^{14} are each independently hydrogen or C_1-C_4-alkyl.

Further preferred amongst the above mentioned compounds where X is a group NR^5 are those where

R^1 is C_1-C_4-alkyl which is optionally substituted by hydroxy, C_2-C_4-alkenyl, C_3-C_5-cycloalkyl which is optionally substituted by carboxy or C_1-C_4-alkoxycarbonyl, benzo-C_5-C_6-cycloalkyl, phenyl-C_1-C_4-alkyl optionally substituted by hydroxy, C_3-C_5-cycloalkyl- C_1-C_4-alkyl, a heterocyclyl radical having 6 ring atoms and one or two nitrogen atoms in the ring optionally substituted on a ring nitrogen atom by phenyl-C_1-C_4-alkyl, or a group of formula IV in which one of R^6, R^7 and R^8 is hydrogen, C_1-C_4-alkyl or C_1-C_4-alkoxy, and (i) the second and third of R^6, R^7 and R^8 are each hydrogen or (ii) the second of R^6, R^7 and R^8 is hydrogen and the third of R^6, R^7 and R^8 is $-N(R^9)R^{10}$ where R^9 is hydrogen or C_1-C_4-alkyl and R^{10} is $-COR^{15}$ where R^{15} is C_1-C_4-alkyl, C_1-C_4-alkoxy, $-SO_2N(R^{11})R^{12}$ where R^{11} and R^{12} are each hydrogen, C_1-C_4-alkyl, or $-CON(R^{13})R^{14}$ where R^{13} and R^{14} are each hydrogen, or (iii) the second and third of R^6, R^7 and R^8 are attached to adjacent carbon atoms in the indicated benzene ring and denote, together with said adjacent carbon atoms, a carbocyclic group having 6 ring atoms or a heterocyclic group having 5 ring atoms, of which two are nitrogen atoms,

one of R^2, R^3 and R^4 is hydrogen, C_1-C_4-alkyl or C_1-C_4-alkoxy, and (a) the second and third of R^2, R^3 and R^4 are each independently hydrogen or C_1-C_4-alkoxy or (b) the second of R^2, R^3 and R^4 is hydrogen and the third of R^2, R^3 and R^4 is carboxy, C_1-C_4-alkoxycarbonyl, carboxy-C_1-C_4-alkyl, C_1-C_4-alkoxycarbonyl-C_1-C_4-alkyl, $-N(R^9)R^{10}$ where R^9 is hydrogen or C_1-C_4-alkyl and R^{10} is hydrogen, C_1-C_4-alkyl, or $-COR^{15}$ where R^{15} is C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-alkoxy-C_1-C_4-alkyl, C_1-C_4-alkoxycarbonyl or C_1-C_4-alkoxycarbonyl-C_1-C_4-alkyl, or R^9 and R^{10} together with the nitrogen atom to which they are attached denote a heterocyclic group having 5 or 6 ring atoms including one or two ring nitrogen atoms, preferably piperazinyl, piperidino, pyrrolidonyl, or one ring nitrogen atom and one ring oxygen atom, preferably morpholino, the heterocyclic group having two ring nitrogen atoms optionally having a C_1-C_4-alkyl, a hydroxy C_1-C_4-alkyl, a C_1-C_4-alkylcarbonyl, a C_1-C_4-alkoxycarbonyl or C_1-C_4-alkoxycarbonylalkyl group attached to the nitrogen atom in the $-R^9$-R^{10}- radical, and the heterocyclic group having one ring nitrogen atom and one ring oxygen atom optionally having one or two C_1-C_4-alkyl groups attached to a ring carbon atom, or the third of R^2, R^3 and R^4 is $-SO_2N(R^{11})R^{12}$ where R^{11} is hydrogen or C_1-C_4-alkyl and R^{12} is hydrogen, C_1-C_4-alkyl, hydroxy-C_1-C_4-alkyl, C_1-C_4-alkoxy-C_1-C_4-alkyl or C_1-C_4-alkoxycarbonyl-C_1-C_4-alkyl, or R^{11} and R^{12} together with the nitrogen atom to which they are attached denote a heterocyclic group having 6 ring atoms including one or two ring nitrogen atoms, e.g. piperidino or piperazinyl, or one ring nitrogen atom and one ring oxygen atom, e.g. morpholino, the heterocyclic group having two ring nitrogen atoms optionally having a C_1-C_4-alkyl group attached to the nitrogen atom in the $-R^{11}$-R^{12}- radical, or the third of R^2, R^3 and R^4 is C_1-C_4-alkylene-$SO_2N(R^{11})R^{12}$

where R^{11} and R^{12} are each independently hydrogen or C_1-C_4-alkyl, or the third of R^2, R^3 and R^4 is -CON(R^{13})R^{14} where R^{13} and R^{14} are each independently hydrogen or C_1-C_4-alkyl, or (c) the second and third of R^2, R^3 and R^4 are attached to adjacent carbon atoms in the indicated benzene ring and denote, together with said adjacent carbon atoms, a heterocyclic group having 5 to 9 ring atoms, of which one or two are hetero atoms selected from nitrogen, oxygen and sulfur, especially an indazolyl, benzothiazolyl, quinolyl, indolyl, benzofuranonyl or dioxanaphthyl group, and
R^5 is hydrogen or C_1-C_4-alkyl.

Other preferred compounds of formula I or III and their salts are those where X is an oxygen atom, R^1 is C_1-C_4-alkyl or C_3-C_{10} cycloalkyl, one of R^2, R^3 and R^4 is hydrogen, and either (i) the second of R^2, R^3 and R^4 is hydrogen and the third of R^2, R^3 and R^4 is carboxy, C_1-C_4-alkoxycarbonyl or -N(R^9)R^{10} where R^9 and R^{10} together with the attached nitrogen atom denote a heterocyclic group having 5 or 6 ring atoms including two ring nitrogen atoms or one ring nitrogen atom and one ring oxygen atom, or (ii) the second and third of R^2, R^3 and R^4 are attached to adjacent carbon atoms on the indicated benzene ring and together with the carbon atoms to which they are attached denote a heterocyclic group having 5 or 6 ring atoms, of which one or two are nitrogen atoms.

Further preferred amongst the compounds of formula I or III and their salts where X is an oxygen atom are those where R^1 is C_1-C_4-alkyl or C_3-C_5-cycloalkyl, one of R^2, R^3 and R^4 is hydrogen and either (a) the second of R^2, R^3 and R^4 is hydrogen and the third of R^2, R^3 and R^4 is carboxy, C_1-C_4-alkoxycarbonyl or -N(R^9)R^{10} where R^9 and R^{10} together with the attached nitrogen atom denote a heterocyclic group having 6 ring atoms including one ring nitrogen atom and one ring oxygen atom, or (b) the second and third of R^2, R^3 and R^4 are attached to adjacent carbon atoms on the indicated benzene ring and denote, together with said adjacent carbon atoms, a heterocyclic group having 5 ring atoms, of which two are nitrogen atoms.

Another group of preferred compounds of formula I or III and their salts are those where X is a sulfur atom, R^1 is C_1-C_4-alkyl, two of R^2, R^3 and R^4 are hydrogen and the third of R^2, R^3 and R^4 is carboxy, C_1-C_4-alkoxycarbonyl, or -N(R^9)R^{10} where R^9 is hydrogen or C_1-C_4-alkyl and R^{10} is -COR^{15} where R^{15} is C_1-C_4-alkyl, or R^9 and R^{10} together with the nitrogen atom to which they are attached denote a heterocyclic group having 5 or 6 ring atoms including one or two ring nitrogen atoms or one ring nitrogen atom and one ring oxygen

atom, preferably a heterocyclic group having 6 ring atoms including one ring nitrogen atom and one ring oxygen atom.

The compounds represented by formula I are capable of forming acid addition salts, particularly pharmaceutically acceptable acid addition salts. Pharmaceutically acceptable acid addition salts of the compound of formula I include those of inorganic acids, for example, hydrohalic acids such as hydrofluoric acid, hydrochloric acid, hydrobromic acid or hydroiodic acid, nitric acid, sulfuric acid, phosphoric acid; and organic acids, for example aliphatic monocarboxylic acids such as formic acid, acetic acid, trifluoroacetic acid, propionic acid and butyric acid, aliphatic hydroxy acids such as lactic acid, citric acid, tartaric acid or malic acid, dicarboxylic acids such as maleic acid or succinic acid, aromatic carboxylic acids such as benzoic acid, p-chlorobenzoic acid, diphenylacetic acid or triphenylacetic acid, aromatic hydroxy acids such as o-hydroxybenzoic acid, p-hydroxybenzoic acid, 1-hydroxynaphthalene-2-carboxylic acid or 3-hydroxynaphthalene-2-carboxylic acid, and sulfonic acids such as methanesulfonic acid or benzenesulfonic acid. These salts may be prepared from compounds of formula I by known salt-forming procedures.

Compounds of formula I which contain acidic, e.g. carboxyl, groups, are also capable of forming salts with bases, in particular pharmaceutically acceptable bases such as those well known in the art; suitable such salts include metal salts, particularly alkali metal or alkaline earth metal salts such as sodium, potassium, magnesium or calcium salts, or salts with ammonia or pharmaceutically acceptable organic amines or heterocyclic bases such as ethanolamines, benzylamines or pyridine. These salts may be prepared from compounds of formula I by known salt-forming procedures.

Specific especially preferred compounds of the invention are those described hereinafter in the Examples. Among these, most preferred compounds include those of formula III in which

(i) X is NH, R^1 is cyclopropyl, R^2 and R^4 are each hydrogen and R^3 is $NHCOOC(CH_3)_3$; or
(ii) X is NH, R^1 is cyclopropyl, R^2 and R^4 are each hydrogen and R^3 is morpholino; or
(iii) X is NH, R^1 is cyclobutyl, R^2 and R^4 are each hydrogen and R^3 is 4-tert-butoxycarbonyl-1-piperazinyl; or
(iv) X is NH, R^1 is cyclobutyl, R^2 and R^4 are each hydrogen and R^3 is $-N(CH_3)COCH_3$; or
(v) X is NH, R^1 is isopropyl, R^2 and R^4 are each hydrogen and R^3 is $-SO_2N(CH_3)_2$; or

(vi) X is NH, R^1 is cyclopropyl, R^2 and R^4 are each hydrogen and R^3 is 4-acetyl-1-piperazinyl; or

(vii) X is NH, R^1 is tert-butyl, R^2 is hydrogen and R^3 and R^4 together denote $-CH_2-O-CO-$; or

(viii) X is O, R^1 is cyclobutyl, R^2 and R^4 are each hydrogen and R^3 is $-N(CH_3)COCH_3$; or

(ix) X is NH, R^1 is cyclopropyl, R^2 and R^4 are each hydrogen and R^3 is 4-methyl-1-piperazinyl; or

(x) X is NH, R^1 is tert-butyl, R^2 and R^4 are each hydrogen and R^3 is $-N(CH_3)COCH_3$; or

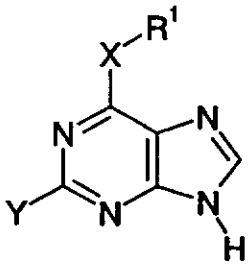
(xi) X is NH, R^1 is isopropyl, R^2 and R^4 are each hydrogen and R^3 is $-N(CH_2CH_3)COCH_3$; or

(xii) X is NH, R^1 is cyclopropyl, R^2 and R^4 are each hydrogen and R^3 is $-N(CH_3)COCH_2CH_3$;

the compounds being in free form or in the form of pharmaceutically acceptable salts, particularly hydrochloride or trifluoroacetate salts.

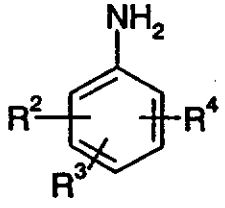
The present invention also provides a process for the preparation of compounds of formula I and their salts which comprises

(A) reacting a compound of formula



V

with a compound of formula



VI

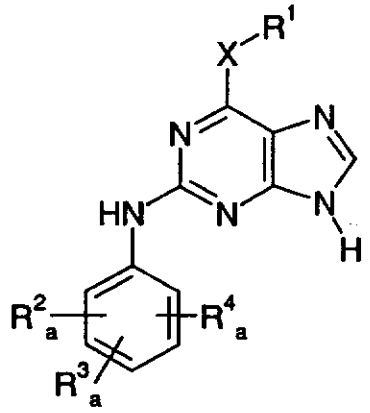
where X, R^1, R^2, R^3 and R^4 are as hereinbefore defined and Y is a leaving group, preferably halogen such as bromine, iodine or, in particular chlorine, a free functional group in the

compounds of formulae V and VI other that those involved in the reaction being protected, if necessary, by a removable protecting group; or

(B) for the preparation of a compound of formula I where R^2, R^3 or R^4 is a carboxy or carboxyalkyl group, cleaving a corresponding compound of formula I in which R^2, R^3 or R^4 is an alkoxycarbonyl or alkoxycarbonylalkyl group respectively; or

(C) for the preparation of a compound of formula I where R^2, R^3 or R^4 is an alkoxycarbonyl or alkoxycarbonylalkyl group, appropriately esterifying a corresponding compound of formula I in which R^2, R^3 or R^4 is a carboxy or carboxyalkyl group; or

(D) for the preparation of a compound of formula I where R^2, R^3 or R^4 is a group of formula $-SO_2N(R^{11})R^{12}$ as hereinbefore defined, appropriately aminating a corresponding compound of formula



VII

where R^1 is as hereinbefore defined and R^2_a, R^3_a and R^4_a are respectively the same as R^2, R^3 and R^4 as hereinbefore defined, with the exception that at least one of them is a group of formula $-SO_2$-Hal, where Hal is halogen, preferably chlorine or bromine; or

(E) for the preparation of a compound of formula I where R^2, R^3 or R^4 is a group of formula $-CON(R^{13})R^{14}$ as hereinbefore defined, appropriately aminating a corresponding compound of formula I where R^2, R^3 or R^4 is a carboxy group;

and optionally converting a resultant compound of formula I in protected form into a corresponding compound in unprotected form;

and recovering the resultant compound of formula I in free or salt form.

Protecting groups, their introduction and their removal are described, for example, in "Protective Groups in Organic Synthesis", T.W. Greene et al., John Wiley & Sons Inc, Second Edition, 1991.

Process variant (A) can be carried out using conventional procedures. It is conveniently, carried out in an inert organic solvent, preferably a polar solvent such as dioxan or N-methylpyrrolidone. The reaction temperature is conveniently from 50 to 250°C, preferably from 100 to 150°C. The reaction may be catalysed by a strong acid, a tertiary base or, preferably, metal ions such as Ag, Cu, Li, Ni, Zn, La, Yb or Sn. The reaction is conveniently carried out using 1 to 5 equivalents, for example 1 to 3 equivalents, of the compound of formula VI, per equivalent of the compound of formula V.

Compounds of formulae V and VI are known or may be prepared by methods analogous to those used for preparation of the known compounds. Thus compounds of formula V may be prepared, for example, as described in WO97/16452 or as described hereinafter in the Examples.

Process variant (B) may be carried out by conventional methods for ester cleavage, for example using conventional acid- or base- catalysed hydrolysis, or analogously as described hereinafter in the Examples.

Process variant (C) may be effected using conventional esterification procedures or analogously as described hereinafter in the Examples.

Process variant (D) may be effected by conventional procedures, for example by reaction of the halosulfonyl compound of formula VII with a compound of formula $HN(R^{11})R^{12}$ where R^{11} and R^{12} are as hereinbefore defined under known conditions or analogously as described hereinafter in the Examples. Compounds of formula VII are known or may be prepared by methods analogous to those used for the preparation of known compounds, for example by reacting a corresponding compound, which is unsubstituted in the position on the benzene ring where the halosulfonyl group is to be introduced, with a halosulfonating agent such as chlorosulfonic acid, e.g. as described hereinafter in the Examples.

Process variant (E) may be effected by conventional methods, for example by conversion of the corresponding carboxy compound into an acid halide and reacting the acid halide with a compound of formula $HN(R^{13})R^{14}$ where R^{13} and R^{14} are as hereinbefore defined under known conditions or analogously as described hereinafter in the Examples.

Compounds of formula I in free form may be converted into salt form, and vice versa, in a conventional manner. The compounds in free or salt form can be obtained in the form of hydrates or solvates containing a solvent used for crystallization.

Compounds of formula I can be recovered from the reaction mixture and purified in a conventional manner. Isomer mixtures can be separated into individual isomers, e.g. enantiomers, in a conventional manner, e.g. by fractional crystallization.

Compounds of formula I in free or salt form are useful as pharmaceuticals. Accordingly the invention also provides a compound of formula I in free or pharmaceutically acceptable salt form for use as a pharmaceutical. The compounds of formula I in free or pharmaceutically acceptable salt form, hereinafter referred to alternatively as "agents of the invention", inhibit the activity of the tyrosine protein kinase syk, which is an activator of pro-inflammatory cells driving an allergic response. This inhibitory property of the agents of the invention can be demonstrated in the following assay:

In this assay the effect of an agent of the invention on the phosphorylation of a peptide by syk kinase is determined. The phosphate is transferred from the terminal phosphate of adenosine triphosphate (ATP) to the biotin-modified peptide biotin-EDPDYEWPSA (available from Genosys) which is a known specific substrate for syk. When ^{33}P-phosphorylated peptide binds to streptavidin-polyvinyltoluene (PVT) Scintillation Proximity Assay (SPA) beads (available from Amersham), the emitted β-particles excite the fluorophore in the beads and produce light. Free ^{33}P-ATP in solution does not excite the fluorophore because the beads are separated from solution by flotation and so it is not in close proximity to the beads. The scintillation count is therefore a measure of the extent to which the test compound inhibits phosphorylation by syk kinase.

To the wells of an Optiplate (Canberra Packard) are added (i) the compound under test in DMSO/distilled water (10µl), (ii) 20µl of a composition formed by mixing 1mM biotin-EDPDYEWPSA (5.5µl), 300µM ATP (18.3 µl), and ^{33}P-ATP in sufficient amount to add 0.1µCi ^{33}P-ATP per well (1.1µl on the day of production) and making up the volume to 2.2ml with a buffer (Buffer A) prepared by dissolving tris-base (0.36g) in distilled water (80ml), adjusting the pH to 7.5 with 1M hydrochloric acid, adding 1M aqueous $MgCl_2$ (1.5ml), 50mM aqueous sodium orthovanadate (30µl) and 1M aqueous dithiothrietol (150µl), and making the volume up to 120 ml with distilled water, (iii) 0.5% w/v syk

kinase in Buffer A (20µl). The plate is incubated at room temperature for 30 minutes with shaking, the reaction is then terminated by addition to all wells of 150 µl of a mixture prepared by reconstituting 500mg Streptavidin-PVT SPA beads in 373 ml of Tris-buffered saline containing 673.6g cesium chloride, 20ml 0.5M EDTA and 27.5mg ATP (disodium salt) per litre. The plate is again incubated at room temperature for 30 minutes with shaking, then sealed using Top Seal-S (Canberra Packard) according to the manufacturer's insturctions and left to stand at room temperature for 1 hour. The resulting scintillations are counted using a Packard TopCount, each well being counted for 1 minute.

The procedure is repeated for different concentrations of test compound selected to cover the range of 0% to 100% inhibition and the concentration at which 50% inhibition of syk kinase phosphorylation occurs (IC_{50}) for each compound is determined from concentration-inhibition curves in a conventional manner.

The compounds of the Examples hereinbelow have IC_{50} values of the order of 1µM or less in the above assay. For instance, the compounds of Examples 1 to 7 hereinbelow have IC_{50} values of 3nM, 4nM, 5nM, 5nM, 9nM, 10nM and 10nM respectively, the compounds of Examples 102 to 104 have IC_{50} values of 5nM, 2nM and 3.6nM respectively and the compunds of Examples 138, 141, 170, 172, 188 and 201 have IC_{50} values of 14nM, 4.5nM, 10nM, 6nM, 5nM and 5nM respectively.

Having regard to their inhibition of syk kinase, and their suppression of IgE-mediated degranulation of mast cells, the agents of the invention are useful in the treatment of conditions which are mediated by syk kinase, particularly inflammatory or allergic conditions. Treatment in accordance with the invention may be symptomatic or prophylactic.

Accordingly, the agents of the invention are useful in the treatment of inflammatory or obstructive airways diseases. Inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics. (For convenience this particular asthmatic condition is referred to as "wheezy-infant syndrome".)

Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g. of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways hyperreactivity. It may further be evidenced by reduced requirement for other, symptomatic therapy, i.e. therapy for or intended to restrict or abort symptomatic attack when it occurs, for example anti-inflammatory (e.g. corticosteroid) or bronchodilatory. Prophylactic benefit in asthma may in particular be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognised asthmatic syndrome, common to a substantial percentage of asthmatics and characterised by asthma attack, e.g. between the hours of about 4 to 6 am, i.e. at a time normally substantially distant form any previously administered symptomatic asthma therapy.

Other inflammatory or obstructive airways diseases and conditions to which the present invention is applicable include adult respiratory distress syndrome (ARDS), chronic obstructive pulmonary or airways disease (COPD or COAD), including chronic bronchitis or dyspnea associated therewith, emphysema, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy. The invention is also applicable to the treatment of bronchitis of whatever type or genesis including, e.g., acute, arachidic, catarrhal, croupus, chronic or phthinoid bronchitis. Further inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis.

Having regard to their anti-inflammatory activity, in particular in relation to inhibition of eosinophil activation, agents of the invention are also useful in the treatment of eosinophil related disorders, e.g. eosinophilia, in particular eosinophil related disorders of the airways (e.g. involving morbid eosinophilic infiltration of pulmonary tissues) including hypereosinophilia as it effects the airways and/or lungs as well as, for example, eosinophil-related disorders of the airways consequential or concomitant to Löffler's syndrome, eosinophilic pneumonia, parasitic (in particular metazoan) infestation (including tropical eosinophilia), bronchopulmonary aspergillosis, polyarteritis nodosa (including Churg-

Strauss syndrome), eosinophilic granuloma and eosinophil-related disorders affecting the airways occasioned by drug-reaction.

Agents of the invention are also useful in the treatment of inflammatory or allergic conditions of the skin, for example psoriasis, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus, pemphisus, epidermolysis bullosa acquisita, and other inflammatory or allergic conditions of the skin.

Agents of the invention may also be used for the treatment of other diseases or conditions, in particular diseases or conditions having an inflammatory component, for example, treatment of diseases and conditions of the eye such as conjunctivitis, keratoconjunctivitis sicca, and vernal conjunctivitis, diseases affecting the nose including allergic rhinitis, and inflammatory bowel disease such as ulcerative colitis and Crohn's disease.

The effectiveness of an agent of the invention in inhibiting inflammatory conditions, for example in inflammatory airways diseases, may be demonstrated in an animal model, e.g. a mouse or rat model, of airways inflammation or other inflammatory conditions, for example as described by Szarka et al, J. Immunol. Methods (1997) 202:49-57; Renzi et al, Am. Rev. Respir. Dis. (1993) 148:932-939; Tsuyuki et al., J. Clin. Invest. (1995) 96:2924-2931; and Cernadas et al (1999) Am. J. Respir. Cell Mol. Biol. 20:1-8.

The agents of the invention are also useful as co-therapeutic agents for use in conjunction with anti-inflammatory or bronchodilatory drug substances, particularly in the treatment of obstructive or inflammatory airways diseases such as those mentioned hereinbefore, for example as potentiators of therapeutic activity of such drugs or as a means of reducing required dosaging or potential side effects of such drugs. An agent of the invention may be mixed with the anti-inflammatory or bronchodilatory drug in a fixed pharmaceutical composition or it may be administered separately, before, simultaneously with or after the anti-inflammatory or bronchodilatory drug. Such anti-inflammatory drugs include steroids, in particular glucocorticosteroids such as budesonide, beclamethasone, fluticasone or mometasone, and dopamine receptor agonists such as cabergoline, bromocriptine or ropinirole. Such bronchodilatory drugs include anticholinergic or antimuscarinic agents, in particular ipratropium bromide, oxitropium bromide and tiotropium bromide. Combinations of agents of the invention and steroids may be used, for example, in the treatment of COPD or, particularly, asthma. Combinations of agents of the invention and

anticholinergic or antimuscarinic agents or dopamine receptor agonists may be used, for example, in the treatment of asthma or, particularly, COPD.

In accordance with the foregoing, the invention also provides a method for the treatment of a condition mediated by syk kinase, for example an inflammatory or allergic condition, particularly an inflammatory or obstructive airways disease, which comprises administering to a subject, particularly a human subject, in need thereof an effective amount of a compound of formula I in a free or pharmaceutically acceptable salt form as hereinbefore described. In another aspect the invention provides a compound of formula I, in free or pharmaceutically acceptable salt form, as hereinbefore described for use in the manufacture of a medicament for the treatment of a condition mediated by syk kinase.

The agents of the invention may be administered by any appropriate route, e.g. orally, for example in the form of a tablet or capsule; parenterally, for example intravenously; by inhalation, for example in the treatment of inflammatory or obstructive airways disease; intranasally, for example in the treatment of allergic rhinitis; topically to the skin, for example in the treatment of atopic dermatitis; or rectally, for example in the treatment of inflammatory bowel disease.

In a further aspect, the invention also provides a pharmaceutical composition comprising a compound of formula I in free or pharmaceutically acceptable salt form together with a pharmaceutically acceptable diluent or carrier therefor. The composition may contain a co-therapeutic agent such as an anti-inflammatory or bronchodilatory drug as hereinbefore described. Such compositions may be prepared using conventional diluents or excipients and techniques known in the galenic art. Thus oral dosage forms may include tablets and capsules. Formulations for topical administration may take the form of creams, ointments, gels or transdermal delivery systems, e.g. patches. Compositions for inhalation may comprise aerosol or other atomizable formulations or dry powder formulations.

The invention includes (A) an agent of the invention in inhalable form, e.g. in an aerosol or other atomisable composition or in inhalable particulate, e.g. micronised form, (B) an inhalable medicament comprising an agent of the invention in inhalable form; (C) a pharmaceutical product comprising such an agent of the invention in inhalable form in association with an inhalation device; and (D) an inhalation device containing an agent of the invention in inhalable form.

Dosages of agents of the invention employed in practising the present invention will of course vary depending, for example, on the particular condition to be treated, the effect desired and the mode of administration. In general, suitable daily dosages for administration by inhalation are of the order of 0.1 to 100 mg/kg while for oral administration suitable daily doses are of the order of 1 to 1000 mg/kg.

The invention is illustrated by the following Examples.

Examples

Intermediates used in the Examples are prepared as follows:

1. Meta-(3,5-dimethylmorpholino) aniline

a. Meta-(3,5-dimethylmorpholino) nitrobenzene.

1-Fluoro-3-nitrobenzene (2.8g, 0.02M) and 2,6-dimethylmorpholine (12.5g, 0.12M) are heated in DMSO(33ml) at 100°C for 66 hours. The cooled mixture is poured into water (300ml). The precipitate is collected by filtration, washed with water and dried under vacuum; ES+ (M+Na) 258.96; mp 126.6-127.8°C.

b. Meta-(3,5-dimethylmorpholino) aniline

Meta-(3,5-dimethylmorpholino) nitrobenzene (1a) (2g, 8.5mmol) is hydrogenated in ethanol (50ml), over 10%Pd on carbon (200mg) for 1.5 hours. The catalyst is removed by filtration and the solvent removed evaporation to yield an oil. The enantiomers can be separated by silica column chromatography. ES+ (M+1) 207.36.

2. Meta-morpholino aniline

a. Meta-morpholino nitrobenzene

Using 1-fluoro-3-nitrobenzene (10g, 0.07M) and morpholine (33.5g, 0.38M) in DMSO (116ml) is prepared using the method described by Brown G.R. *et al* ., Tet. Lett. 40 (1999) 1219-1222. Filtration of the precipitated product yields the product; mp 113.8-115.5°C.

b. Meta-morpholino aniline

Meta-morpholino nitrobenzene (2a) (2g, 9.6mmol) is hydrogenated in a mixture of ethanol and ethyl acetate (50ml/10ml), over 10% Pd on carbon (200mg) for 1 hour. The catalyst is removed by filtration and the solvent removed by evaporation to yield a solid, which is dried under vacuum; ES+ (M+1) 179.35; mp 125.4-127.6°C.

3. Meta-(1-methylpiperazine) aniline

a. Meta-(1-methylpiperazine) nitrobenzene.

1-Fluoro-3-nitrobenzene (8.5ml, 0.08M) and 1-methyl piperazine (22.5ml, 0.247M) are heated in DMSO(100ml) at 100°C for 48 hours. The cooled mixture is poured into water (500ml). The aqueous mixture is cooled at 0°C and after 48 hours the precipitate is collected by filtration, washed with cold water and dried under vacuum; ES+ (M+1) 222, mp 107.5-108.2°C.

b. Meta-(1-methylpiperazine) aniline

Meta-(1-methylpiperazine) nitrobenzene (3a) (2g, 0.009M) is hydrogenated in ethanol (50ml), over 10%Pd on carbon (100mg) for 0.5 hours. The catalyst is removed by filtration and the solvent removed by evaporation to yield an oil; ES+ (M+1) 191.5; mp.87.6-89.0°C.

4. Para-(1-methylpiperazine) aniline

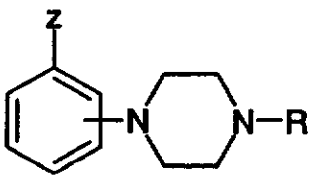
a. Para-(1-methylpiperazine) nitrobenzene

1-Fluoro-4-nitrobenzene (8.5ml, 0.08M) and 1-methyl piperazine (22.5ml, 0.247M) are heated in DMSO(100ml) at 100°C for 60 hours. The cooled mixture is poured into water (500ml) and the precipitate collected by filtration, washed with water and dried under vacuum; ES+ (M+1) 222; mp 57.4-58.9°C.

b. Para-(1-methylpiperazine) aniline

Para-(1-methylpiperazine) nitrobenzene (4a) (2g, 0.009M) is hydrogenated in ethanol (50ml), over 10%Pd on carbon (250mg) for 5 hours. The catalyst is removed by filtration and the solvent removed by evaporation to yield a solid. ES+ (M+1) 191.8; mp 101.5-103.4°C.

Intermediates 5a to 8b of formula



VIII

where Z is NO_2 or NH_2 and the substituted piperazinyl group is meta or para to Z are prepared analogously to those above. These are shown in the following table, together with the analogous method of preparation:

No.	Z	meta/ para	R	Method	ES+(M+1)	mp(°C)
5a	NO_2	m-	$COCH_3$	3(a)		151.3-153.6
5b	NH_2	m-	$COCH_3$	3(b)	220	127.8-129.4
6a	NO_2	p-	$COCH_3$	4(a)	250	98.2-101.3
6b	NH_2	p-	$COCH_3$	4(b)	220	138.8-140.7
7a	NO_2	m-	$COC(CH_3)_3$	3(a)		146.1-147.0
7b	NH_2	m-	$COC(CH_3)_3$	3(b)		
8a	NO_2	p-	$COC(CH_3)_3$	4(a)		88.4-90.1
8b	NH_2	p-	$COC(CH_3)_3$	4(b)	278	

9. N-acetyl-N-ethyl –4-aminoaniline

a. N-acetyl-N-ethyl-4-nitroaniline

To a suspension of N-ethyl 4-nitroaniline (1.5g, 9.026mmol) in benzene (15ml), is added acetylchloride (10ml) and the mixture refluxed for 40 minutes. The solvent is removed by evaporation. The residue is dissolved in ethyl acetate prior to washing with 2N sodium bicarbonate and water, drying ($MgSO_4$) and evaporation. The product is dried under vacuum; ES+ (M+1) 208.57.

b. N-acetyl-N-ethyl –4-aminoaniline

N-acetyl-N-ethyl-4-nitroaniline (9a) (1.8g, 8.64mmol) is hydrogenated in THF (30ml), over 10%Pd on carbon (100mg) for 1.5 hours. The catalyst is removed by filtration and the solvent removed evaporation. The product crystalises on standing in hexane, and following filtration, is dried under vacuum; ES+ (M+1) 178.88.

10. N-propionyl-N-methyl –4-aminoaniline

a. N-propionyl-N-methyl-4-nitroaniline.

The reaction is carried out using an analogous method to (9a), using N-methyl-4-nitroaniline (5g, 32.86mmol) in benzene (30ml), treated with propionyl chloride (15ml). ES+ (M+1) 208.88.

b. N-propionyl-N-methyl –4-aminoaniline

The reaction is carried out using an analogous method to (9b), using N-propionyl-N-methyl-4-nitroaniline (10a)(6.8g, 32.86mmol), 10%Pd on carbon (447mg) in THF (75ml). The hydrogenation yields an oil. ES+ (M+1) 178.87.

11. 4-(Ethyloxalylamido) aniline

a. 4-(Ethyloxalylamido) –1-*tert*-butyl carboxylate aniline.

To a solution of N-*tert*-butyl carboxylate-1,4-phenylenediamine (1g, 4.8mmol) and triethylamine (1.34ml) in dichloromethane (15ml), is added ethyl oxalyl chloride (0.655g, 4.8mmol) at 10°C. The mixture is stirred at ambient temperature for 10 minutes. The mixture is partitioned between dichloromethane and water. The organic layer is separated and washed with water, dried ($MgSO_4$) and evaporated. The residue is suspended in diethyl ether and hexane. Following filtration and washing with further diethyl ether/hexane, the product is dried under vacuum.

b. 4-(Ethyloxalylamido) aniline

To a solution of 4-(ethyloxalylamido) –1-*tert*-butyl carboxylate aniline (11a)(1.3g, 4.2mmol) in dichloromethane (25ml) at 10°C, is added trifluoroacetic acid (5ml) and stirred for 48 hours at 5°C. The mixture is basified with the addition of conc. ammonium hydroxide and diluted with ethyl acetate (200ml). This is washed with water/ice and with brine, dried ($MgSO_4$) and evaporated prior to purification by silica column chromatography. The product is obtained as orange crystals; mp 110-113°C.

12. 4-(Methyl malonylamido) aniline

a. 4-(Methyl malonylamido) –1-*tert*-butyl carboxylate aniline

To a solution of N-*tert*-butyl carboxylate-1,4-phenylenediamine (1g, 4.8mmol) and triethylamine (2ml) in dichloromethane (15ml), is added methyl malonyl chloride (1ml, 9.6mmol) at 10°C. The mixture is stirred at ambient temperature for 1 hour and then at 40°C for 30 minutes. The suspension is partitioned between dichloromethane and water. The organic layer is separated and washed with water, dried ($MgSO_4$) and evaporated. The product is purified by silica column chromatography.

b. 4-(Methyl malonylamido) aniline

To a solution of 4-(methyl malonylamido) –1-*tert*-butyl carboxylate aniline (12a)(1.3g, 4.2mmol) in dichloromethane (25ml) at 10°C, is added trifluoroacetic acid (5ml) and stirred for 48 hours at 5°C. The biphasic mixture is stirred at 0°C and basified with the

addition of conc. ammonium hydroxide and diluted with ethyl acetate (200ml). This is washed with water/ice and with brine, dried ($MgSO_4$) and evaporated prior to purification by silica column chromatography. The product is obtained as yellow crystals; mp 103-105°C.

13. 4-Butylamido aniline

a. 4-(Butylamido) –1-*tert*-butyl carboxylate aniline

To a solution of N-*tert*-butyl carboxylate-1,4-phenylenediamine (0.6g,2.88mmol) and triethylamine (0.803ml) in dichloromethane (10ml), is added butyryl chloride (0.299ml, 2.88mmol) at 10°C. The mixture is stirred at ambient temperature for 1 hour. The suspension is partitioned between dichloromethane and water. The organic layer is separated and washed with water, dried ($MgSO_4$) and evaporated to yield a crystalline product; ES+ (M+Na) 301.23.

b. 4-(Butylamido) aniline

To a solution of 4-(butylamido) –1-*tert*-butyl carboxylate aniline (13a)(0.77g, 2.77mmol) in dichloromethane (75ml) at 10°C, is added trifluoroacetic acid (2ml) and stirred for 18 hours at ambient temperature. The biphasic mixture is stirred at 0°C and basified with the addition of conc. ammonium hydroxide. This is washed with water, dried ($MgSO_4$) and evaporated prior to purification by silica column chromatography. The product is obtained in crystalline form.

14. N-Methyl cyclopropylamine

a. N-Carbobenzyloxy cyclopropylamine

The synthesis of N-carbobenzyloxy cyclopropylamine is carried out according to the method outlined in J. Heterocycl. Chem (1983), 1035, using carbobenzyloxychloride (56.3g, 0.33M), cyclopropylamine (19.6g, 0.344M), sodium carbonate (36.1g, 0.34M) in toluene (400ml) and water (400ml). The product is obtained as colourless crystals; ES+ (M+1) 192.6.

b. N-Methyl-N-carbobenzyloxy cyclopropylamine

The synthesis of N-carbobenzyloxy cyclopropylamine is carried out according to the method outlined in J. Heterocycl. Chem (1983), 1035, using N-carbobenzyloxy cyclopropylamine (14a)(10.5g, 0.055M) in DMF (80ml), sodium hydride(1.4g) and methyl iodide (4ml). The product is purified by vacuum distillation. Bp 86-92°C, 0.02 Torr.

c. N-Methyl cyclopropylamine

The sythesis of N-methyl cyclopropylamine is carried out according to the method outlined in J. Heterocycl. Chem (1983), 1035, using N-methyl-N-carbobenzyloxy cyclopropylamine(14b)(11.45g, 0.055M), concentrated hydrochloric acid(4.32ml), 10%Pd on carbon (700mg) in ethanol(135ml). The product is obtained and used as an ethereal solution.

15. Para-(1-ethylpiperazine) aniline

a. Para-(1-ethylpiperazine) nitrobenzene

1-Fluoro-4-nitrobenzene (0.54ml, 0.005M), 1-ethyl piperazine (1.9ml, 0.015M) and potassium carbonate (0.69g, 0.005M) are heated in acetonitrile (7ml) at 85°C under N_2 for 24 hours. The cooled mixture is partitioned between dichloromethane and water. The organic layer is separated and the aqueous extracted twice with dichloromethane. The combined organics are washed twice with brine, dried ($MgSO_4$), filtered and evaporated to yield a solid, which can be purified further by column chromatography if required. ES+(M+1) 236; mp. 79-81°C

b. Para-(1-ethylpiperazine) aniline

Para-(1-ethylpiperazine) nitrobenzene (0.5g, 0.002M) is hydrogenated in ethanol/ethyl acetate mixture (12.5ml/2.5ml), over 10% Pd on carbon (50mg) for 24 hours. The catalyst is removed by filtration and the solvent removed by evaporation to yield a solid which is dried under vaccum. ES+(M+1) 206; mp. 77-78°C

Intermediates 16a to 18b of formula VIII are prepared analogously to 15a and 15b. These are shown in the following table.

No.	Z	meta/ para	R	Method	ES+(M+1)	mp(°C)
16a	NO_2	p-	CH_2CH_2OH	15(a)	252	98-100.5
16b	NH_2	p-	CH_2CH_2OH	15(b)	222	-
17a	NO_2	p-	$CH_2COOCH_2CH_3$	15(a)	-	-
17b	NH_2	p-	$CH_2COOCH_2CH_3$	15(b)	264	-
18a	NO_2	p-	$COOCH_2CH_3$	15(a)	-	114-117
18b	NH_2	p-	$COOCH_2CH_3$	15(b)	-	-

Para-(1-hydroxypiperidine) nitrobenzene (19(a)) is prepared from 1-fluoro-4-nitrobenzene and 4-hydroxypiperidine analogously to 15(a); ES+(M+1) 223.

Para-(1-hydroxypiperidine) aniline (19(b)) is prepared analogously to 15(b) from 19(a); TOF ES+(M+1)193.

20. 1-(4-Anilino)-2-pyrrolidione

1-(4-nitrophenyl)-2-pyrrolidione (1g, 0.004M) is hydrogenated in ethyl acetate (75ml), over 5% Pd on carbon (160mg) for 18 hours. The catalyst is removed by filtration and the solvent removed by evaporation to yield a solid. ES+(M+1) 177; mp.129-130°C

21. 3,3-Dimethyl-1-(4-anilino)-2-azetidinone

3,3-Dimethyl-1-(4-nitrophenyl)-2-azetidinone (985mg, 0.004M) is hydrogenated in ethyl acetate (100ml), over 5% Pd on carbon (150mg) for 1 hour. The catalyst is removed by filtration and the solvent removed by evaporation to yield a solid. ES+(M+1)191; mp.113-114°C.

Compounds of formula III are prepared by one of the following general methods:

Method A: The corresponding 2-chloro-6-substituted purine of formula V is heated with 1.5 to 3 equivalents of the appropriate aniline of formula VI at temperatures between 90 and 190°C for times between 3 and 78 hours. The required product is isolated by (i) precipitation from the reaction mixture, washing with methanol, ethanol, water or dioxan and optionally isolation of a hydrochloride salt by treatment with HCl in dioxan or (ii) concentration from methanol or ethanol or (iii) concentration followed by flash silica chromatopgraphy or direct purification by preparative HPLC.

Method B: As Method A, except that the purine of formula V is heated with 1.5 equivalents of the aniline of formula VI and 1.5 equivalents of diisopropylethylamine at 130°C for 16-96 hours and the product is isolated by partitioning between ethyl acetate and water, followed by extraction with ethyl acetate, concentration and purification by flash silica chromatography.

Method C: As Method A, except that the reaction mixture is partitioned between ethyl acetate and water, basified with 1N NaOH or saturated aqueous $NaHCO_3$, extracted with ethyl acetate, concentrated and purified by flash silica chromatography.

Method D: The corresponding ester in ethanol, THF/aqueous methanol or THF/water is treated with 2.5 to 13 equivalents of 1N NaOH or LiOH at room temperature. The mixture is neutralised with 1N hydrochloric acid and solvent removed. The product is isolated by dissolution in ethanol, filtration and evaporation of the filtrate.

Method E: As method A, with the addition of concentrated hydrochloric acid or trifluoroacetic acid to the heated reaction mixture.

Method F: As Method A, followed by treatment of the product with chlorosulfonic acid. 400µL of a solution of the resulting sulfonyl chloride is added to a 1M solution of the appropriate amine of formula $HN(R^{11})R^{12}$ and, after 2 hours, the solvent is removed and the product purified by preparative HPLC.

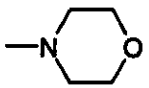
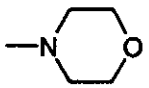
Method G: As Method A, with the addition of silver triflate (1 equivalent) to the heated reaction mixture.

Method H: The corresponding carboxylic acid is stirred in DMF, with 1 equivalent of the appropriate amine of formula $HN(R^{13})R^{14}$ dissolved in THF, and equivalent amounts of N-dimethylaminopyridine and benzotriazol-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate at 20°C for 16 hours. The product is isolated by precipitation from the reaction mixture on treatment with 1N hydrochloric acid, followed by purification by flash silica chromatography.

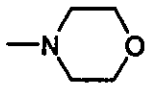
Method I: The corresponding carboxylic acid is reacted with excess thionyl chloride to give the corresponding acid chloride, which is treated with the appropriate amine of formula $HN(R^{13})R^{14}$), or appropriate alcohol, in benzene. The product is isolated by evaporation, and purified by preparative HPLC.

Method J: The corresponding 2-chloro-6-substituted purine of formula V and the appropriate aniline of formula VI (2.2 equivalents) are microwaved at 140°C, 50% power, for 10 minutes, followed by trituration with methanol. The product is isolated by filtration.

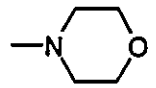
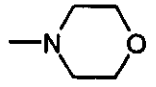
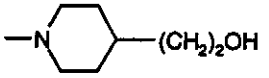
The prepared compounds of formula III, designated Examples 1 to 221, are shown in the table below, together with the general method used. In the table, CyPr denotes cyclopropyl, CyBu denotes cyclobutyl, CyPe denotes cyclopentyl and BnPp denotes N-benzylpiperidyl.

Ex.	X	R^1	R^2	R^3	R^4	Method
1	NH	CyPr	-CH=N-NH-		H	A
2	NH	CyPr	H	-CH=N-NH-		A
3	NH	CyPr	H	$NHCOOC(CH_3)_3$	H	C
4	NH	CH_3CH_2-	H	-CH=N-NH-		A
5	NH	CyPr	H		H	B
6	NH	CyBu	H	$-N(CH_3)COCH_3$	H	A
7	NH	CyBu	-NH-N=CH-		H	A
8	NH	$CyPrCH_2$-	H	-CH=N-NH-		A
9	NH	CyPr	H	$-CONHCH(CH_3)_2$	H	C
10	NH	CH_3CH_2-	H	$-N(CH_3)COCH_3$	H	A
11	NH	CyPr	H		H	B
12	NH	CyBu	H	-NH-N=CH-		A
13	NH	CyPr	H	$-N(CH_3)COCH_3$	H	A
14	O	CyBu	-CH=N-NH-		H	A
15	NH	$(CH_3)_3C$-	-CH=N-NH-		H	E
16	NH	$CyPrCH_2$-	-NH-N=CH-		H	E
17	NH	$CyPrCH_2$-	H	$-N(CH_3)COCH_3$	H	A

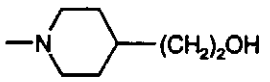
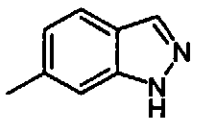
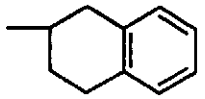
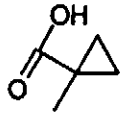
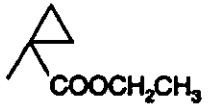
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18	O	CyBu	-NH-N=CH-		H	E
19	NH	CyPr	H	$-COOCH_3$	H	C
20	NH	CyBu	H	$-CONHCH(CH_3)_2$	H	C
21	NH	CyBu	H	$-CH=N-N(CH_3)-$		A
22	NH	CyPr	H	$-CH=N-N(CH_3)-$		A
23	NH	CyBu	H	$-NHCOCH_2COOCH_3$	H	A
24	NH	$-CH_2-CH=CH_2$	-CH=N-NH-		H	E
25	$N(CH_3)$	CyPr	-NH-N=CH-		H	E
26	NH	CyBu	H	$-COOCH_3$	H	C
27	NH	CyPr	H	H	H	A
28	NH	$(CH_3)_2CH-$	H	$-N(CH_3)COCH_3$	H	A
29	NH	CyPr	H	$-CH_2COOCH_2CH_3$	H	C
30	NH	CyPr	H	$-CH_2COOCH_2CH_3$	H	C
31	NH	CH_2CH_2OH	H	$-N(CH_3)COCH_3$	H	A
32	NH	CH_2CH_2OH	H		H	A
33	NH	CyBu	H	$-NHCOCH_3$	H	A
34	$N(CH_3)$	CyPr	-CH=N-NH-		H	E
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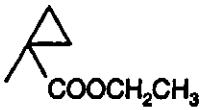
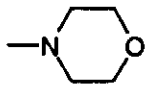
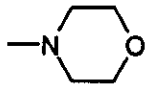
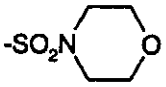
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37	NH	CyBu	H		H	C
38	NH	CyBu	H	$-NH_2$	H	C
39	NH	BnPp	$-OCH_3$	H	$-OCH_3$	E
40	$N(CH_3)$	CH_3	H	$-N(CH_3)COCH_3$	H	A
41	NH	CyPr	H	H	$-OCH_3$	A
42	NH	CyBu	H	$-NHCH_3$	H	A
43	NH	CyBu	H	$-NHCO(CH_2)_2CH_3$	H	A
44	NH	CyPr	$-OCH_3$	H	$-OCH_3$	A
45	NH	CyPr	H	H	$-SO_2NH_2$	A
46	NH	CyBu	H	$-NHCOOC(CH_3)_3$	H	C
47	$N(CH_3)$	CH_3	H		H	A
48	NH	CyPr	H	$-CH_2COOH$	H	D
49	NH	CyBu	H	$-CH_2COOCH_2CH_3$	H	C
50	NH	CyPr	H	H		B
51	NH	CyBu	H	H	$-OCH_3$	E
52	NH	CyPr	H	H	$-COOCH_2CH_3$	C
53	NH	$(CH_3)_2CH-$	H	H	$-OCH_3$	E
54	NH	CyPr	$-OCH_3$	$-OCH_3$	$-OCH_3$	A

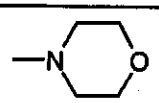
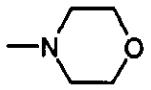
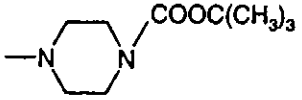
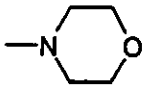
29 JAN 2004

55	NH	CyPe	H	H	-OCH_3	A
56	NH	CyBu	H	H	-$COOCH_2CH_3$	C
57	NH	CyPe	H	H	-OCH_3	A
58	NH	CyBu	H	-CH_2COOH	H	D
59	NH	CyBu	H	H		B
60	NH	BnPp	H	-$N(CH_3)COCH_3$	H	E
61	NH	CyBu	H	H	-COOH	D
62	NH	BnPp	H	H	H	A
63	NH		-OCH_3	H	-OCH_3	A
64	NH		H	$CH_2SO_2NHCH_3$	H	A
65	NH	CyPr	H	-NH_2	H	D
66	NH		H	-$N(CH_3)COCH_3$	H	D
67	NH	CH_3	H	-$N(CH_3)COCH_3$	H	A
68	NH		H	-$N(CH_3)COCH_3$	H	A

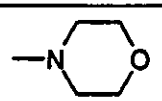
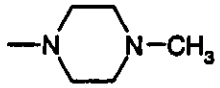
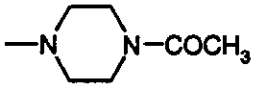
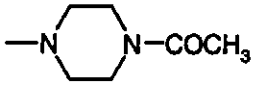
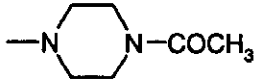
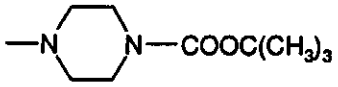
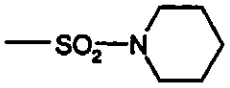
29 JAN 2004

69	NH		-NH-N=CH-		H	A
70	NH	$-CH_2CH_3$	H		H	A
71	NH	CH_3	H		H	A
72	NH	CyBu	H	$-NHCOCOCH_2CH_3$	H	A
73	NH	$-CH_2CH_3$	H	$-COOCH_3$	H	A
74	NH	CyBu	H	$-SO_2NH_2$	H	F
75	NH	CyBu	H	$-SO_2NHCH_3$	H	F
76	NH	CyBu	H	$-SO_2N(CH_3)_2$	H	F
77	NH	CyBu	H		H	F
78	NH	CyBu	H	$-SO_2NHCH_2CH_2OCH_3$	H	F
79	NH	$-CH_2CH_3$	H	-COOH	H	D
80	NH	$-CH_2CH_3$	H	$-CONHCH_2CH_3$	H	H
81	NH	CyPr	H	$-CONHCH_3$	H	C
82	NH	CyPr	H	H	$-CONHCH_3$	C
83	NH	CyBu	H	H	$-CONHCH_3$	C
84	NH	$-(CH_2)_2CH_3$	H	$-N(CH_3)COCH_3$	H	A

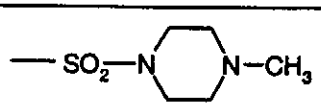
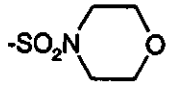
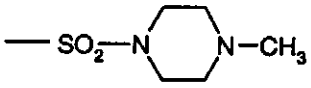
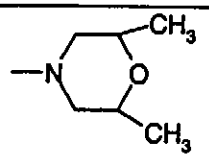
29 JAN 2004

85	NH	$-(CH_2)_2CH_3$	H		H	A
86	NH	$-(CH_2)_3CH_3$	H	$-N(CH_3)COCH_3$	H	A
87	NH	$-(CH_2)_3CH_3$	H		H	A
88	NH	CyPr	H	$-NHCOCF_3$	H	B
89	NH	$-CH_2CH_3$	H	$-CON(CH_3)_2$	H	I
90	NH	CyBu	H	$-N(CH_2CH_3)COCH_3$	H	A
91	NH	CyPr	H		H	C
92	NH	CyPr	H	-COOH	H	D
93	NH	CyBu	H	-COOH	H	D
94	NH	$-CH_2CH_3$	H	$-COOCH(CH_3)_2$	H	I
95	NH	CyBu	H	$-N(CH_3)COCH_2CH_3$	H	A
96	O	CyBu	H	$-N(CH_3)COCH_3$	H	G
97	O	CyBu	H	$-COOCH_3$	H	G
98	O	CyBu	H		H	G
99	O	$-CH_2CH_3$	H	$-N(CH_3)COCH_3$	H	G
100	O	$-CH_2CH_3$	H	$-COOCH_3$	H	G

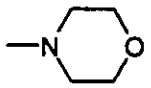
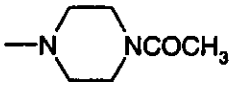
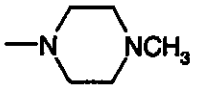
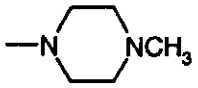
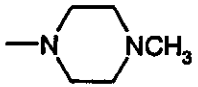
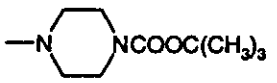
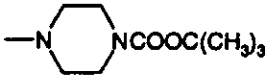
29 JAN 2004

101	O	$-CH_2CH_3$	H		H	G
102	NH	CyPr	H		H	A
103	NH	CyPr	H		H	A
104	NH	CyBu	H		H	A
105	NH	CyBu	H	H		A
106	NH	CyBu	H		H	A
107	NH	CyBu	H	$-SO_2NHCH_2CH_3$	H	F
108	NH	CyBu	H	$-SO_2N(CH_2CH_3)_2$	H	F
109	NH	CyBu	H	$-SO_2N(CH_2)_3CH_3$	H	F
110	NH	CyBu	H	$-SO_2NH(CH_2)_2OH$	H	F
111	NH	CyBu	H	$-SO_2NH(CH_2)_4OH$	H	F
112	NH	CyBu	H		H	F

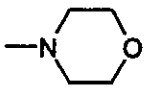
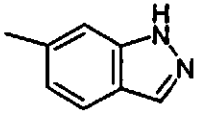
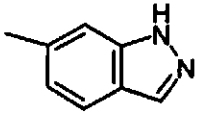
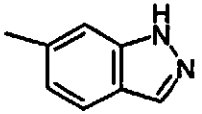
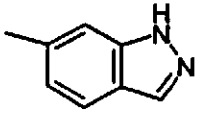
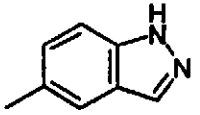
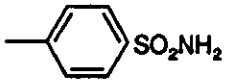
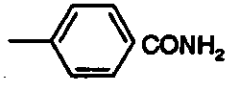
29 JAN 2004

113	NH	CyBu	H		H	F
114	NH	CyBu	H	$-SO_2NHCH_2COOCH_3$	H	F
115	NH	CyBu	H	$-SO_2NH(CH_2)_3COOCH_2CH_3$	H	F
116	NH	$-CH_2CH_3$	H	$-SO_2NH_2$	H	F
117	NH	$-CH_2CH_3$	H	$-SO_2NHCH_3$	H	F
118	NH	$-CH_2CH_3$	H	$-SO_2N(CH_3)_2$	H	F
119	NH	$-CH_2CH_3$	H		H	F
120	NH	$-CH_2CH_3$	H		H	F
121	NH	CyBu	H	H	H	A
122	NH	$-CH_2CH_3$	H	H	H	A
123	NH	$CyPrCH_2-$	H	H	H	A
124	NH	CyPr	H		H	B
125	NH	$-CH_2CH_3$	H	$-CONHCH_3$	H	C
126	NH	$-CH_2CH_3$	H	$-CONHCH(CH_3)_2$	H	C

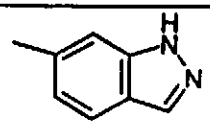
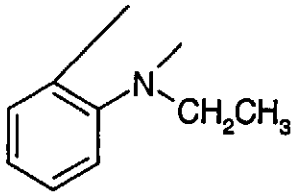
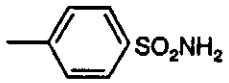
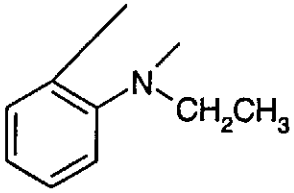
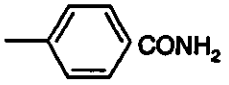
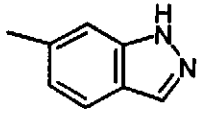
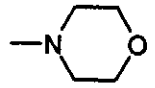
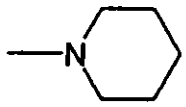
29 JAN 2004

127	NH	-C(CH_3)$_3$	H		H	A
128	NH	-C(CH_3)$_3$	H	-COOCH_3	H	A
129	NH	CyPr	H	H		A
130	NH	CyBu	H	-CONHCH_3	H	C
131	S	-CH_2CH_3	H	-N(CH_3)COCH_3	H	C
132	NH	CyBu	H		H	A
133	NH	CyPr	H	H		A
134	NH	CyBu	H	H		A
135	NH	CyPr	H	H		A
136	NH	CyBu	H	H		A
137	S	-CH_2CH_3	H	-COOCH_3	H	C
138	NH	-C(CH_3)$_3$	H	-N(CH_3)COCH_3	H	A

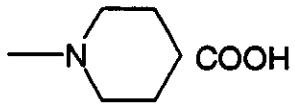
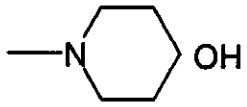
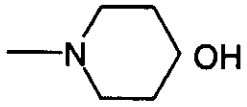
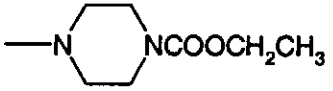
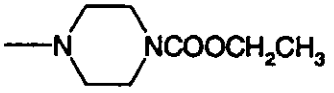
29 JAN 2004

139	S	$-CH(CH_3)_2$	H		H	C
140	S	$-CH(CH_3)_2$	H	$-COOCH_3$	H	C
141	NH		-CH=CH-CH=N-		H	A
142	NH		H	H	$-OCH_3$	A
143	NH		H	$-N(CH_3)COCH_3$	H	A
144	NH		H	H	H	A
145	NH		$-OCH_3$	H	$-OCH_3$	A
146	NH		H	$-N(CH_3)COCH_3$	H	A
147	NH		$-OCH_3$	H	$-OCH_3$	A

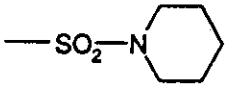
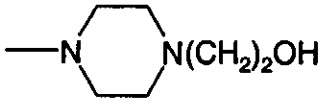
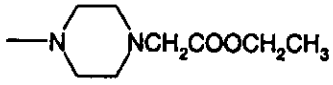
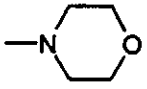
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148	NH				H	A
149	NH		H	-N(CH$_3$)COCH$_3$	H	A
150	NH				H	A
151	NH		-OCH$_3$	-OCH$_3$	-OCH$_3$	A
152	NH		-OCH$_3$	H	-OCH$_3$	A
153	S	-CH$_2$CH$_3$	H		H	C
154	NH	-CH$_2$CH$_3$	-S-CH=N-		H	C
155	NH	CyPr	H		H	A

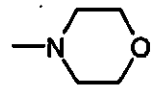
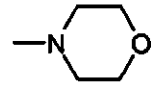
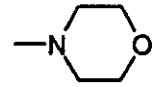
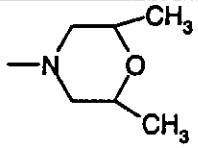
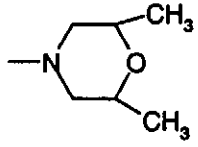
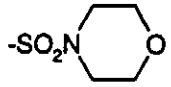
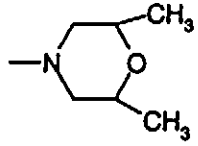
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156	NH	$-CH_2CH_3$	-CH=CH-CH=N-		H	A
157	NH	CyBu	H		H	D
158	NH	CyBu	H		H	A
159	NH	CyPr	H		H	A
160	NH	CyPr	-S-CH=N-		H	J
161	NH	CyBu	-S-CH=N-		H	J
162	NH	$-C(CH_3)_3$	-S-CH=N-		H	J
163	NH	CyPr	$-O-CH_2-CH_2-O-$		H	J
164	NH	CyPr	H		H	B
165	NH	CyPr	H	$-N(CH_2CH_3)COCH_3$	H	A
166	NH	$-CH_2CH_3$	H	$-N(CH_2CH_3)COCH_3$	H	A
167	NH	CyBu	H		H	B

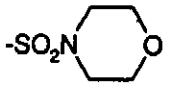
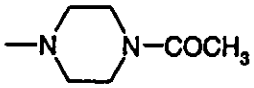
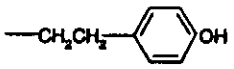
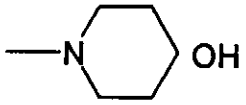
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168	NH	$-CH_2CH_3$	H	$-NHCOOC(CH_3)_3$	H	A
169	NH	$-CH_2CH_2CH_3$	H	$-NHCOOC(CH_3)_3$	H	A
170	NH	$-CH(CH_3)_2$	H	$-N(CH_2CH_3)COCH_3$	H	A
171	NH	$-(CH_2)_3CH_3$	H	$-N(CH_2CH_3)COCH_3$	H	A
172	NH	CyPr	H	$-N(CH_3)COCH_2CH_3$	H	A
173	NH	$-CH_2CH_3$	H	$-N(CH_3)COCH_2CH_3$	H	A
174	NH	$-CH(CH_3)_2$	H	-N=CH-S-		A
175	NH	$-(CH_2)_2CH_3$	H	-N=CH-S-		A
176	NH	$-CH_3$	H	$-SO_2N(CH_3)_2$	H	F
177	NH	CyPe	H	$-SO_2N(CH_3)_2$	H	F
178	NH	$-CH_2CH_3$	H	$-SO_2N(CH_2CH_3)_2$	H	F
179	NH	$-CH_2CH_3$	H		H	F
180	NH	CyBu	H		H	B
181	NH	CyPr	H		H	B
182	NH	$-CH_2$CyPr	H		H	A

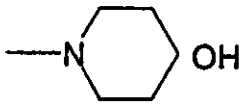
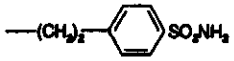
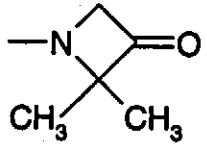
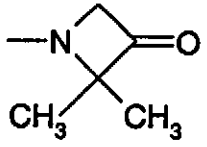
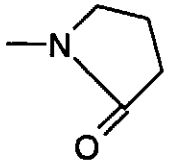
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183	NH	$-CH(CH_3)_2$	H		H	A
184	$N(CH_3)$	CyPr	H		H	A
185	NH	CyPe	H		H	A
186	NH	$-CH(CH_3)_2$	H	$-SO_2N(CH_2CH_3)_2$	H	F
187	NH	CyPe	H		H	A
188	NH	$-CH(CH_3)_2$	H	$-SO_2N(CH_3)_2$	H	F
189	NH	$-CH_3$	H		H	A
190	NH	$-CH(CH_3)_2$	H		H	F
191	NH	$-(CH_2)_2CH_3$	H		H	A
192	NH	$-(CH_2)_3CH_3$	H	$-SO_2N(CH_3)_2$	H	F

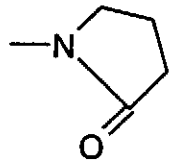
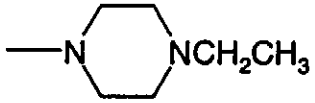
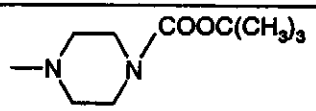
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193	NH	$-CH_3$	H	$-SO_2N(CH_2CH_3)_2$	H	F
194	NH	$-CH_3$	H		H	F
195	NH	$-C(CH_3)_3$	H		H	A
196	NH	$-(CH_2)_2CH_3$	H	$-SO_2N(CH_3)_2$	H	F
197	NH	CyBu	H	$-COOCH_2CH_3$	H	A
198	NH	$-C(CH_3)_3$	H	H	H	A
199	NH	$-C(CH_3)_3$	H	$-O-CH_2-CH_2-O-$		A
200	NH	$-CH_2$CyPr	H	$-CH_2-O-CO-$		A
201	NH	$-C(CH_3)_3$	H	$-CH_2-O-CO-$		A
202	NH	CyPe	H	$-CH_2-O-CO-$		A
203	NH	CyPr	H	$-COOCH_2CH_3$	H	A
204	NH		H	$-N(CH_3)COCH_3$	H	A
205	NH	$-C(CH_3)_3$	H	$-N(CH_2CH_3)COCH_3$	H	A
206	NH	$-CH_2$CyPr	H	$-N=CH-S-$		A
207	NH	$-CH_2$CyPr	H		H	A

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208	NH	$-CH(CH_3)_2$	H		H	A
209	NH	CyBu	H	$-N(COCH_3)-CH_2-CH_2-$		A
210	NH		H	$-N(CH_3)COCH_3$	H	A
211	NH	CyBu	H	$-COOCH(CH_3)_2$	H	I
212	NH	CyBu	H		H	A
213	NH	CyPr	H		H	A
214	NH	$-CH(CH_3)_2$	H	$-N(CH_3)COCH_2CH_3$	H	A
215	NH	$-(CH_2)_2CH_3$	H	$-N(CH_3)COCH_2CH_3$	H	A
216	NH	CyPr	H		H	A
217	NH	CyPr	H	$-NHCOOCH_3$	H	A

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218	NH	$-C(CH_3)_3$	H		H	A
219	NH	CyBu	H		H	B
220	NH	CyBu	H	$-N(CH_3)COCH_3$	H	A
221	NH	CyPe	H		H	A

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The preparations of certain of the above Examples are described in more detail below:

Abbreviations use are as follows:

NMP : N-methylpyrrolidone
DCM : dichloromethane
THF : tetrahydrofuran
PyBOP : benzotriazol-1-yloxy-tris-pyrrolidino-phosphonium hexafluorophosphate
DMAP : N,N-dimethyl-4-aminopyridine
DMF : dimethyl formamide
HPLC : high performance liquid chromatography
TLC : thin layer chromatography

Example 5

a. Cyclopropylamine (6.65g, 0.116M) and N,N-diisopropylethylamine (20.8ml, 0.116M) is added to a suspension of 2,6-dichloropurine (20g,0.106M) in n-butanol (200ml). The mixture is stirred at 60°C for 20 hours. The mixture is cooled and the precipitate isolated by filtration, washed with n-butanol and dried under vacuum to give 6-cyclopropylamino-2-chloropurine; ES+ (M+1) 209.5; mp 249.7°C dec.

b. A solution of 6-cyclopropylamino-2-chloropurine (0.535g, 2.5mmol) and 4-morpholinoaniline (0.683g, 3.8mmol) in NMP(2.5ml) is stirred at 130°C. After the solid has dissolved, N,N-diisopropylethylamine (0.65ml, 3.8mmol) is added and the mixture stirred at 130°C for 48 hours. The mixture is cooled and partitioned between ethyl acetate and water. The layers are separated and the aqueous layer extracted with ethyl acetate (2x100ml). The combined organics are evaporated and the residue purified by silica column chromatography (4%Methanol:DCM). The product is isolated as a brown solid which is dried under vacuum; ES+ (M+1) 352; mp 201.9-203.7°C.

Example 6

a. Cyclobutylamine (20g, 0.28M) and N,N-diisopropylethylamine (50.4ml, 0.28M) is added to a suspension of 2,6-dichloropurine (48.4g, 0.25M) in n-butanol (480ml). The mixture is stirred at 60°C for 20 hours. The mixture is cooled and the precipitate isolated

by filtration, washed with n-butanol and dried under vacuum to give 6-cyclobutylamino-2-chloropurine;ES+ (M-1) 222.5; mp 237.8°C dec.

b. A solution of 6-cyclobutylamino-2-chloropurine (100mg, 0.447mmol), 4-amino-N-methylacetanilide(220mg, 1.34mmol) in NMP(1ml) is stirred at 145°C, under argon. After 7 hours the solvent is removed by evaporation, the residue suspended in methanol and the suspension ultrasonicated for 3 minutes. The solid is separated by filtration, washed with cold methanol and dried under vacuum; ES- (M-1) 350; mp 314-318°C.

Example 19

a. A solution of 6-cyclopropylamino-2-chloropurine (5a)(0.209g, 1mmol) and methyl 4-aminobenzoate (0.377g, 2.5mmol) in NMP (2ml) is stirred at 130°C, for 16 hours. The mixture is diluted with water and treated with 4N sodium hydroxide to achieve pH14. The solution is extracted with ethyl acetate (4x100ml). The combined organics are washed with water, dried($MgSO_4$), filtered and evaporated. The residue is purified further by silica column chromatography, to yield a colourless oil; ES+ (M+1) 325.3.

Example 34

a. To a stirred ethereal solution of N-methylcyclopropylamine (50ml), is added 2,6-dichloropurine(1.3g, 6.8mmol). After 15 minutes n-butanol(3ml) is added and the suspension ultrasonicated at 40°C for 1 hour. A further aliquot of n-butanol is added and the ultrasonication continued for 2.5 hours. The mixture is stirred at ambient temperature for 16 hours. The precipitate isolated by filtration, washed with ether/methanol and dried under vacuum at 115°C to give 6-N-methylcyclopropylamino-2-chloropurine; ES+ (M+1) 223.5; mp 234-235°C dec.

b. To a hot solution of 6-N-methylcyclopropylamino-2-chloropurine (0.2g, 0.89mmol) in NMP(1.7ml), is added N-aminoindazole (0.26g, 1.96mmol) and conc. hydrochloric acid (7.7ml). The mixture is stirred at 107°C, for 20 hours and stirred at ambient temperature for 48 hours. The solvent is removed by evaporation and the residue triterated with methanol. The solid is isolated by filtration,washed with methanol and dried under vacuum, at 100°C. The solid is purified further by silica gel chromatography, and crystallised from methanol; ES+ (M+1) 321.3; mp 289-292°C.

Example 75

a. A solution of 6-cyclobutylamino-2-chloropurine(6a) (5g, 22.35mmol) and aniline (6.1ml, 67mmol) in NMP (25ml) is heated at 150°C, for 6 hours and allowed to cool. Upon standing at ambient temperature for 16 hours, the resulting crystals are isolated by filtration, washed with dioxane(50ml) and dried to give 6-cyclobutylamino-2-anilinopurine; ES+ (M+1) 280.86; mp 312-314°C.

b. 6-Cyclobutylamino-2-anilinopurine (200mg, 0.631mmol) is added cautiously to chlorosulfonic acid (2ml). The solution is stired at 50°C, for 2 hours. After cooling to ambient temperature, the mixture is added dropwise to ice/water(20ml). The precipitate is filtered and washed with cold water (5ml). The solid, 6-cyclobutylamino-2-(4-chlorosulfonylanilino)purine, is dissolved in NMP (2ml).

c. To a 1M solution of methylamine in ethanol(1ml), is added 400µl of the solution of 6-cyclobutylamino-2-(4-chlorosulfonylanilino)purine in NMP. After 2 hours, the solvent is removed and the residue purified using preparative HPLC; ES+ (M+1) 374.4.

Example 79

a. To a suspension of 2,6-dichloropurine (2g, 10.6mmol) in n-butanol (3ml), is added ethylamine (2M in THF)(15ml). The solution is stirred at 84°C for 2.5 hours and then cooled to ambient and stirred for a further 2 hours. The resulting precipitate is isolated by filtration, washed with n-butanol, methanol and ethyl acetate. The solid is dried at 70°C, under vacuum, for 16 hours to give 6-ethylamino-2-chloropurine; ES+ (M+1)197.5,198.2; mp 237-239°C.

b. A solution of 6-ethylamino-2-chloropurine (200mg, 1mmol), methyl –4-aminobenzoate (382mg, 2.5mmol) in NMP(0.77ml) is stirred at 123°C, under argon. After 22 hours the solvent is removed by evaporation, the residue suspended in methanol and the suspension ultrasonicated for 3 minutes. The solid is separated by filtration, washed with cold methanol and dried under vacuum, prior to further purification by silica column chromatography. The product is crystallised from methanol to give 6-ethylamino-2-(methyl-4-aminobenzoate)purine; ES+ (M+1) 312.84; mp 229-230°C.

c. To a suspension of 6-ethylamino-2-(methyl-4-aminobenzoate)purine (0.7g, 2mmol) in THF/water(1:1)(55ml), is added a solution of lithium hydroxide monohydrate (1.1g, 26mmol) in water (17ml). The mixture is stirred at 55°C for 48 hours. The solvent is removed by evaporation and the residue ultrasonicated in water. The solid is removed by filtration and the filtrate neutralised with conc. hydrochloric acid. The precipitate is isolated by filtration, washed with water and dried under vacuum, at 75°C; ES+ (M+1) 398.71; mp 301-303°C dec.

Example 80

To a solution of 6-ethylamino-2-(methyl-4-aminobenzoic acid)purine (79c)(50mg, 0.1493mmol) in DMF(1ml), stirring at 45°C, is added DMAP(20mg) and 2M ethylamine in THF(0.5ml). The mixture is cooled to 25°C and PyBOP (78mg) added. The mixture is stirred at ambient temperature for 20 hours, prior to the removal of solvent. The residue is suspended in water and ultrasonicated for 2 minutes. The mixture is acidified to pH4 with the addition of 1N hydrochloric acid. The product is isolated by filtration, washed with water and dried under vacuum. The product can be further purified using preparative TLC, to yield a crystalline solid; ES+ (M+1) 325; mp 295°C dec.

Example 89

A mixture of 10ml of the suspension of 6-ethylamino-2-(methyl-4-aminobenzoyl chloride)purine in benzene prepared in Example 94a and dimethylamine (33% solution in methanol)(2ml) is ultrasonicated for 40 minutes. and stirred at ambient temperature for 48 hours. The solvent is removed *in vacuo* and the residue suspended in water. The water is decanted and the oily residue purified by preparative HPLC. The product is crystallised from hot methanol and dried under vacum at 70°C; ES+ (M+1) 325.64; mp 262-264°C dec.

Example 94

a. A suspension of 6-ethylamino-2-(methyl-4-aminobenzoic acid)purine(79c)(150mg, 0.502mmol) in thionyl chloride(12ml) is agitated by the bubbling through of argon at ambient temperature for 16 hours. A further portion of thionyl chloride (5ml) is added and

the reaction continued for 20 hours. The residue, 6-ethylamino-2-(methyl-4-aminobenzoyl chloride)purine, is suspended in benzene (20ml).

b. To 10ml of the suspension of 6-ethylamino-2-(methyl-4-aminobenzoyl chloride)purine in benzene, is added iso-propanol (1.5ml)and triethylamine (0.2ml). The mixture is ultrasonicated for 30 minutes and stirred at ambient temperature for 48 hours. The solvent is removed *in vacuo* and the residue heated with water. The resultant crystalline solid is isolated by filtration and washed with water. It is purified further by preparative HPLC, to yield a colourless solid; ES-(M-1) 340.

Example 96

a. Sodium metal (1.53g, 0.067M) is dissolved in a mixture of cyclobutanol (8g, 0.11M) and dry THF (20ml), at 90°C, under nitrogen, for 4 hours. The mixture is cooled to 0°C and 2,6-dichloropurine (4.39g, 0.024M) added. The mixture is stirred at ambient temperature for 0.5 hours, prior to the addition of glacial acetic acid (10ml) and water (30ml). The precipitate is isolated by fitration, washed with water and dried under vacuum to yield a colourless solid, 6-cyclobutylether-2-chloropurine; ES+ (M+1) 224.74; mp 247.6-249.7°C dec.

b. To a suspension of 6-cyclobutylether-2-chloropurine (0.22g, 0.98mmol) in NMP(2ml), is added silver triflate(0.252g, 0.98mmol). The mixture is heated to 120°C to achieve dissolution. To this solution is added 4-amino-N-methyl acetanilide (0.402g, 2.4mol) and the mixture stirred at 120°C, for 16 hours. The mixture is cooled and water (10ml) and ethyl acetate(20ml) added. The phases are separated and the aqueous phase extracted with ethyl acetate(2x30ml). The combined organics are washed with water (30ml), saturated brine (50ml), dried ($MgSO_4$), filtered and evaporated. The residue is purified further by silica column chromatography; ES+ (M+1) 352.72.

Example 131

a. To a solution of ethanethiol (0.93ml, 12.5mmol) in dry THF(8ml), is added sodium hydride (0.48g, 12.5mmol). Once the effervesence has subsided, 2,6-dichloropurine (0.945g, 5mmol) is added. The mixture is stirred at ambient temperature, under nitrogen for 1.5 hours and then heated to reflux for 2 hours. The mixture is cooled, the solvent

removed by evaporation and purified by silica column chromatography, to yield 6-ethanemercapto-2-chloropurine; ES+ (M+1) 215.3, 217.2; mp 262-263°C.

b. A solution of 6-ethanemercapto-2-chloropurine (107mg, 0.5mmol) and 4-amino-N-methylacetanilide (246mg, 1.5mmol) in NMP (0.5ml), is heated at 140°C, for 17 hours. The cooled mixture is poured into water and extracted with ethyl acetate (3x50ml). The combined organics are dried($MgSO_4$), filtered and evaporated. The residue is purified by silica column chromatography, to yield a colourless crystalline product; ES+ (M+1) 342.76/343.46; mp 219-220C.

Example 220

The product of Example 6 (500mg, 1.42 mmol) is slurried in a mixture of dichloromethane (5ml) and water (5ml). Aqueous 4N sodium hydroxide is added to adjust the aqueous layer to pH 10. The organic layer is discarded and the aqueous layer is extracted with ethyl acetate. The solvent is removed to give a solid which is slurried in dichloromethane, filtered and dried; to yield a colourless solid. HPLC retention time 2.669 min (Hewlett Packard Chemstation at λ = 254nm, Phenomenex Luna C8 50 mm x 0.2 mm column, pore size 3µm, at 50°C; A = citrate-phosphate buffer pH3; B = acetonitrile; gradient 0 to 95% B in 3 minutes at 0.7 ml/min.

The other Examples are prepared analogously to the respective detailed Example above appropriate for the synthetic method (A to J) shown in the above table.

Characterising mass spectrometry and melting point data for the above Examples are shown, together with details of the salt-forming acid where the Example is a salt, in the following table:

Ex	Acid	ES+/ES-	MP°C	Ex	Acid	ES+/ES-	MP°C
1	HCl	MH+307	302-305	2	-	MH+307	315-317
3	-	MH+382	-	4	-	MH+295.4	329-330
5	-	MH+352	201.9-203.7	6	HCl	MH-350	314-318
7	-	MH+321	289-291	8	-	MH+321	322-324
9	-	MH-350	231.8-232.5	10	-	MH+325.6	300-302

11	HCl	MH+352	198.7-199.8	12	HCl	MH+320.7	380 dec
13	-	MH+327.6	-	14	-	M-H320.5	265-271
15	-	MH+323.2	198-220 dec	16	-	MH+321.3	319-321
17	-	MH+352.2	305-308	18	-	MH-320.3	248 dec
19	-	MH+325.3	164.5-169.1	20	-	MH-364	124.3-128.5
21	HCl	MH+335.0	350-355	22	-	MH+321.2	182-185
23	-	MH+396	182-185	24	HCl	MH+307	292-296
25	-	MH+320.7	292-296	26	-	MH+339	105.5-110.3
27	HCl	MH+267.2 M-H265.1	253-254	28	HCl	MH+340	303-305
29	-	MH+353	161.9-162.6	30	HCl	MH+353	216.8-219.4
31	HCl	MH+342	287-289	32	HCl	MH+356	302-305
33	HCl	M-H336	316-319	34	-	MH+321.3	289-292
35	-	MH+352.4	280-282	36	-	MH+366.2	271-273
37	-	MH+353	161.9-162.6	38	-	MH+353	216.8-219.4
39	HCl	MH+460	297-299	40	-	MH+325.6	314-317
41	-	MH+297.1	-	42	-	M-H307.9	214-216
43	HCl	-	337-339	44	-	MH+327.2	-
45	HCl	MH+346.2	250-300	46	-	MH+396	-
47	-	MH+339.67	225-228	48	HCl	MH+325	280 dec
49	-	MH+367	193.2-195.0	50	-	MH+394	148-150
51	HCl	MH+310.7	307-310	52	-	MH+339	189.6-192.4
53	HCl	MH+298.8	304-307	54	HCl	MH+357.3	251-252
55	-	MH+324.7	127-130	56	-	MH+353	113.2-115.7
57	HCl	MH+325	284-286	58	HCl	M-H337	290 dec
59	-	M-H406	136.3-138.4	60	HCl	M-H469.4	245-251
61	HCl	MH+325	350 dec	62	-	MH+399.8	-

63	-	MH+403.1	179-183	64	-	MH+464	-
65	HCl	MH+281	-	66	-	M-H379.98	225-230
67	HCl	MH+212.2	294-297	68	-	MH+410.07	253-255
69	HCl	MH+378.8	231-233	70	HCl	MH+340.17	317-321
71	HCl	MH+326.2	318-322	72	-	MH+396.14	240-241
73	-	MH+312.71	229-230	74	CF_3CO_2H	MH+360.4	-
75	CF_3CO_2H	MH+374.4	-	76	CF_3CO_2H	MH+388.4	-
77	CF_3CO_2H	MH+430.4	-	78	CF_3CO_2H	MH+418.4	-
79	-	MH+398.71	301-303	80	-	MH+325	295 dec
81	-	M-H322	227.6-229.3	82	-	M-H322	228.9-230.2
83	-	M-H336	214.3-216.7	84	-	MH+339.7	291 dec
85	-	MH+353.67	307 dec	86	-	MH+353.62	286 dec
87	-	MH+367.84	295 dec	88	-	MH+377.61	258-261 dec
89	CF_3CO_2H	MH+325.64	262-264 dec	90	HCl	MH+365.74	295-298
91	-	MH-449	226.7-228.4	92	-	MH-309	278.2-280.1
93	-	MH-323	-	94	CF_3CO_2H	M-H340	-
95	-	MH+365.78	243-245	96	-	MH+352.72	-
97	-	MH+339.68	-	98	-	MH+366.80	-
99	-	MH+326.80	-	100	-	MH+313.75	-
101	-	MH+340.51	-	102	-	MH-363	-
103	-	MH-391	-	104	-	MH-405	-
105	-	MH-405	-	106	-	MH-463	-
107	-	MH+387.83	257 dec	108	-	MH+415.64	263 dec
109	-	MH+415.69	278 dec	110	-	MH+403.66	242 dec
111	-	MH+431.79	231 dec	112	-	MH+427.76	255 dec
113	CF_3CO_2H	MH+442.69	250 dec	114	-	MH+431.57	240 dec
115	-	MH+473.67	237 dec	116	-	MH+333.59	267 dec
117	-	MH+347.53	260 dec	118	-	MH+361.78	231 dec
119	-	MH+403.72	252 dec	120	-	MH+416.69	246 dec
121	-	MH+280.86	312-314	122	-	MH+254.69	305-306
123	-	MH+280.76	304-306	124	-	MH+379.56	212-214 dec

125	-	MH+312.5	>250	126	-	M-1338.5	243-244
127	-	MH+368.1	227-229	128	-	MH+341.5	163-165
129	-	MH-391	-	130	-	MH-337	256.4-257.6
131	-	MH+342.76/ 343.46	219-220	132	-	MH-377	-
133	-	MH-363	-	134	-	MH-377	-
135	-	MH+451	-	136	-	MH+465	-
137	-	MH+330.5	196-199	138	-	MH+354.5	273-274
139	-	MH+371.5	138-140	140	-	MH+344.4	224-226
141	-	MH+393.7	327-332	142	HCl	MH+373.35	348-351
143	-	MH+414.2	-	144	HCl	MH+343.26	380-388
145	-	MH+403.3	331-334	146	-	MH+453.1	-
147	-	MH+406.3	-	148	-	MH+460.1	-
149	-	MH+445.3	-	150	-	MH+499.1	-
151	-	MH+436.8	-	152	-	MH+403.3	179-183

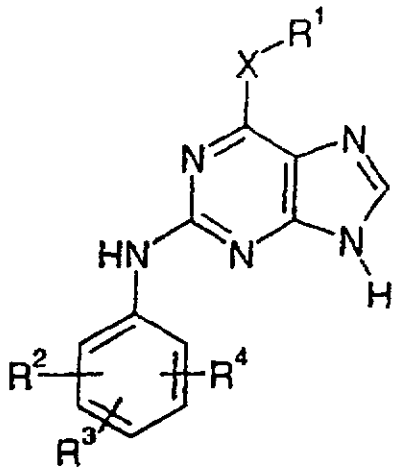
Ex	Acid	Mass Method	M+/M-	MP°C
153	-	AP+	MH+ 357.5	115-116
154	-	AP+	MH+ 312.8	222-224
155	-	ES+	MH+ 350	168.4-169.2
156	-	AP+	MH+ 306.5	254-256
157	-	ES+	MH+ 408	>300
158	-	ES+	MH+ 380	248.8-250.9
159	-	ES+	MH+ 366	244.4-245.2
160	-	AP+	MH+ 324.4	-
161	-	AP+	MH+ 338.4	-
162	-	AP+	MH+ 340.5	-
163	-	AP+	MH+ 325.5	-
164	-	ES+	MH+ 422.79	162-165
165	-	ES+	MH+ 351.85	-
166	-	ES+	MH+ 365.76	-
167	-	ES+	MH+ 436.88	-
168	-	TOF ES+	MH- 368.2	-
169	-	TOF ES+	MH- 382.2	-

170	-	TOF ES+	MH+ 354.2	-
171	-	TOF ES+	MH+ 366.2	-
172	-	TOF ES+	MH+ 352.8	-
173	-	TOF ES+	MH+340.14	-
174	-	TOF ES+	MH+ 326.7	-
175	-	TOF ES+	MH+ 326.8	-
176	CF_3COOH	TOF ES+	MH+ 347.78	264-267
177	CF_3COOH	ES+	MH+ 402.19	242-243
178	CF_3COOH	ES+	MH+ 389.82	248-250
179	CF_3COOH	ES+	MH+ 401.89	250-252
180	CF_3COOH	ES+	MH+ 408.79	143-144 dec
181	CF_3COOH	ES+	MH+ 436.86	146-148 dec
182	-	TOF ES+	MH+ 366	-
183	-	TOF ES+	MH+ 354	-
184	-	TOF ES+	MH+ 366	-
185	-	TOF ES+	MH+ 380	-
186	CF_3COOH	AP+	MH+ 404.5	267-268
187	-	TOF ES+	MH+ 408	-
188	CF_3COOH	AP-	M- 376.4	261-262
189	-	TOF ES+	MH+ 354	-
190	CF_3COOH	AP+	MH+ 416.3	245-247
191	-	TOF ES+	MH+ 382	-
192	CF_3COOH	AP+	MH+ 390.3	259-260
193	CF_3COOH	ES+	MH+ 376.14	267-268
194	CF_3COOH	ES+	MH+ 388.11	249-252
195	-	TOF ES+	MH+ 408.99	-
196	CF_3COOH	ES+	MH+ 375.74	245-246
197	CF_3COOH	ES+	MH+ 352.78	-
198	CF_3COOH	TOF ES+	MH+ 283.11	>280
199	-	TOF ES+	MH+ 341.22	-
200	-	TOF ES+	MH+ 337.17	-
201	-	TOF ES+	MH+ 339.16	-
202	-	TOF ES+	MH+ 351.19	-
203	CF_3COOH	TOF ES+	MH+ 339.12	-

204	CF_3COOH	TOF ES+	MH+ 418.11	-
205	-	TOF ES+	MH+ 368.15	-
206	-	TOF ES+	MH+ 338.07	-
207	-	TOF ES+	MH+ 380.19	-
208	-	TOF ES+	MH+ 368.18	-
209	-	AP+	MH+ 364.5	-
210	CF_3COOH	TOF ES+	MH+ 481.03	242-243
211	CF_3COOH	ES+	MH+ 366.9	258-259
212	CF_3COOH	ES+	MH+ 378	>285
213	CF_3COOH	ES+	MH+ 363.8	-
214	CF_3COOH	TOF ES+	MH+ 354.8	103.5-105.8
215	CF_3COOH	-	-	129.3-131.4
216	HCl	ES+	MH+ 349.9	280-283
217	-	-	-	-
218	-	-	-	-
219	CF_3COOH	ES+	MH+ 392.93	184-186 dec
220	-			
221	-	TOF ES+	MH+ 479.22	

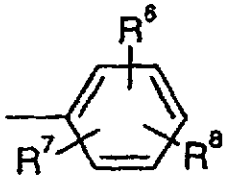
Claims

1. A compound of formula



I

in free or salt form, where
X is an oxygen or sulfur atom or a group NR^5,
R^1 is a C_{1-10}-alkyl, C_{2-10}-alkenyl, C_{3-10}-cycloalkyl, benzo-C_{3-10}-cycloalkyl, C_{3-10}-cycloalkyl-C_{1-10}-alkyl or C_{6-10}-aryl-C_{1-10}-alkyl group which optionally may be substituted by hydroxy, C_{1-10}-alkoxy, carboxy or C_{1-10}-alkoxycarbonyl or, when X is NR^5, R^1 may alternatively be a monovalent heterocyclic radical having up to 20 carbon atoms and one to four heteroatoms selected from nitrogen, oxygen and sulfur, or a group of formula



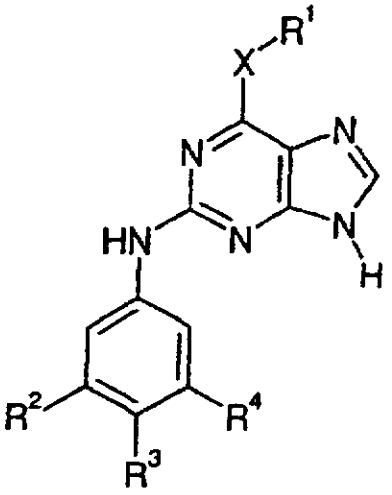
II

R^2, R^3, R^4, R^6, R^7 and R^8 are each independently hydrogen, halogen, C_{1-10}-alkyl, halo-C_{1-10}-alkyl, C_{1-10}-alkoxy, carboxy, C_{1-10}-alkoxycarbonyl, carboxy-C_{1-10}-alkyl, C_{1-10}-alkoxycarbonyl-C_{1-10}-alkyl, $-N(R^9)R^{10}$, $-SO_2N(R^{11})R^{12}$, C_1-C_4-alkylene-$SO_2N(R^{11})R^{12}$ or $-CON(R^{13})R^{14}$ or, when two of R^2, R^3 and R^4, or two of R^6, R^7 and R^8, are attached to adjacent carbon atoms on the indicated benzene rings, they denote, together with the carbon atoms to which they are attached, a carbocyclic group having 5 to 10 ring atoms or a heterocyclic group having 5 to 10 ring atoms of which one, two or three are hetero atoms selected from nitrogen, oxygen and sulfur,
R^5 is hydrogen or C_{1-10}-alkyl,
R^9 is hydrogen or C_{1-10}-alkyl and R^{10} is hydrogen, C_{1-10}-alkyl or $-COR^{15}$ where R^{15} is C_{1-10}-alkyl, halo-C_{1-10}-alkyl, C_{1-10}-alkoxy, C_{1-10}-alkoxy-C_{1-10}-alkyl, C_{1-10}-alkoxycarbonyl, carboxy-C_{1-10}-alkyl or C_{1-10}-alkoxycarbonyl-C_{1-10}-

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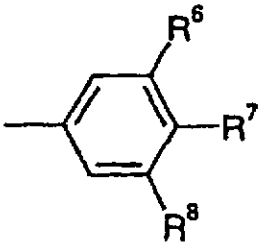
alkyl, or R^9 and R^{10}, together with the nitrogen atom to which they are attached, denote a heterocyclic group having 5 or 6 ring atoms of which one or two are hetero atoms selected from nitrogen, oxygen and sulfur,
R^{11} is hydrogen or C_{1-10}-alkyl and R^{12} is hydrogen, C_{1-10}-alkyl, hydroxy-C_{1-10}-alkyl, C_{1-10}-alkoxy-C_{1-10}-alkyl, carboxy-C_{1-10}-alkyl or C_{1-10}-alkoxycarbonyl-C_{1-10}-alkyl, or R^{11} and R^{12} together with the nitrogen atom to which they are attached denote a heterocyclic group having 5 or 6 ring atoms of which one or two are hetero atoms selected from nitrogen, oxygen and sulfur, and
R^{13} and R^{14} are each independently hydrogen or C_{1-10}-alkyl;
with the exception of 2-(p-n-butylanilino)-6-methoxypurine, 2-(p-n-butylanilino)-6-(methylthio)purine, 2,6-di(phenylamino)purine, 2,6-di(p-tolylamino)purine, and 2-(p-tolylamino)-6-(phenylamino)purine.

2. A compound according to claim 1, which is a compound of formula



III

in free or salt form, where
R^1 is as defined in claim 1 and, when it is a group of formula II, it is a group of formula



IV

and R^2, R^3, R^4, R^6, R^7 and R^8 are as defined in claim 1.

3. A compound according to claim 1 or 2, in which R^1 is a C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl, C_3-C_{10}-cycloalkyl, benzo-C_3-C_{10}-cycloalkyl, phenyl-C_1-C_{10}-alkyl or C_3-C_{10}-cycloalkyl-C_1-C_4-alkyl group which is optionally substituted by a hydroxy, carboxy or C_1-C_4-alkoxycarbonyl group, or R^1 is a heterocyclyl radical having 5 or 6 ring atoms and one or two nitrogen atoms, or one nitrogen atom and one oxygen atom, in the ring and optionally substituted on a ring nitrogen atom by C_1-C_4-alkyl, hydroxy-C_1-C_4-alkyl, C_1-C_4-alkylcarbonyl or phenyl-C_1-C_4-alkyl, or
R^1 is a group of formula II or formula IV respectively in which one of R^6, R^7 and R^8 is hydrogen, C_1-C_4-alkyl or C_1-C_4-alkoxy, and (i) the second and third of R^6, R^7 and R^8 are each independently hydrogen, C_1-C_4-alkyl or C_1-C_4-alkoxy or (ii) the second of R^6, R^7 and
R8 is hydrogen and the third of R^6, R^7 and R^8 is carboxy, C_1-C_{10}- alkoxycarbonyl, carboxy C_1-C_{10}-alkyl, C_1-C_{10}-alkoxycarbonyl-C_1-C_{10}-alkyl, -$N(R^9)R^{10}$, -$SO_2N(R^{11})R^{12}$, C_1-C_4-alkylene-$SO_2N(R^{11})R^{12}$ or -$CON(R^{13})R^{14}$, or (iii) the second and third of R^6, R^7 and R^8 are attached to adjacent carbon atoms in the indicated benzene ring and, together with said adjacent carbon atoms, denote a carbocyclic group having 5 or 6 ring atoms or a monocyclic heterocyclic group having 5 or 6 ring atoms and one or two nitrogen atoms in the ring,
one of R^2, R^3 and R^4 is hydrogen, C_1-C_4-alkyl or C_1-C_4-alkoxy and (a) the second and third of R^2, R^3 and R^4 are each independently hydrogen, C_1-C_4-alkyl or C_1-C_4-alkoxy, or (b) the second of R^2, R^3 and R^4 is hydrogen and

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the third of R^2, R^3 and R^4 is carboxy, C_1-C_{10}-alkoxycarbonyl, carboxy-C_1-C_{10}-alkyl, C_1-C_{10}-alkoxycarbonyl-C_1-C_{10}-alkyl, -$N(R^9)R^{10}$, -$SO_2N(R^{11})R^{12}$, C_1-C_4-alkylene-$SO_2N(R^{11})R^{12}$ or -$CON(R^{13})R^{14}$, or (c) the second and third of R^2, R^3 and R^4 are attached to adjacent carbon atoms in the indicated benzene ring and, together with said adjacent carbon atoms, denote a carbocyclic group having 5 or 6 ring atoms or a heterocyclic group having S to 10 ring atoms, of which one or two are hetero atoms selected from nitrogen, oxygen and sulfur,
R^9 is hydrogen or C_1-C_{10}- and R^{10} is hydrogen, C_1-C_{10}-alkyl, or -COR^{15} where R^{15} is C_1-C_{10}-alkyl, C_1-C_{10}-haloalkyl, C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl, C_1-C_{10}-alkoxycarbonyl, carboxy-C_1-C_{10}-alkyl, or C_1-C_{10}-alkoxycarbonyl-C_1-C_{10} alkyl, or R^9 and R^{10} together with the nitrogen atom to which they are attached, denote a heterocyclic group having 5 or 6 ring atoms and one or two nitrogen atoms, or one nitrogen atom and one oxygen atom, in the ring,
R^{11} is hydrogen or C_1-C_{10}-alkyl and R^{12} is hydrogen, C_1-C_{10}-alkyl, hydroxy-C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl, carboxy-C_1-C_{10}-alkyl, or C_1-C_{10}-alkoxycarbonyl-C_1-C_{10}-alkyl, or R^{11} and R^{12} together with the nitrogen atom to which they are attached denote a heterocyclic group having 5 or 6 ring atoms and one or two nitrogen atoms, or one nitrogen atom and one oxygen atom, in the ring,
and R^{13} and R^{14} are each independently hydrogen or C_1-C_{10}-alkyl.

4. A compound according to claim 1 or 2 in which:

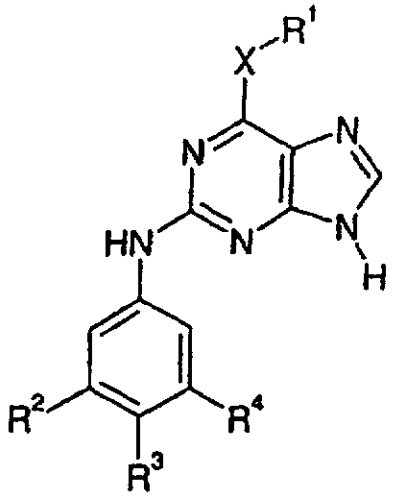
X is a group NR^5,
R^1 is a C_1-C_4-alkyl, C_2-C_4-alkenyl, C_3-C_5 cycloalkyl, benzo-C_5-C_6-cycloalkyl, phenyl-C_1-C_4-alkyl or C_3-C_5 cycloalkyl-C_1-C_4-alkyl group, which is optionally substituted by a hydroxy, carboxy or C_1-C_4-alkoxycarbonyl group, or R^1 is a heterocyclyl radical having 5 or 6 ring atoms and one or two nitrogen atoms, or one nitrogen atom and one oxygen atom, in the ring and optionally substituted on a ring nitrogen atom by C_1-C_4 alkyl, C_1-C_4-hydroxyalkyl, C_1-C_4-alkylcarbonyl or phenyl-C_1-C_4-alkyl, or R^1 is a group of formula IV in which one of R^6, R^7 and R^8 is hydrogen, C_1-C_4-alkyl or alkoxy, and (i) the second and third of R^6, R^7 and R^8 are each independently hydrogen, C_1-C_4-alkyl or C_1-C_4-alkoxy or (ii) the second of R^6, R^7 and R^8 is hydrogen and the third of R^6, R^7 and R^8 is -$N(R^9)R^{10}$, -$SO_2N(R^{11})R^{12}$ or -$CON(R^{13})R^{14}$, or (iii) the second and third of R^6, R^7 and R^8 are attached to adjacent carbon atoms in the indicated benzene ring and together with said adjacent carbon atoms denote a carbocyclic group having 5 or 6 ring atoms or a heterocyclic group having 5 or 6 ring atoms, of which one or two are nitrogen atoms,
one of R^2, R^3 and R^4 is hydrogen, C_1-C_4-alkyl or C_1-C_4-alkoxy and (a) the second and third of R^2, R^3 and R^4 are each independently hydrogen, C_1-C_4-alkyl or C_1-C_4-alkoxy or (b) the second of R^2, R^3 and R^4 is hydrogen and the third of R^2, R^3 and R^4 is carboxy, C_1-C_4-alkoxycarbonyl, carboxy-C_1-C_4-alkyl, C_1-C_4-alkoxycarbonyl-C_1-C_4-alkyl, -$N(R^9)R^{10}$, -$SO_2N(R^{11})R^{12}$, C_1-C_4-alkylene-$SO_2N(R^{11})R^{12}$ or -$CON(R^{13})R^{14}$, or (c) the second and third of R^2, R^3 and R^4 are attached to adjacent carbon atoms in the indicated benzene ring and denote, together with said adjacent carbon atoms, a heterocyclic group having 5 to 10 ring atoms, of which one or two are hetero atoms selected from nitrogen, oxygen and sulfur,
R^5 is hydrogen or C_1-C_4-alkyl,
R^9 is hydrogen or C_1-C_4 alkyl and R^{10} is hydrogen, C_1-C_4 alkyl, or -COR^{15} where R^{15} is C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-alkoxy-C_1-C_4 alkyl, C_1-C_4-alkoxycarbonyl, or C_1-C_4-alkoxycarbonyl-C_1-C_4-alkyl, or R^9 and R^{10} together with the nitrogen atom to which they are attached denote a heterocyclic group having 5 or 6 ring atoms including one or two ring nitrogen atoms, or one nitrogen ring atom and one oxygen ring atom,
R^{11} is hydrogen or C_1-C_4-alkyl and R^{12} is hydrogen, C_1-C_4-alkyl, hydroxy-C_1-C_4-alkyl, C_1-C_4-alkoxy- C_1-C_4-alkyl or C_1-C_4-alkoxycarbonyl- C_1-C_4-alkyl, or R^{11} and R^{12} together with the nitrogen atom to which they are attached denote a heterocyclic group having 5 or 6 ring atoms including one or two ring nitrogen atoms, or one nitrogen ring atom and one oxygen ring atom, and
R^{13} and R^{14} are each independently hydrogen or C_1-C_4-alkyl.

5. A compound according to claim 1 or 2, in which X is an oxygen atom, R^1 is C_1-C_4-alkyl or C_3-C_{10} cycloalkyl, one of R^2, R^3 and R^4 is hydrogen, and either (i) the second of R^2, R^3 and R^4 is hydrogen and the third of R^2, R^3 and R^4 is carboxy, C_1-C_4-alkoxycarbonyl or -$N(R^9)R^{10}$ where R^9 and R^{10} together with the attached nitrogen atom denote a heterocyclic group having 5 or 6 ring atoms including two ring nitrogen atoms or one ring nitrogen atom and one ring oxygen atom, or (ii) the second and third of R^2, R^3 and R^4 are attached to adjacent carbon atoms on the indicated benzene ring and together with the carbon atoms to which they are attached denote a heterocyclic group having 5 or 6 ring atoms, of which one or two are nitrogen atoms.

6. A compound according to claim 1 or 2, in which X is a sulfur atom, R^1 is C_1-C_4-alkyl, two of R^2, R^3 and R^4 are

hydrogen and the third of R^2, R^3 and R^4 is carboxy, C_1-C_4-alkoxycarbonyl, or -N(R^9)R^{10} where R^9 is hydrogen or C_1-C_4-alkyl and R^{10} is -COR^{15} where R^{15} is C_1-C_4-alkyl, or R^9 and R^{10} together with the nitrogen atom to which they are attached denote a heterocyclic group having 5 or 6 ring atoms including one or two ring nitrogen atoms or one ring nitrogen atom and one ring oxygen atom.

7. A compound for formula III



III

in free or pharmaceutically acceptable salt form, where

(i) X is NH, R^1 is cyclopropyl, R^2 and R^4 are each hydrogen and R^3 is $NHCOOC(CH_3)_3$; or
(ii) X is NH, R^1 is cyclopropyl, R^2 and R^4 are each hydrogen and R^3 is morpholino; or
(iii) X is NH, R^1 is cyclobutyl, R^2 and R^4 are each hydrogen and R^3 is 4-tert-butoxycarbonyl-1-piperazinyl; or
(iv) X is NH, R^1 is cyclobutyl, R^2 and R^4 are each hydrogen and R^3 is $-N(CH_3)COCH_3$; or
(v) X is NH, R^1 is isopropyl, R^2 and R^4 are each hydrogen and R^3 is $-SO_2N(CH_3)_2$; or
(vi) X is NH, R^1 is cyclopropyl, R^2 and R^4 are each hydrogen and R^3 is 4-acetyl-1-piperazinyl; or
(vii) X is NH, R^1 is tert-butyl, R^2 is hydrogen and R^3 and R^4 together denote $-CH_2-O-CO-$; or
(viii) X is O, R^1 is cyclobutyl, R^2 and R^4 are each hydrogen and R^3 is $-N(CH_3)COCH_3$; or
(ix) X is NH, R^1 is cyclopropyl, R^2 and R^4 are each hydrogen and R^3 is 4-methyl-1-piperazinyl; or
(x) X is NH, R^1 is tert-butyl, R^2 and R^4 are each hydrogen and R^3 is $-N(CH_3)COCH_3$; or
(xi) X is NH, R^1 is isopropyl, R^2 and R^4 are each hydrogen and R^3 is $-N(CH_2CH_3)COCH_3$; or
(xii) X is NH, R^1 is cyclopropyl, R^2 and R^4 are each hydrogen and R^3 is $-N(CH_3)COCH_2CH_3$;

8. A compound according to any preceding claim for use as a pharmaceutical.

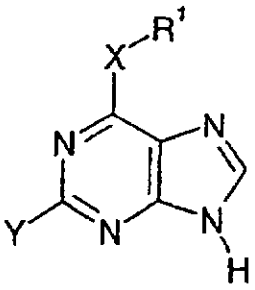
9. A pharmaceutical composition comprising a compound according to any one of claims 1 to 8 together with a pharmaceutically acceptable diluent or carrier therefor.

10. Use of a compound according to any one of claims 1 to 8 for the preparation of a medicament for the treatment of an inflammatory or obstructive airways disease.

11. A process for the preparation of compounds of formula I and their salts which comprises

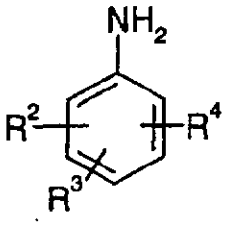
(A) reacting a compound of formula

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V

with a compound of formula



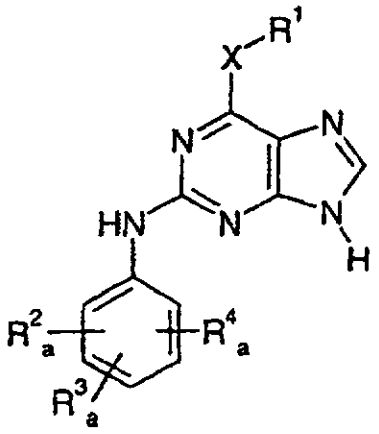
VI

where X, R^1, R^2, R^3 and R^4 are as hereinbefore defined and Y is a leaving group, a free functional group in the compounds of formulae V and VI other that those involved in the reaction being protected, if necessary, by a removable protecting group; or

(B) for the preparation of a compound of formula I where R^2, R^3 or R^4 is a carboxy or carboxy-C_{1-10}-alkyl group, cleaving a corresponding compound of formula I in which R^2, R^3 or R^4 is an C_{1-10}-alkoxycarbonyl or C_{1-10}-alkoxycarbonyl-C_{1-10}-alkyl group respectively; or

(C) for the preparation of a compound of formula I where R^2, R^3 or R^4 is an C_{1-10}-alkoxycarbonyl or C_{1-10}-alkoxycarbonyl-C_{1-10}-alkyl group, appropriately esterifying a corresponding compound of formula I in which R^2, R^3 or R^4 is a carboxy or carboxy-C_{1-10}-alkyl group; or

(D) for the preparation of a compound of formula I where R^2, R^3 or R^4 is a group of formula $-SO_2N(R^{11})R^{12}$ as hereinbefore defined, appropriately aminating a corresponding compound of formula



VII

where R^1 is as hereinbefore defined and $R^2{}_a$, $R^3{}_a$ and $R^4{}_a$ are respectively the same as R^2, R^3 and R^4 as hereinbefore defined, with the exception that at least one of them is a group of formula $-SO_2$-Hal, where Hal is halogen; or

(E) for the preparation of a compound of formula I where R^2, R^3 or R^4 is a group of formula $-CON(R^{13})R^{14}$ as hereinbefore defined, appropriately aminating a corresponding compound of formula I where R^2, R^3 or R^4 is a carboxy group;

and optionally converting a resultant compound of formula I in protected form into a corresponding compound in unprotected form;

and recovering the resultant compound of formula I in free or salt form.