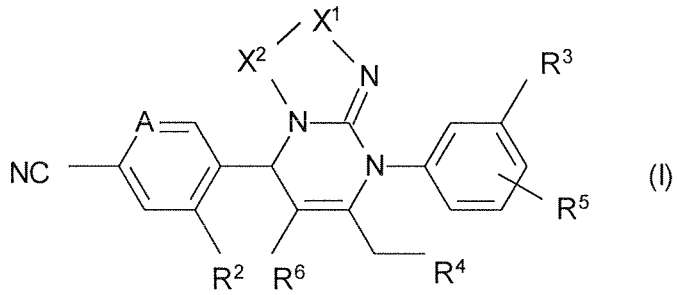
Rev. Respir. Dis. 1989, *140*, 1527-1537). The major pathogenic determinant in COPD has long been considered to be the protease-anti-protease balance (also known as the 'elastase:anti-elastase hypothesis'), in which an imbalance of HNE and endogenous antiproteases such as α 1-antitrypsin (α_1-AT), secretory leukocyte protease inhibitor (SLPI) and pre-elafin leads to the various inflammatory disorders of COPD. Individuals that have a genetic deficiency of the protease inhibitor α 1-antitrypsin develop emphysema that increases in severity over time (Laurrell, C. B.; Erikkson, S *Scand. J. Clin. Invest.* 1963 *15*, 132-140). An excess of HNE is therefore destructive, leading to the breakdown of pulmonary morphology with loss of elasticity and destruction of alveolar attachments of airways in the lung (emphysema) whilst simultaneously increasing microvascular permeability and mucus hypersecretion (chronic bronchitis).

Brief description of the invention

This invention provides novel compounds which are inhibitors of HNE, and are useful in the treatment of diseases or conditions in which HNE activity plays a part.

Detailed Description of the Invention

In one embodiment, the invention provides a compound of formula (I):



(I)

wherein

A is C-R^1 ~~or N~~;

$\mathbf{R^1}$ and $\mathbf{R^2}$ are ~~selected from~~ hydrogen~~, halogen, nitro, cyano, -S(O)$_n$$\mathbf{R^7}$, amino, mono- or di-$C_1$-$C_6$-alkylamino, -NHCO$\mathbf{R^8}$, -NH(C=O)NH$\mathbf{R^9}$, -NHSO$_2$$\mathbf{R^{10}}$, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, hydroxyl, C_1-C_6-alkoxy or C_2-C_6-alkenyloxy wherein C_1-C_6-alkyl and C_1-C_6-alkoxy can be further substituted with one to three identical or different radicals selected from the group consisting of halogen, hydroxy and C_1-C_4-alkoxy~~;

$\mathbf{R^3}$~~**n**~~ is 3-trifluoromethyl~~0~~, 3-chloro~~1~~ or 3-bromo~~2~~;

$\mathbf{R^4}$ is hydrogen;

R^3 and R^5 areis independently selected from hydrogen, halogen and C_1-C_6-alkyl which can be further substituted with halogen;

R^7 is selected from C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, C_1-C_4-alkoxy, amino, mono- or di-C_1-C_4-alkylamino, hydroxycarbonyl, aminocarbonyl, C_3-C_6-cycloalkyl, phenyl or C_2-C_6-alkenyl; wherein C_3-C_6-cycloalkyl can be substituted with one or more of C_1-C_4-alkyl, hydroxyl and C_1-C_4-alkoxy and phenyl can be substituted with one or more of halogen, cyano, C_1-C_4-alkyl, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy and C_1-C_4-alkoxy;

R^8 and R^9 are independently selected from hydrogen and C_1-C_6-alkyl, and R^{10} is C_1-C_6-alkyl;

R^6 is $-CO_2R^{11}$, $-CONR^{12}R^{13}$ or $-COR^{14}$;

$-X^1-X^2-$ is $-CR^{15}=N-$ or $-NR^{19}-CO-$;

R_{12} is hydrogen or C_1-C_6-alkyl;

R^{11}, R^{13}, R^{14} each independently represents a radical of formula $-[Alk^1]_p-[Q]_t-[Alk^2]_q-Z$ wherein

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

provided that p, q and t isare not simultaneously 0;

Alk^1 and **Alk**^{2} each independently represent a C_1-C_6 alkylene radical;

Q represents a divalent mono- or bicyclic carbocyclic or heterocyclic radical having 3-9 ring members;

Z is

(i) a monocyclic heterocyclic ring of 5 or 6 ring members or a bridged heterocyclic ring system of 7 or 8 ring members, wherein the ring heteroatoms are nitrogen, said monocyclic ring or bridged ring system being linked to the rest of the molecule via a ring carbon, and wherein a ring nitrogen may be

quaternised by substitution by C_1-C_3 alkyl or benzyl the latter being optionally substituted in the phenyl ring thereof; or

(ii) $-N(R^A)(R^B)$ wherein R^A and R^B are independently hydrogen, or a C_1-C_6-alkyl, C_3-C_6-cycloalkyl group, or a phenyl(C_1-C_6)alkyl- group optionally substituted in the phenyl ring thereof; or, taken together with the nitrogen to which they are attached form a monocyclic heterocyclic ring of 5 to 7 ring atoms which may contain a further heteroatom selected from N, O and S; or

(iii) $-N^+(R^A)(R^B)(R^C)$ wherein

R^A, R^B and R^C are independently a C_1-C_6-alkyl, C_3-C_6-cycloalkyl group, or a phenyl(C_1-C_6)alkyl- group optionally substituted in the phenyl ring thereof; or

R^A is a C_1-C_6-alkyl, C_3-C_6-cycloalkyl group, or a phenyl(C_1-C_6)alkyl- group optionally substituted in the phenyl ring thereof and R^B and R^C taken together with the nitrogen to which they are attached form a monocyclic heterocyclic ring of 5 to 7 ring atoms which may contain a further heteroatom selected from N, O and S; or

R^A, R^B and R^C taken together with the nitrogen to which they are attached form a bridged heterocyclic ring system of 7 or 8 ring members;

(iv) $-NR^AC(=NR^B)NR^CR^D$ wherein

R^A, R^B, R^C and R^D are independently hydrogen or C_1-C_6-alkyl; or any two of R^A, R^B, R^C and R^D are independently hydrogen or C_1-C_6-alkyl, while the other two taken together represent a C_1-C_6 alkylene radical; or

(v) $-C(=NR^A)NR^BR^C$, wherein

R^A, R^B and R^C are independently hydrogen or C_1-C_6-alkyl; or any one of R^A, R^B and R^C is hydrogen or C_1-C_6-alkyl, while the other two taken together represent a C_1-C_6 alkylene radical;

(vi) $-NR^AC(=NR^C)R^B$, wherein

~~R^A, R^B and R^C are independently hydrogen or C_1-C_6-alkyl; or any one of R^A, R^B and R^C is hydrogen or C_1-C_6-alkyl, while the other two taken together represent a C_4-C_6-alkylene radical;~~

R^{19} is selected from hydrogen, and $(C_1$-$C_6)$alkyl~~, phenyl, monocyclic heteroaryl having 5 or 6 ring atoms, phenyl$(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkyl, and trifluoromethyl;~~

~~R^{15} is selected from phenyl$(C_1$-$C_6)$alkyl, nitrile (-CN), NH_2-$(C_1$-$C_6)$alkyl, NHR^E-$(C_1$-$C_6)$alkyl, NR^ER^F-$(C_1$-$C_6)$alkyl, -COOH, $-COR^E$, $-SO_2R^E$, $-CONH_2$, $-CONHR^E$, $-SO_2NHR^E$, $-CONR^ER^F$, and $-SO_2NR^ER^F$, wherein R^E and R^F are independently a $(C_1$-$C_6)$alkyl, phenyl or monocyclic heteroaryl having 5 or 6 ring atoms, or R^E and R^F when attached to the same nitrogen atom form a cyclic amino ring~~.

Compounds of formula (I) above thereof may be prepared in the form of salts, particularly pharmaceutically acceptable salts, N-oxides, hydrates and solvates thereof. Any claim to a compound herein, or reference to "compounds of the invention", "compounds with which the invention is concerned", and "compounds of formula (I)" includes such compounds whether or not in salt, N-oxide, hydrate or solvate form.

Compounds of the invention may be used in the treatment or prevention of diseases in which HNE is implicated, for example chronic obstructive pulmonary disease (COPD), chronic bronchitis, lung fibrosis, pneumonia, acute respiratory distress syndrome (ARDS), pulmonary emphysema, smoking-induced emphysema and cystic fibrosis.

Hence other aspects of the invention are (i) a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable carrier or excipient; and (ii) the use of a compound of the invention for the manufacture of a medicament for the treatment or prevention of a disease or condition in which HNE is implicated.

Terminology

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

$-SO_2NHR^G$, $-CONR^GR^H$, $-SO_2NR^GR^H$, $-NH_2$, $-NHR^G$, $-NR^GR^H$, $-OCONH_2$, $-OCONHR^G$, $-OCONR^GR^H$, $-NHCOR^G$, $-NHCOOR^G$, $-NR^HCOOR^G$, $-NHSO_2OR^G$, $-NR^HSO_2OH$, $-NR^HSO_2OR^G$,$-NHCONH_2$, $-NR^GCONH_2$, $-NHCONHR^H$, $-NR^GCONHR^H$, $-NHCONR^GR^H$, or $-NR^GCONR^GR^H$ wherein R^G and R^H are independently a C_1-C_6-alkyl, C_3-C_6-cycloalkyl , phenyl or monocyclic heteroaryl having 5 or 6 ring atoms, or R^G and R^H when attached to the same nitrogen atom form a cyclic amino ring, such as piperidinyl, morpholinyl or piperazinyl. An "optional substituent" may be one of the foregoing substituent groups.

As used herein the term "salt" includes base addition and acid addition salts Compounds of the invention which are acidic can form salts, including pharmaceutically acceptable salts, with bases such as alkali metal hydroxides, e.g. sodium and potassium hydroxides; alkaline earth metal hydroxides e.g. calcium, barium and magnesium hydroxides; with organic bases e.g. N-methyl-D-glucamine, choline tris(hydroxymethyl)amino-methane, L-arginine, L-lysine, N-ethyl piperidine, and dibenzylamine. Those compounds (I) which are basic can form salts, including pharmaceutically acceptable salts with inorganic acids, e.g. with hydrohalic acids such as hydrochloric or hydrobromic acids, sulphuric acid, and nitric acid or phosphoric acid, and with organic acids e.g. with acetic, tartaric, succinic, fumaric, maleic, malic, salicylic, citric, methanesulphonic, p-toluenesulphonic, benzoic, benzenesunfonic, glutamic, lactic, and mandelic acids. Those compounds (I) which have a quaternary nitrogen can also form quaternary salts with a pharmaceutically acceptable counter-ion such as chloride, bromide, acetate, formate, p-toluenesulfonate, succinate, hemi-succinate, naphthalene-bis sulfonate, methanesulfonate, and xinafoate.

Compounds of the invention which contain one or more actual or potential chiral centres, because of the presence of asymmetric carbon atoms, can exist as a number of diastereoisomers with R or S stereochemistry at each chiral centre. The invention includes all such diastereoisomers and mixtures thereof.

In the compounds of the invention of formula (I), in any compatible combination:

The ring containing A is a phenyl ~~or 3-pyridyl~~ ring.

R^1 and R^2 are ~~selected from any of the substituent types for which they are defined in relation to formula (I), including~~ hydrogen~~, halogen such as fluoro and chloro, nitro, cyano, $-S(O)_2(C_1$-C_3alkyl) such as methanesulfonyl, amino, mono- or di-C_1-C_6-~~

~~alkylamino such as methylamino and dimethylamino, $-NHCOCH_3$, $-NH(C=O)NHCH_3$, $-NHSO_2CH_3$, C_1-C_6-alkyl such as methyl, ethyl or n- or iso-propyl, C_2-C_6-alkenyl such as vinyl or allyl, C_2-C_6-alkynyl such as CH≡C-, hydroxyl, C_1-C_6-alkoxy such as methoxy or ethoxy or C_2-C_6-alkenyloxy such as allyloxy, wherein C_1-C_6-alkyl and C_1-C_6-alkoxy can be further substituted with one to three identical or different radicals selected from the group consisting of halogen such as fluoro, hydroxy and C_1-C_4-alkoxy.~~

~~In one type of compound of the invention, the ring containing A is phenyl, R^1 is hydrogen, and R^2 is hydrogen or 2-methanesulphonyl. In another type, the ring containing A is 3-pyridyl and R^2 is hydrogen or 2-methanesulphonyl.~~

~~R^3 and R^5 too may be selected from any of the substituent types for which they are defined in relation to formula (I), such as hydrogen, fluoro, chloro or bromo, and C_1-C_6-alkyl such as methyl which can be further substituted with halogen as in the case of trifuoromethyl.~~ In one type of compound of the invention R^5 is hydrogen and R^3 is 3-trifluoromethyl, 3-chloro or 3-bromo.

R^6 is $-CO_2\mathbf{R^{11}}$, ~~$-CONR^{12}R^{13}$ or $-COR^{14}$~~ wherein **R^{11}**, ~~**R^{13}**, **R^{14}** each independently~~ represents a radical of formula $-[Alk^1]_p-[Q]_t-[Alk^2]_q-Z$ wherein

p, and **q** ~~and **t**~~ are independently 0 or 1;

~~provided that p, q and t~~ is~~are not simultaneously~~ 0;

Alk^1 and **Alk^2** each independently represent a C_1-C_6 alkylene radical such as $-CH_2-$, $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$;

Q represents a divalent mono- or bicyclic carbocyclic or heterocyclic radical having 3-9 ring members, such as a 1,3-cyclopentylene, 1,4-cyclohexylene, 1-4-phenylene, 2,5-pyridinylene, 1,4-piperidinylene, or 1,4-piperazinylene radical;

Z is

~~(i) a monocyclic nitrogen heterocycle of 5 or 6 ring members such as a pyridyl or imidazolyl ring or a bridged nitrogen heterocyclic system of 7 or 8 ring members such as a 1-aza-bicyclo[2.2.2]octane ring, said monocyclic ring or bridged ring system being linked to the rest of the molecule via a ring carbon, and wherein a ring nitrogen may be quaternised by substitution by C_1-C_3-alkyl~~

such as methyl, by phenyl or by benzyl the latter being optionally substituted in the phenyl ring thereof; or

(ii) -N(R^A)(R^B) wherein R^A and R^B are independently hydrogen, or a C_1-C_6-alkyl group such as methyl, ethyl or n- or isopropyl, a C_3-C_6-cycloalkyl group such as cyclopropyl, cyclopentyl or cyclohexyl, or a phenyl(C_1-C_6)alkyl- group such as benzyl, optionally substituted in the phenyl ring thereof; or, taken together with the nitrogen to which they are attached form a monocyclic heterocyclic ring of 5 to 7 ring atoms which may contain a further heteroatom selected from N, O and S, such as a piperidine, piperazine or morpholine ring; or

(iii) -N^+(R^A)(R^B)(R^C) wherein

R^A, R^B and R^C are independently a C_1-C_6-alkyl group such as methyl, ethyl or n- or isopropyl, a C_3-C_6-cycloalkyl group such as cyclopropyl, cyclopentyl or cyclohexyl, or a phenyl(C_1-C_6)alkyl- group such as benzyl, optionally substituted in the phenyl ring thereof ; or

R^A is a C_1-C_6-alkyl group such as methyl, ethyl or n- or isopropyl, a C_3-C_6-cycloalkyl group such as cyclopropyl, cyclopentyl or cyclohexyl, or a phenyl(C_1-C_6)alkyl- group such as benzyl, optionally substituted in the phenyl ring thereof and R^B and R^C taken together with the nitrogen to which they are attached form a monocyclic heterocyclic ring of 5 to 7 ring atoms which may contain a further heteroatom selected from N, O and S, such as a piperidine, piperazine or morpholine ring; or

R^A, R^B and R^C taken together with the nitrogen to which they are attached form a bridged heterocyclic ring system of 7 or 8 ring members;

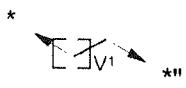
(iv) -$NR^AC(=NR^B)NR^CR^D$ wherein
R^A, R^B, R^C and R^D are independently hydrogen or C_1-C_6-alkyl such as methyl; or any two of R^A, R^B, R^C and R^D are independently hydrogen or C_1-C_6-alkyl, while the other two taken together represent a C_1-C_6 alkylene radical such as $-CH_2-$, $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$; or

(v) -$C(=NR^A)NR^BR^C$, wherein
R^A, R^B and R^C are independently hydrogen or C_1-C_6-alkyl such as

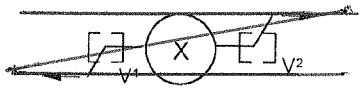
~~methyl; or any one of R^A, R^B and R^C is hydrogen or C_1-C_6-alkyl such as methyl, while the other two taken together represent a C_1-C_6 alkylene radical such as $-CH_2-$, $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$;~~

~~(vi) $-NR^AC(=NR^C)R^B$, wherein R^A, R^B and R^C are independently hydrogen or C_1-C_6-alkyl such as methyl; or any one of R^A, R^B and R^C is hydrogen or C_1-C_6-alkyl such as methyl, while the other two taken together represent a C_1-C_6 alkylene radical such as $-CH_2-$, $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$.~~

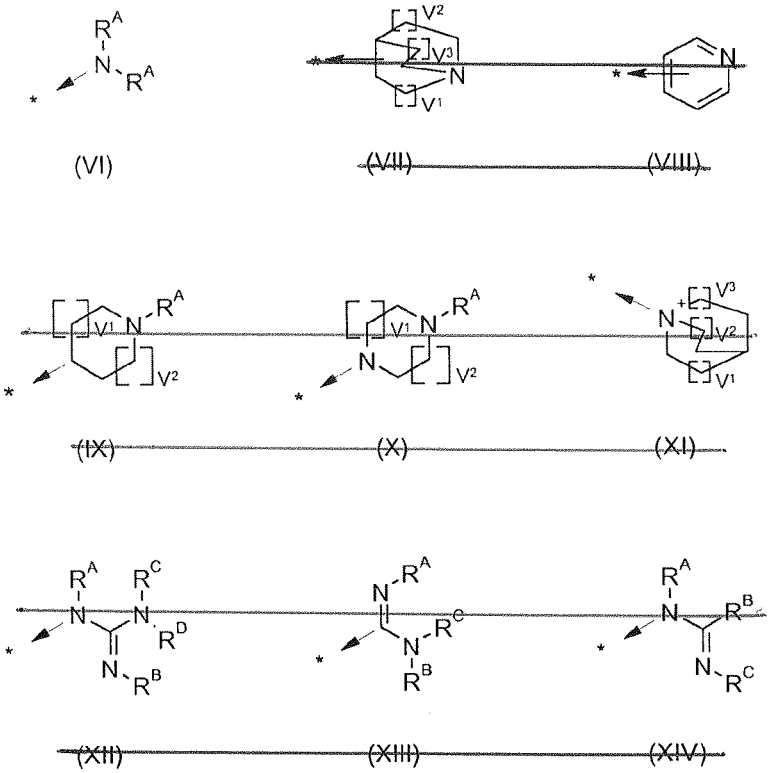
More complex R^6 substituents include those represented by $-CO_2\mathbf{R^{11}}$, ~~$-CONR^{12}R^{13}$ or $-COR^{14}$~~ wherein R^{11}, ~~R^{13} and R^{14}~~ has<u>ve</u> the formula $-[Alk^1]_p-[Q]_t-[Alk^2]_q-Z$ wherein $-[Alk^1]_p-[Q]_t-[Alk^2]_q-$ is ~~selected from~~ structures (IV) ~~and (V)~~ wherein V^1 is<u></u>~~and V^2 are each independently~~ 0, 1, 2, 3 or 4 ~~and X is a divalent mono- or bicyclic carbocyclic or heterocyclic radical having 3-9 ring members such as 1,4-cyclohexylene, 1,3 cyclopentylene, 1,4 phenylene, or 2,4 pyridinylene~~, and Z is ~~selected from~~ structures (VI)~~-(XVI)~~ wherein R^A, R^B, R^C, ~~and R^D~~ is<u></u>~~are~~ as defined in relation to formula (I)~~, and V^1, V^2, and V^3 are each independently 0, 1, 2, 3 or 4~~.



(IV)



~~(V)~~



(VI) (VII) (VIII)

(IX) (X) (XI)

(XII) (XIII) (XIV)

Amine and pyridine nitrogen atoms, where present in groups (VI)-~~(XIV)~~, may be quaternised with an optionally substituted C_1-C_6-alkyl~~ or benzyl group~~.

In one type of compound of the invention, R^6 has the formula $-CO_2R^{11}$ wherein R^{11}, represent a radical of formula $-Alk^2$-Z, wherein Alk^2 and Z are as defined and discussed above. For example in this type of compound, Alk^2 may be $–CH_2$-, $–CH_2CH_2$- or $–CH_2CH_2CH_2$- and Z may be $-N(R^A)(R^B)$ or $-N^+(R^A)(R^B)(R^C)$ wherein R^A, R^B and R^C are independently a C_1-C_6-alkyl group such as methyl, ethyl or n- or isopropyl~~, a C_3-C_6-cycloalkyl group such as cyclopropyl, cyclopentyl or cyclohexyl, or a phenyl(C_1-C_6)alkyl- group such as benzyl, optionally substituted in the phenyl ring thereof~~. Thus, R^6 may be $–CO_2CH_2CH_2N(CH_3)_2$ or $–CO_2CH_2CH_2N^+(CH_3)_3$

$-X^1-X^2-$ is ~~$–CR^{15}=N-$ or~~ $-NR^{19}$-CO-, wherein ~~R15 and~~ R19 is~~are~~ as defined above in relation to formula (I). Thus

R^{19} may be, for example hydrogen, methyl, ethyl, n- or iso-propyl~~, 2-, 3- or 4-pyridyl, 2- or 3- thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzyl, hydroxymethyl, 2-hydroxyethyl, or trifluoromethyl; and~~

~~R^{15} may be, for example benzyl; nitrile (-CN); aminomethyl; 2-aminoethyl; NHR^E-(C_1-C_6)alkyl wherein R^E is methyl or ethyl and (C_1-C_6)alkyl is $-CH_2-$ or $-CH_2CH_2-$; NR^ER^F-(C_1-C_6)alkyl wherein R^E and R^F are independently methyl or ethyl and (C_1-C_6)alkyl is $-CH_2-$ or $-CH_2CH_2-$; -COOH; or $-COR^E$, $-SO_2R^E$, $-CONH_2$, $-CONHR^E$, $-SO_2NHR^E$, $-CONR^ER^F$, or $-SO_2NR^ER^F$, wherein R^E and R^F are independently methyl or ethyl, or R^E and R^F when attached to the same nitrogen atom form a cyclic amino ring.~~

Examples of specific groups R^1-R^6 include those present in the compounds of the Examples herein.

The therapeutic utility of the present compounds is pertinent to any disease that is known to be at least partially mediated by the action of human neutrophil elastase. For example, the present compounds may be beneficial in the treatment of chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), acute respiratory distress syndrome (ARDS), pulmonary emphysema, pneumonia and lung fibrosis.

The present invention is also concerned with pharmaceutical formulations comprising, as an active ingredient, a compound of the invention. Other compounds may be combined with compounds of this invention for the prevention and treatment of inflammatory diseases of the lung. Thus the present invention is also concerned with pharmaceutical compositions for preventing and treating inflammatory diseases of the lung comprising a therapeutically effective amount of a compound of the invention and one or more other therapeutic agents.

Suitable therapeutic agents for a combination therapy with compounds of the invention include: (1) a corticosteroid, for example fluticasone or budesonide; (2) a β2-adrenoreceptor agonist, for example salmeterol or formeterol; (3) a leukotriene modulator, for example montelukast or pranlukast; (4) anticholinergic agents, for example selective muscarinic-3 (M3) receptor antagonists such as tiotropium bromide; (5) phosphodiesterase-IV (PDE-IV) inhibitors, for example roflumilast or cilomilast; (6) an antitussive agent, such as codeine or dextramorphan; and (7) a non-steroidal anti-inflammatory agent (NSAID), for example ibuprofen or ketoprofen.

The weight ratio of the first and second active ingredients may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used.

Compounds of the invention may be used in combination with other drugs that are used in the treatment/prevention/suppression or amelioration of the diseases or conditions for which present compounds are useful. Such other drugs may be administered, by a route and in an amount commonly used therefore, contemporaneously or sequentially with a compound of the invention. When a compound of the invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the invention is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the invention.

The agents of the invention may be administered in inhaled form. Aerosol generation can be carried out using, for example, pressure-driven jet atomizers or ultrasonic atomizers, preferably using propellant-driven metered aerosols or propellant-free administration of micronized active compounds from, for example, inhalation capsules or other "dry powder" delivery systems.

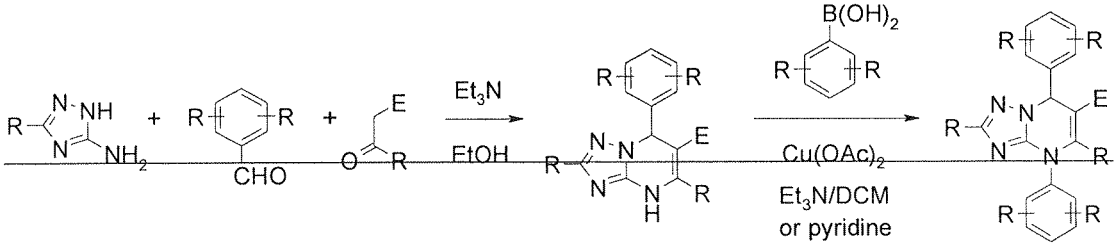
The active compounds may be dosed as described depending on the inhaler system used. In addition to the active compounds, the administration forms may additionally contain excipients, such as, for example, propellants (e.g. Frigen in the case of metered aerosols), surface-active substances, emulsifiers, stabilizers, preservatives, flavorings, fillers (e.g. lactose in the case of powder inhalers) or, if appropriate, further active compounds.

For the purposes of inhalation, a large number of systems are available with which aerosols of optimum particle size can be generated and administered, using an inhalation technique which is appropriate for the patient. In addition to the use of adaptors (spacers, expanders) and pear-shaped containers (e.g. Nebulator®, Volumatic®), and automatic devices emitting a puffer spray (Autohaler®), for metered aerosols, in particular in the case of powder inhalers, a number of technical solutions are available (e.g. Diskhaler®, Rotadisk®, Turbohaler® or the inhalers for example as described EP-A-0505321).

Methods of Synthesis

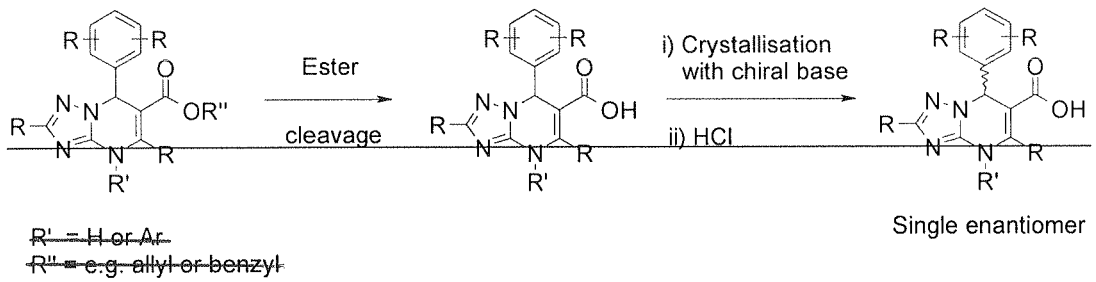
~~The examples of the invention wherein X^1-X^2 is $-CR^{15}=N-$ can be prepared according to Schemes 1-4.~~ Compounds wherein X^1-X^2 is $-NR^{19}-CO-$ can be prepared according to Schemes 5-10. Group R^{11}, ~~group R^{13} and group R^{14}~~ is a group of formula $-[Y]_m-[Alk^1]_p-[Q]_t-[Alk^2]_q-Z$ or a group which can be later converted into such. For compounds wherein X^1-X^2 is ~~$-CR^{15}=N-$ or~~ $-NR^{19}-CO-$, the group may be incorporated for example, but not exclusively, according to Scheme 11.

~~In Scheme 1, a 3-amino-1,2,4-triazole, an aldehyde such as 4-cyanobenzaldehyde and a ketone with a beta electron-withdrawing group E (e.g. an ester, amide or ketone) may be reacted to form an intermediate (1), which can then be arylated with a suitable arylboronic acid, such as 3-(trifluoromethyl)phenylboronic acid, under copper catalysis to give examples of type (2). The reaction may be performed in the presence of base e.g. pyridine or triethylamine, either in the presence or absence of a solvent such as dichloromethane. All of the reactions may be performed in various solvents that must be compatible with the reagents used, and may be carried out at various suitable temperatures, typically 0-80°C dependent on the solvent used.~~



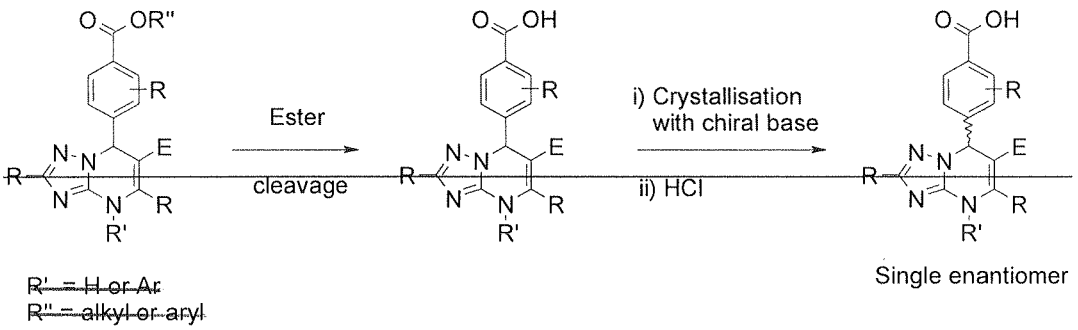
~~Scheme 1~~

~~The enantiomers of the racemic mixture (1) or (2) could be separated by chiral HPLC. Alternatively, where a carboxylic acid can be incorporated into the structure of (1) or (2) for example, but not exclusively, by the cleavage of a corresponding ester, resolution could be carried out by crystallisation with a chiral base (Schemes 2 and 3).~~



~~R' = H or Ar~~
~~R'' = e.g. allyl or benzyl~~

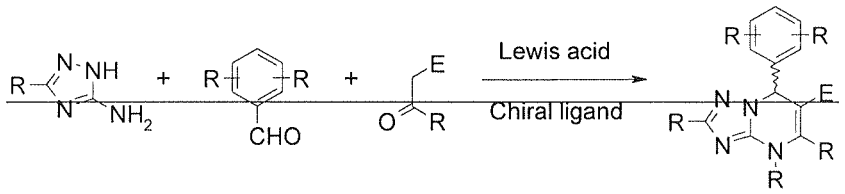
~~Scheme 2~~



~~R' = H or Ar~~
~~R" = alkyl or aryl~~

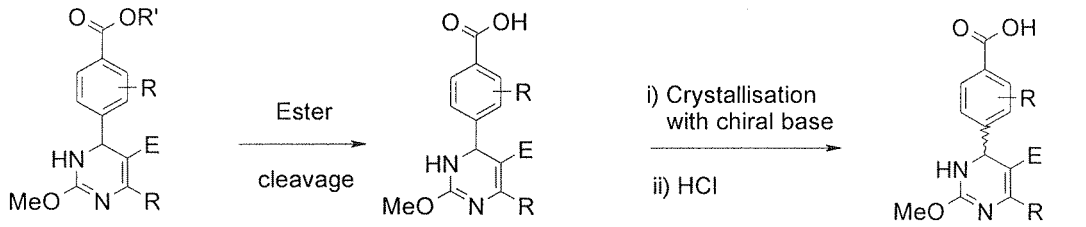
~~Scheme 3~~

~~The three component reaction in Scheme 1 may also be carried out in a stereospecific manner using a chiral Lewis acid (Scheme 4) providing the required stereoisomer exclusively or in excess of its enantiomer (J. Am. Chem. Soc., 2005, 127, 16386-16387).~~

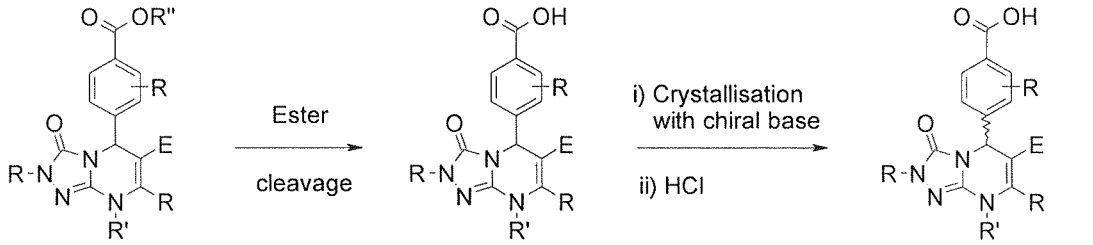


~~Scheme 4~~

Other examples of the invention (6) can be prepared according to Scheme 5. *O*-Methylurea, an aldehyde and a ketone with a beta electron-withdrawing group E (e.g. an ester, amide or ketone) may be reacted in the presence of a base, such as sodium hydrogen carbonate, to form an intermediate (3). Reaction with an activated chloroformate, such as 4-nitrophenylchloroformate or pentafluorophenylchloroformate, produces (4). Ring closure can then be achieved using a substituted hydrazine to give (5). Arylation of (5) can be effected using an arylboronic acid, such as 3-(trifluoromethyl)phenylboronic acid, under copper catalysis and in the presence of a base e.g. pyridine or triethylamine. The reaction can be carried out with or without solvent. The group R' may be removed under suitable conditions and when R' = H, the nitrogen atom may be alkylated or acylated using standard chemistry. All of the reactions may be performed in various solvents that must be compatible with the reagents used, and may be carried out at various suitable temperatures, typically 0-80°C depending on the solvent used.

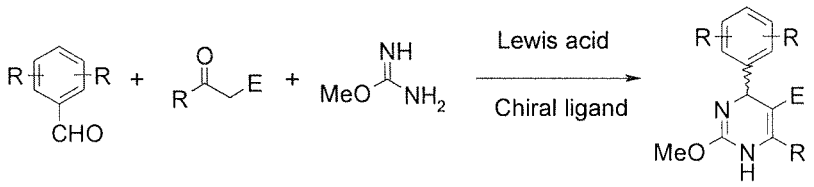


Scheme 8



Scheme 9

The three component reaction of Scheme 5 may also be carried out in a stereospecific manner providing exclusively, or an enantiomeric excess of, the more active enantiomer (J. Am. Chem. Soc., 2005, 127, 16386-16387).

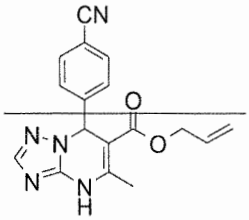


Scheme 10

In Schemes ~~1, 3, 4,~~ 5, 8, 9 and 10, group E may be modified at various stages using standard chemical methods. Scheme 11 describes how, when group E is an ester, this functional group may be transformed using chemistries available to those skilled in the art.

DCM	dichloromethane
DIPEA	Di-isopropylethylamine
DMF	*N*,*N*-dimethylformamide
HATU	*O*-(7-Azabenzotriazole-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluoro-phosphate
HPLC	high performance liquid chromatography
IPA	Isopropyl alcohol
RT	room temperature
Rt	retention time

~~Intermediate 1~~



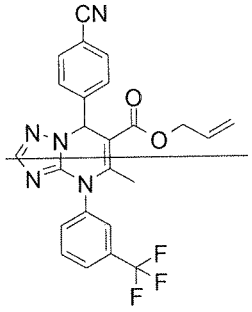
~~7-(4-Cyanophenyl)-5-methyl-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylic acid allyl ester~~

~~3-amino-1,2,4-triazole (1.28 mg, 15.24 mmol) and triethylamine (2.2 ml, 15.25 mmol) were heated in IPA (30 ml) at 90°C until most of the solid had dissolved. 4-Cyanobenzaldehyde (2.0 g, 15.27 mmol) and allyl acetoacetate (2.17 g, 15.28 mmol) were added and the reaction was heated at 90°C overnight. The volatiles were evaporated and the residue was partitioned between ethyl acetate and water. Some solid material was filtered off and the ethyl acetate layer was separated, washed with brine, dried (Na_2SO_4) and the volume reduced. The solid which precipitated was filtered, washed with ethyl acetate and combined with the solid obtained earlier. The pale yellow product was dried in vacuo at 40°C.~~

~~Yield: 1.42 g (29%)~~

~~LC-MS (Method 1): Rt = 2.88 min, m/z = 322 $[M+H]^+$~~

~~Intermediate 2~~



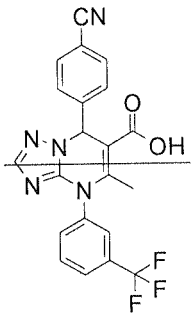
7-(4-Cyanophenyl)-5-methyl-4-(3-trifluoromethylphenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylic acid allyl ester

Intermediate 1 (1.42 g, 4.42 mmol), 3-(trifluoromethyl)phenylboronic acid (1.68 g, 8.85 mmol), copper (II) acetate (1.08 g, 8.85 mmol) and triethylamine (1.23 ml, 8.85 mmol) were dissolved in DCM (15 ml) and the reaction was stirred in air for 7 days. Further quantities of the boronic acid, triethylamine and copper (II) acetate were added and, after a further 7 days, the mixture was diluted with DCM and 1M HCl(aq) and filtered through Celite®. The organic layer was separated, washed with brine, dried (Na_2SO_4) and evaporated. The crude brown oil was dissolved in methanol and eluted through an Isolute® PE-AX cartridge which had been conditioned with methanol. The solvent was evaporated and the crude product was chromatographed on a RediSep® Si cartridge (120 g) eluting with 5-100% ethyl acetate in pentane. The product was obtained as a yellow foam.

Yield: 276 mg (13%)

LC-MS (Method 1): Rt = 3.90 min, m/z = 466 $[M+H]^+$

Intermediate 3



7-(4-Cyanophenyl)-5-methyl-4-(3-trifluoromethylphenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylic acid

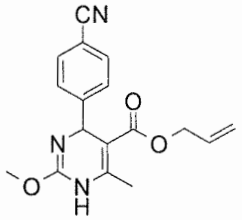
Intermediate 2 (276 mg, 0.594 mmol), morpholine (206 mg, 2.37 mmol) and tetrakis(triphenylphosphine)palladium(0) (68 mg, 0.059 mmol) were dissolved in DCM (5 ml) and the solution was allowed to stand at RT for 1 hour. The reaction mixture was diluted with DCM and water was added. Solid material was filtered off. The DCM was

~~separated, dried (Na_2SO_4) and evaporated. The residue was triturated with acetonitrile to give more solid. A further quantity of product was obtained from the mother liquor by using HPLC system 1.~~

~~Yield: 183 mg (72%)~~

~~LC-MS (Method 2): Rt = 4.26 min, m/z = 426 $[M+H]^+$~~

Intermediate 4



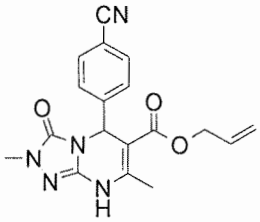
4-(4-Cyanophenyl)-2-methoxy-6-methyl-1,4-dihydro-pyrimidine-5-carboxylic acid allyl ester

4-Cyanobenzaldehyde (13.1 g, 100 mmol) was dissolved in DMF (200 ml) and sodium bicarbonate (33.4 g, 400 mmol) was added, followed by *O*-methylisourea hemisulphate (14.8 g, 120 mmol) and allyl acetoacetate (15.06 g, 110 mmol). The mixture was heated under nitrogen at 70°C overnight. After allowing to cool to RT, the mixture was filtered and the filtrate was evaporated. The resulting orange oil was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried (Na_2SO_4) and evaporated. The crude product was purified by flash silica chromatography eluting with 0-30% ethyl acetate in DCM to give pure Intermediate 4 as a yellow foam.

Yield: 16.8 g (53%)

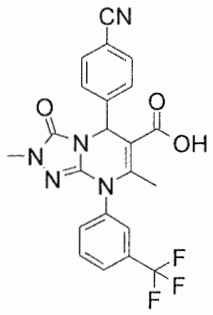
LC-MS (Method 1): Rt = 2.18 min, m/z = 312 $[M+H]^+$

Intermediate 5



5-(4-Cyanophenyl)-2,7-dimethyl-3-oxo-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid allyl ester

Intermediate 4 (2.15 g, 6.91 mmol) and pyridine (4.5 ml) were dissolved in DCM (20 ml) and the solution was cooled in an ice bath. 4-Nitrophenyl chloroformate (1.38 g, 6.91 mmol) was added and the reaction was stirred whilst cooling was maintained.

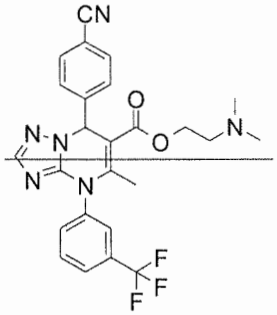


5-(4-Cyanophenyl)-2,7-dimethyl-3-oxo-8-(3-trifluoromethylphenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid

Using a method similar to that described for Intermediate 3, Intermediate 7 was prepared from Intermediate 6.

LC-MS (Method 1): Rt = 3.20 min, m/z = 456 $[M+H]^+$

~~Example 1~~



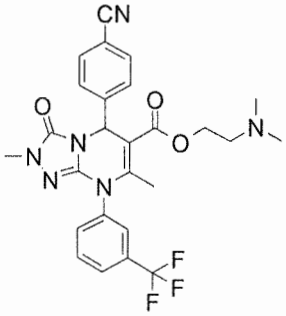
~~7-(4-Cyanophenyl)-5-methyl-4-(3-trifluoromethylphenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylic acid 2-dimethylaminoethyl ester~~

~~Intermediate 3 (50 mg, 0.118 mmol), *N,N*-dimethylethanolamine (209 mg, 2.35 mmol) and HATU (53 mg, 0.141 mmol) were dissolved in DMF (1 ml) and the solution was allowed to stand at RT overnight. The solvent was evaporated and the product was purified using HPLC system 1.~~

~~Yield: 10 mg (17%)~~

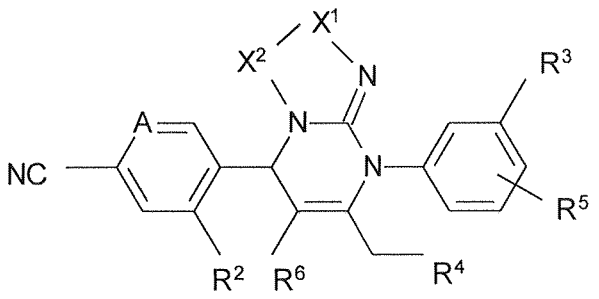
~~LC-MS (Method 2): Rt = 3.41 min, m/z = 497.18 $[M+H]^+$~~

Example 2



Claims

1. A compound of formula (I):



(I)

wherein

A is C-R^1;

$\mathbf{R^1}$ and $\mathbf{R^2}$ are hydrogen;

$\mathbf{R^3}$ is 3-trifluoromethyl, 3-chloro or 3-bromo;

$\mathbf{R^4}$ is hydrogen;

$\mathbf{R^5}$ is hydrogen;

$\mathbf{R^6}$ is $-CO_2\mathbf{R^{11}}$;

$-\mathbf{X^1}-\mathbf{X^2}-$ is $-NR^{19}-CO-$;

$\mathbf{R^{11}}$ represents a radical of formula $-[Alk^1]_p-[Q]_t-[Alk^2]_q-Z$ wherein

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

t is 0;

Alk^1 and **Alk**^{2} each independently represent a C_1-C_6 alkylene radical;

Q represents a divalent mono- or bicyclic carbocyclic or heterocyclic radical having 3-9 ring members;

Z is

(i) -$N(R^A)(R^B)$ wherein R^A and R^B are independently hydrogen, or a C_1-C_6-alkyl; or

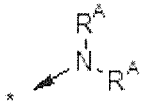
(ii) -$N^+(R^A)(R^B)(R^C)$ wherein R^A, R^B and R^C are independently a C_1-C_6-alkyl;

R^{19} is selected from hydrogen, and (C_1-C_6)alkyl.

2. A compound as claimed in claim 1 wherein R^{11} has the formula -$[Alk^1]_p$-$[Q]_t$-$[Alk^2]_q$ -Z wherein -$[Alk^1]_p$-$[Q]_t$-$[Alk^2]_q$- is structure (IV) wherein V^1 is 0, 1, 2, 3 or 4, and Z is structure (VI) wherein R^A is as defined in claim 1,



(IV)



(VI)

and wherein amine nitrogen atoms, may be quaternised with a (C_1-C_6)alkyl.

3. A compound as claimed in any of the preceding claims wherein **-X^1-X^2-** is -N**R**^{19}-CO- and R^{19} is methyl.

4. A compound as claimed in any of the preceding claims, in the form of a pharmaceutically acceptable salt.

5. A pharmaceutical composition comprising a compound as claimed in any of the preceding claims and a pharmaceutically acceptable carrier or excipient.

6. A pharmaceutical composition as claimed in claim 5 which is adapted for oral administration or administration by the pulmonary route.

7. A compound as claimed in any of claims 1 to 7 for the treatment of, or for use in the manufacture of a medicament for use in the treatment of, a disease or condition in which HNE is implicated, wherein the disease or condition is chronic obstructive pulmonary disease (COPD), chronic bronchitis, lung fibrosis,

pneumonia, acute respiratory distress syndrome (ARDS), pulmonary emphysema, smoking-induced emphysema or cystic fibrosis.