(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 $C_1$-$C_6$ alkylene radical;

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

$\mathbf{R^{15}}$ 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)", ~~and the like~~ 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 ~~and the like~~. 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 the like~~, 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 ~~and the like~~. 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 ~~, and the like~~.

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.

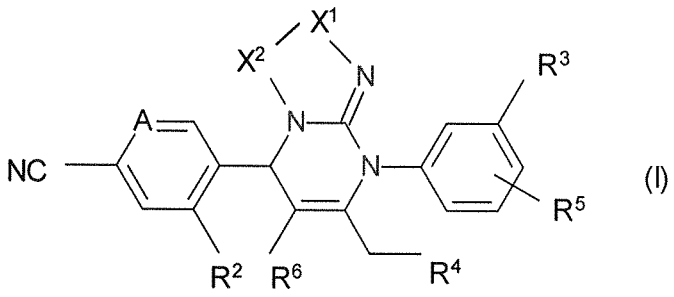
In the compounds of the invention of formula (I), in any compatible combination:

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,

**Claims**

1. A compound of formula (I):




(I)

wherein

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

$R^1$ and $R^2$ are ~~selected from~~ hydrogen~~, halogen, nitro, cyano, -S(O)$_n$$R^7$, amino, mono- or di-$C_1$-$C_6$-alkylamino, -NHCO$R^8$, -NH(C=O)NH$R^9$, -NHSO$_2$$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~~;

$R^3$~~n~~ is trifluoromethyl~~0~~, 3-chloro~~1~~ or 3-bromo~~2~~;

$R^4$ is hydrogen;

$R^3$ ~~and $R^5$ are independently selected from~~is 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 is are 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 $C_1$-$C_6$-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;~~

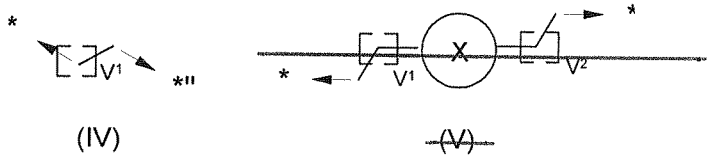
~~$R^{15}$ is selected from phenyl$(C_1$-$C_6)$alkyl, nitrile (-CN), $NH_2$-$(C_1$-$C_6)$alkyl, $NHR^E$-$(C_1$-$C_6)$alkyl, $NR^ER^F$-$(C_1$-$C_6)$alkyl, -COOH, $-COR^E$, $-SO_2R^E$, $-CONH_2$, $-CONHR^E$, $-SO_2NHR^E$, $-CONR^ER^F$, and $-SO_2NR^ER^F$, wherein $R^E$ and $R^F$ are independently a $(C_1$-$C_6)$alkyl, 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.~~

~~2. A compound as claimed in claim 1 wherein $R^2$ is hydrogen or 2-methanesulphonyl.~~

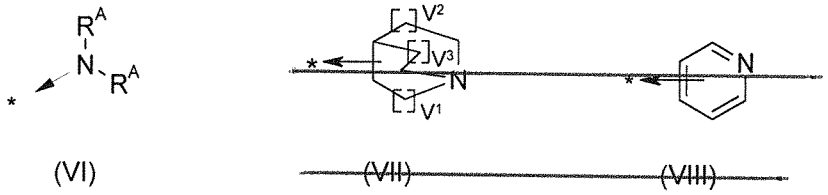
~~3. A compound as claimed in any of the preceding claims wherein $R^5$ is hydrogen and $R^3$ is 3-trifluoromethyl, 3-chloro or 3-bromo.~~

24. A compound as claimed in ~~any of the preceding~~ claims 1 wherein $R^{11}$, ~~$R^{13}$ and $R^{14}$~~ hashave 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 $V^1$ isand ~~$V^2$ are each independently~~ 0, 1, 2, 3 or 4 ~~and X is a divalent mono- or bicyclic carbocyclic or~~

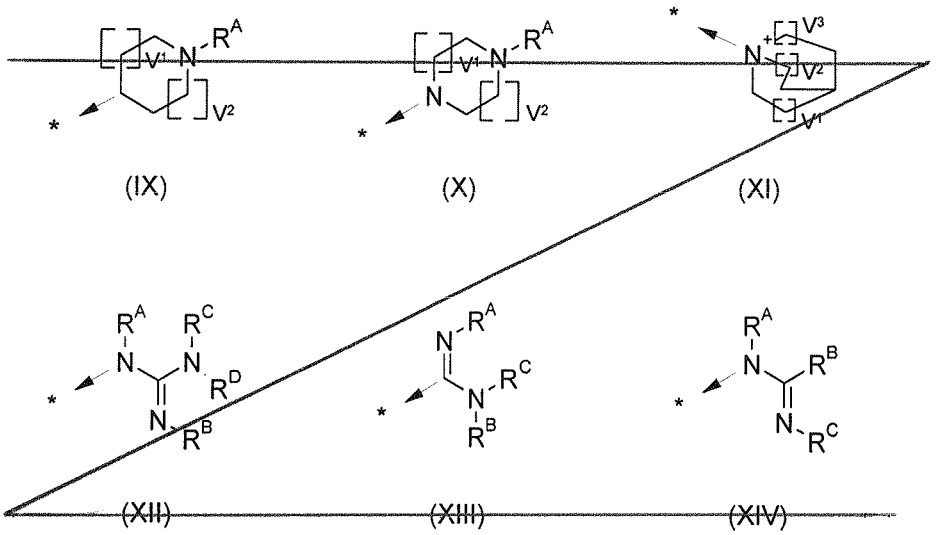
~~heterocyclic radical having 3-9 ring members~~, and Z is ~~selected from~~ structures (VI)~~-(XVI)~~ wherein $R^A$~~, $R^B$, $R^C$, and $R^D$~~ isare as defined in claim 1, ~~and $V^1$, $V^2$, and $V^3$ are each independently 0, 1, 2, 3 or 4.~~



(IV) ~~(V)~~



(VI) ~~(VII)~~ ~~(VIII)~~



(IX) (X) (XI)

(XII) ~~(XIII)~~ ~~(XIV)~~

and wherein amine ~~and pyridine~~ nitrogen atoms, ~~where present in groups (VI)-(XIV),~~ may be quaternised with a ($C_1$-$C_6$)alkyl.

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

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

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

68. A pharmaceutical composition as claimed in claim 57 which is adapted for oral administration or administration by the pulmonary route.

79. AUse of 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.

~~10. Use according to claim 9~~, 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.

~~11. Use according to claim 9 wherein the disease or condition is asthma, rhinitis, psoriasis, atopic dermatitis, non-atopic dermatitis, Crohn's disease, ulcerative colitis, or irritable bowel disease.~~