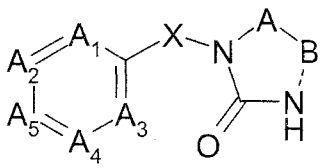
carbonyl/thiocarbonyl groups (thereby forming e.g. a 3,5-dioxo-thiadiazolidine or a 3-thioxo-5-oxo-thiadiazolidine). Further, it mainly relates to compounds in which both nitrogen atoms of the thiadiazolidine are substituted. The document does not relate to thiadiazolidines substituted at the 2-position with a group bearing an aromatic group and at the 5-position with an amino or amido derivative bearing an aromatic group.

International patent applications WO 2007/010273 and WO 2007/010281 both disclose e.g. thiazolidin-4-one and 1,1-dioxo-1,5-dihydro-[1,4,2]dithiazole compounds that are able to antagonize the stimulatory effect of FFAs on cell proliferation when tested in an assay using a human breast cancer cell line (MDA-MB-231). Such compounds are thus indicated in the treatment of cancer and/or as modulators of FFAs. However, these documents do not disclose or suggest thiadiazolidinones.

Summary

~~In a first aspect, t~~There is provided a compound of formula I,



I

wherein:

A represents C(=N-W-D) or S;

B represents S or C(-NH-W-D);

when:

A represents C(=N-W-D) and B represents S then the dashed line between B and the adjacent NH atom is a single bond; or

A represents S and B represents C(-NH-W-D) then the dashed line between B and the adjacent NH atom is a double bond; and the hydrogen shown attached to that N atom is absent;

X represents -Q-$[CR^xR^y]_n$-;

W represents -$[CR^xR^y]_m$- or -C(O)-$[CR^xR^y]_p$-;

Q represents a bond, -N(R^a)-, -S-, or -O-;

A_1 to A_5 respectively represent C(R^1), C(R^2), C(R^3), C(R^4) and C(R^5), or, alternatively, up to two of A_1 to A_5 may independently represent N;

n represents 1 or 2;

m represents 0, 1 or 2;

p represents 0, 1 or 2;

or a pharmaceutically-acceptable salt or solvate, or a pharmaceutically functional derivative thereof,

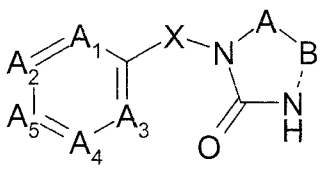
provided that:

(A) when D is phenyl, then at least one of A_1 to A_5 is not (C-H) and/or D is substituted by one or more $-R^6$ groups, and:

Further provided that:

(B) when X represents $-CH_2-$, the A_1 to A_5-containing ring represents unsubstituted phenyl, A represents S, B represents C(-NH-W-D), W represents $-[CR^xR^y]_m-$ in which m represents 0, then D does not represent 2,4-6-tri-nitrophenyl and (C) the compound of formula I, or pharmaceutically acceptable salt or solvate or pharmaceutically functional derivative thereof, is not 4-benzyl-5-picrylimino-1,2,4-thiadiazolidin-3-one.

In a first aspect, there is provided a compound of formula I,



I

wherein:

A represents C(=N-W-D) or S;

B represents S or C(-NH-W-D);

when:

A represents C(=N-W-D) and B represents S then the dashed line between B and the adjacent NH atom is a single bond; or

A represents S and B represents C(-NH-W-D) then the dashed line between B and the adjacent NH atom is a double bond; and the hydrogen shown attached to that N atom is absent;

X represents $-Q-[CR^xR^y]_n-$;

W represents $-[CR^xR^y]_m-$ or $-C(O)-[CR^xR^y]_p-$;

Q represents a bond, $-N(R^a)-$, -S-, or -O-;

A_1 to A_5 respectively represent $C(R^1)$, $C(R^2)$, $C(R^3)$, $C(R^4)$ and $C(R^5)$, or, alternatively, up to two of A_1 to A_5 may independently represent N;

D represents phenyl, pyridyl or pyrimidinyl optionally substituted by one or more R^6 groups;

R^x and R^y, on each occasion when used herein, are independently selected from H, halo, C_{1-6} alkyl (optionally substituted by one or more halo atoms), aryl (optionally substituted by one or more halo atoms) or R^x and R^y are linked to form, along with the carbon atom to which they are attached, a non-aromatic 3- to 8-membered ring, optionally containing 1 to 3 heteroatoms selected from O, S and N, which ring is itself optionally substituted by one or more substituents selected from halo or C_{1-6} alkyl (optionally substituted by one or more halo atoms);

R^1 to R^5 independently represent H, halo, $-R^7$, $-CF_3$, $-CN$, $-NO_2$, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)-N(R^{7a})R^{7b}$, $-N(R^{7a})R^{7b}$, $-N(R^7)_3^+$, $-SR^7$, $-OR^7$, $-NH(O)R^7$, $-SO_3R^7$, aryl or heteroaryl (which aryl and heteroaryl groups are themselves optionally and independently substituted by one or more groups selected from halo and R^{16}), or any two of R^1 to R^5 which are adjacent to each other are optionally linked to form, along with two atoms of the essential benzene ring in the compound of formula I, an aromatic or non-aromatic 3- to 8-membered ring, optionally containing 1 to 3 heteroatoms selected from O, S and N, which ring is itself optionally substituted by one or more substituents selected from halo, $-R^7$, $-OR^7$ and =O;

R^6 independently represents, on each occasion when used herein, cyano, $-NO_2$, halo, $-R^{16}$, $-OR^8$, $-N(R^8)C(O)R^8$, $-NR^9R^{10}$, $-SR^{11}$, $-Si(R^{12})_3$, $-OC(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)R^{14}$, $-C(O)NR^{15a}R^{15b}$, $-S(O)_2NR^{15c}R^{15d}$, aryl or heteroaryl (which aryl and heteroaryl groups are themselves optionally and independently substituted by one or more groups selected from halo and R^{16}), or any two R^6 groups which are adjacent to each other are optionally linked to form, along with two atoms of the essential benzene ring in the compound of formula I, an aromatic or non-aromatic 3- to 8-membered ring, optionally containing 1 to 3 heteroatoms selected from O, S and N, which ring is itself optionally substituted by one or more substituents selected from halo, $-R^7$, $-OR^7$ and =O;

R^7, on each occasion when used herein, is selected from H or C_1-C_6 alkyl, C_1-C_6 cycloalkyl, aryl and heteroaryl (wherein the latter four groups are optionally substituted by one or more halo atoms);

R^{7a} and R^{7b} are independently selected from H, or C_1-C_6 alkyl, C_1-C_6 cycloalkyl, aryl and heteroaryl, or R^{7a} and R^{7b} are optionally linked to form, along with the nitrogen atom to which they are attached, an aromatic or non-aromatic 3- to 8-membered ring, optionally containing 1 to 3 heteroatoms selected from O, S and N, which ring is itself optionally substituted by one or more substituents selected from halo, $-R^7$, $-OR^7$ and =O;

R^a, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15a}, R^{15b}, R^{15c} and R^{15d}, on each occasion where used herein, independently represent H or R^{16};

R^{16} represents, on each occasion when used herein, C_{1-6} alkyl optionally substituted by one or more halo atoms;

n represents 1 or 2;

m represents 0, 1 or 2;

p represents 0, 1 or 2;

or a pharmaceutically-acceptable salt or solvate, or a pharmaceutically functional derivative thereof,

provided that:

(A) when D is phenyl, then at least one of A_1 to A_5 is not (C-H) and/or D is substituted by one or more $-R^6$ groups, and:

Further provided that:

(B) when X represents $-CH_2-$, the A_1 to A_5-containing ring represents unsubstituted phenyl, A represents S, B represents C(-NH-W-D), W represents $-[CR^xR^y]_m-$ in which m represents 0, then D does not represent 2,4-6-tri-nitrophenyl and (C) the compound of formula I, or pharmaceutically acceptable salt or solvate or pharmaceutically functional derivative thereof, is not 4-benzyl-5-picrylimino-1,2,4-thiadiazolidin-3-one.

In a second aspect, there is provided a compound as defined herein, or a pharmaceutically-acceptable salt or solvate, or a pharmaceutically functional derivative thereof, but without provisos (B) and (C), for use as a pharmaceutical.

In a third aspect, there is provided a pharmaceutical formulation including a compound as defined herein, or a pharmaceutically-acceptable salt or solvate, or a pharmaceutically functional derivative thereof, but without provisos (B) and (C), in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

In a fourth aspect, there is provided a combination product comprising: (A) a compound of formula I as defined herein, or a pharmaceutically-acceptable salt or solvate, or a pharmaceutically functional derivative thereof, but without provisos (B) and (C); and (B) another therapeutic agent useful in the treatment of cancer, wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

In a fifth aspect, there is provided the use of a compound of formula I as defined herein, or a pharmaceutically-acceptable salt or solvate, or a pharmaceutically functional derivative thereof but without provisos (B) and (C), or a combination product as defined herein, for the manufacture of a medicament for the treatment of cancer.

of R^1 to R^5 which are adjacent to each other are optionally linked to form, along with two atoms of the essential benzene ring in the compound of formula I, an aromatic or non-aromatic 3- to 8-membered ring, optionally containing 1 to 3 heteroatoms selected from O, S and N, which ring is itself optionally substituted by one or more substituents selected from halo, $-R^7$, $-OR^7$ and =O;

R^6 independently represents, on each occasion when used herein, cyano, $-NO_2$, halo, $-R^{816}$, $-OR^8$, $-N(R^8)C(O)R^8$, $-NR^9R^{10}$, $-SR^{11}$, $-Si(R^{12})_3$, $-OC(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)R^{14}$, $-C(O)NR^{15a}R^{15b}$, $-S(O)_2NR^{15c}R^{15d}$, aryl or heteroaryl (which aryl and heteroaryl groups are themselves optionally and independently substituted by one or more groups selected from halo and R^{16}), or any two R^6 groups which are adjacent to each other are optionally linked to form, along with two atoms of the essential benzene ring in the compound of formula I, an aromatic or non-aromatic 3- to 8-membered ring, optionally containing 1 to 3 heteroatoms selected from O, S and N, which ring is itself optionally substituted by one or more substituents selected from halo, $-R^7$, $-OR^7$ and =O;

R^7, on each occasion when used herein, is selected from H or C_1-C_6 alkyl, C_1-C_6 cycloalkyl, aryl and heteroaryl (wherein the latter four groups are optionally substituted by one or more halo atoms);

R^{7a} and R^{7b} are independently selected from H, or C_1-C_6 alkyl, C_1-C_6 cycloalkyl, aryl and heteroaryl, or R^{7a} and R^{7b} are optionally linked to form, along with the nitrogen atom to which they are attached, an aromatic or non-aromatic 3- to 8-membered ring, optionally containing 1 to 3 heteroatoms selected from O, S and N, which ring is itself optionally substituted by one or more substituents selected from halo, $-R^7$, $-OR^7$ and =O;

R^a, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15a}, R^{15b}, R^{15c} and R^{15d}, on each occasion where used herein, independently represent H or R^{16};

R^{16} represents, on each occasion when used herein, C_{1-6} alkyl optionally substituted by one or more halo atoms;

n represents 1 or 2;

m represents 0, 1 or 2;

p represents 0, 1 or 2;

or a pharmaceutically-acceptable salt or solvate, or a pharmaceutically functional derivative thereof,

provided that:

(A) when D is phenyl, then at least one of A_1 to A_5 is not (C-H) and/or D is substituted by one or more $-R^6$ groups, and:

further provided that:

9. A compound of formula I as claimed in any one of the preceding claims, wherein R^6 independently represents $-C(O)NR^{15a}R^{15b}$, cyano, $-NO_2$, -Br, -Cl, -F, $-R^{816}$, $-OR^8$, $-NR^9R^{10}$, $-SR^{11}$, $-C(O)OR^{13}$, $-C(O)R^{14}$, $-S(O)_2NR^{15c}R^{15d}$, aryl or heteroaryl (which aryl and heteroaryl groups are themselves optionally and independently substituted by one or more groups selected from halo and R^{16}), or any two R^6 groups which are adjacent to each other are optionally linked to form, along with two atoms of the essential benzene ring in the compound of formula I, quinoline, tetrahydroquinoline, isoquinoline or tetrahydroisoquinoline, wherein the additional ring system of the quinoline, tetrahydroquinoline, isoquinoline or tetrahydroisoquinoline moiety is itself optionally substituted by one or more substituents selected from halo, $-R^7$, $-OR^7$ and =O.

10. A compound of formula I as claimed in Claim 9, wherein R^6 independently represents $-R^{816}$, -CN, $-OCF_3$, $-NO_2$, -Br, -Cl, -F, $-OR^8$, $-NR^9R^{10}$ or $-SR^{11}$.

11. A compound of formula I as claimed in any one of the preceding claims, wherein n represents 1 or 2; m represents 0 or 1; and/or p represents 0 or 1.

12. A compound of formula I as claimed in any one of the preceding claims, wherein W represents a direct bond, $-CH_2-$, -C(O)- or $-C(O)CH_2-$.

13. A compound as claimed in Claim 11, wherein W represents -C(O)- or $-C(O)CH_2-$.

14. A compound as claimed in Claim 1, which is selected from the group:

i) 5-(3,4-dichlorophenyl)imino-4-[[3-(trifluoromethyl)phenyl]methyl]-1,2,4-thiadiazolidin-3-one;

ii) 5-(3,4-dichlorophenyl)imino-4-[(4-methoxyphenyl)methyl]-1,2,4-thiadiazolidin-3-one;

iii) 4-[(4-chlorophenyl)methyl]-5-(3,4-dichlorophenyl)imino-1,2,4-thiadiazolidin-3-one;

iv) 5-(3,4-dichlorophenyl)imino-4-[(3,4-difluorophenyl)methyl]-1,2,4-thiadiazolidin-3-one;

v) 5-(3,4-dichlorophenyl)imino-4-[(3-fluorophenyl)methyl]-1,2,4-thiadiazolidin-3-one;

vi) 5-(3,4-dichlorophenyl)imino-4-[phenyl)methyl]-1,2,4-thiadiazolidin-3-one;

vii) 5-(3,4-dichlorophenyl)imino-4-phenethyl-1,2,4-thiadiazolidin-3-one;

viii) 4-[2-[(4-chlorophenyl)-methyl-amino]ethyl]-5-(3,4-dichlorophenyl)imino-1,2,4-thia-diaz-olidin-3-one;