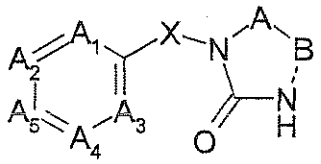
carbonyl/thiocarbonyl groups (thereby forming e.g. a 3,5-dioxo-thiadiazolidine or a 3-thioxo-5-oxo-thiadiazolidine). Further, it mainly relates to compounds in which both nitrogen atoms of the thiadiazolidine are substituted. The document does not relate to thiadiazolidines substituted at the 2-position 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, 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 N 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 N 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, $-R^8$, $-OR^8$, $-N(R^8)C(O)R^8$, $-NR^9R^{10}$, $-SR^{11}$, $-Si(R^{12})_3$, $-OC(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)R^{14}$, $-C(O)NR^{15a}R^{15b}$, $-S(O)_2NR^{15c}R^{15d}$, 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.

In a sixth 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), or a combination product as defined herein, for use in the treatment of cancer.

In a seventh 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, in the manufacture of medicament for inhibiting cell proliferation.

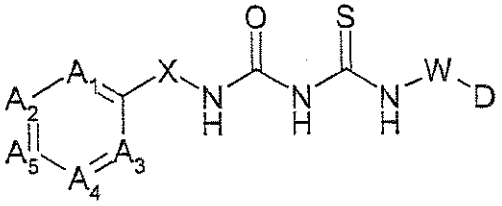
In an eighth aspect, there is provided a kit of parts comprising: (I) one of components (a) and (b) as defined herein; together with (II) instructions to use that component in conjunction with the other of the two components.

In a ninth aspect, there is provided a method of making a kit of parts as defined herein, which method comprises bringing a component (a) into association with a component (b), thus rendering the two components suitable for administration in conjunction with each other.

In a tenth 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), for the manufacture of a medicament for the treatment of diabetes.

In an eleventh 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 in the treatment of diabetes.

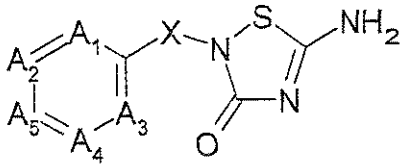
In a twelfth aspect, there is provided a process for the preparation of a compound of formula I as defined herein, (i) for compounds of formula I wherein A represents S, cyclisation of a compound of formula IIa,



IIa

wherein A_1 to A_5, X, W and D are as defined herein;

(ii) for compounds of formula I wherein A represents S, W represents $-[CR^xR^y]_m-$ and m represents 1 or 2, reaction of a compound of formula III,



III

wherein A_1 to A_5 and X are as defined herein, with a compound of formula IV,

$$L_2\text{-}W^1\text{-}D \qquad \text{IV}$$

wherein L_2 represents a suitable leaving group, W^1 represents $-[CR^xR^y]_m-$ in which m represents 1, and D is as defined herein;

(iii) for compounds of formula I wherein A represents S, W represents $-[CR^xR^y]_m-$ and m represents 0, reaction of a compound of formula III as hereinbefore defined with a compound of formula V,

$$L_3\text{-}D \qquad \text{V}$$

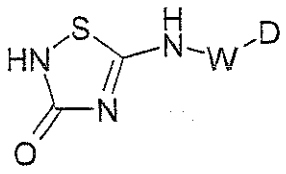
wherein L_3 is a suitable leaving group and D is as defined herein;

(iv) for compounds of formula I wherein A represents S, W represents $-C(O)-[CR^xR^y]_p-$, reaction of a compound of formula III as hereinbefore defined, with a compound of formula VI,

$$L_4\text{-}W^2\text{-}D \qquad \text{VI}$$

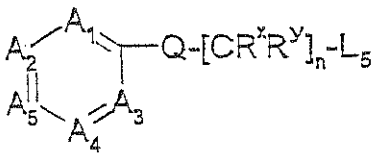
wherein L_4 is a suitable leaving group or -OH, W^2 represents $-C(O)-[CR^xR^y]_p-$, and D is as defined herein;

(v) for compounds of formula I wherein A represents S, and Q is a bond, -O- or -S-, reaction of a compound of formula VII,



VII

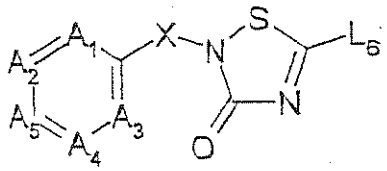
wherein W and D are as defined herein, with a compound of formula VIII,



VIII

wherein A_1 to A_5, n, R^X and R^Y are as defined herein, L_5 is a suitable leaving group and Q is a bond, -O- or -S-;

(vi) for compounds of formula I wherein W is $-[CR^XR^Y]_m-$, reaction of a compound of formula IX,



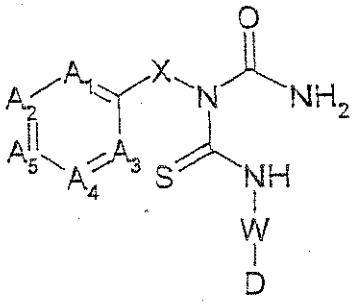
IX

wherein L_6 represents a suitable leaving group and A_1 to A_5 and X are as defined herein, with a compound of formula X,

$H_2N\text{-}W\text{-}D$ X

wherein W and D are as defined herein; and

vii) for compounds of formula I wherein B represents S, cyclisation of a compound of formula IIb,



IIb

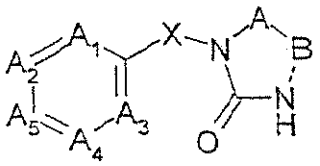
wherein A_1 to A_5, X, W and D are as defined herein.

In a thirteenth aspect, there is provided a process for the preparation of a pharmaceutical formulation as defined herein, which process comprises bringing into association 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), with a pharmaceutically-acceptable adjuvant, diluent or carrier.

In a fourteenth aspect, there is provided a process for the preparation of a combination product as defined herein, which process comprises bringing into association 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), with the other therapeutic agent that is useful in the treatment of cancer.

Disclosure of the Invention

According to embodiments of the invention, 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 bond between B and the NH atom is a single bond; or

A represents S and B represents C(-NH-W-D) then the bond between B and the NH atom is a double bond;

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;

(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.

2. A compound as claimed in Claim 1, wherein each R^6 independently represents -CN, $-CF_3$, $-OCF_3$, -F or –Cl.

3. A compound as claimed in Claim 1 or Claim 2, wherein 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.

4. A compound of formula I as claimed in any one of Claims 1 to 3, wherein B represents S.

5. A compound of formula I as claimed in any one of Claims 1 to 4, wherein R^x and R^y are independently selected from H, C_{1-6} alkyl (optionally substituted by one or more fluoro atoms), aryl (optionally substituted by one or more halo, e.g. chloro 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 6-membered unsubstituted ring.

6. A compound of formula I as claimed in any one of Claims 1 to 5, wherein X represents $-CH_2-$, $-CH_2CH_2-$, $-O-CH_2CH_2-$, $-N(CH_3)-CH_2CH_2-$, $-S-CH_2CH_2-$, 1,1-cyclopropyl or -C(H)(4-chlorophenyl)-.

7. A compound of formula I as claimed in any one of Claims 1 to 6, wherein at least one of R^1 to R^5, when present, represents halo, $-R^7$, $-CF_3$, -CN, $-C(O)R^7$, $-C(O)OR^7$, $-C(O)-N(R^{7a})R^{7b}$, $-N(R^7)_3^+$, $-SR^7$, $-OR^7$ or $-NH(O)R^7$, 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.

8. A compound of formula I as claimed in Claim 7, wherein at least one of R^1 to R^5, when present, represents 4H-[1,2,4]-triazolyl, $-OR^7$, -Cl, -F, $-CF_3$, -CN or $-C(O)-N(R^{7a})R^{7b}$.

liv) 3-[[5-[(4-chlorophenyl)amino]-3-oxo-1,2,4-thiadiazol-2-yl]methyl]-N-methyl-benzamide;

lv) 5-[(6-chloro-3-pyridyl)amino]-2-[(3,4-difluorophenyl)methyl]-1,2,4-thiadiazol-3-one;

lvi) 2-[(3,4-difluorophenyl)methyl]-5-[[4-(trifluoromethyl)phenyl]amino]-1,2,4-thiadiazol-3-one;

lvii) 2-[(3,4-difluorophenyl)methyl]-5-[[4-(trifluoromethoxy)phenyl]amino]-1,2,4-thiadiazol-3-one;

lviii) 5-[(4-chlorophenyl)amino]-2-[1-(4-chlorophenyl)cyclopropyl]-1,2,4-thiadiazol-3-one;

lix) 5-[(3,4-dichlorophenyl)methylamino]-2-[(3,4-difluorophenyl)methyl]-1,2,4-thiadiazol-3-one;

lx) 3,4-dichloro-N-[4-[(4-fluorophenyl)methyl]-3-oxo-1,2,4-thiadiazolidin-5-ylidene]benzamide;

lxi) 2-[(4-methoxyphenyl)methyl]-5-[[4-(trifluoromethyl)phenyl]amino]-1,2,4-thiadiazol-3-one;

lxii) 2-[(4-chlorophenyl)methyl]-5-[[4-(trifluoromethyl)phenyl]amino]-1,2,4-thiadiazol-3-one;

lxiii) 2-[(3-fluorophenyl)methyl]-5-[[4-(trifluoromethyl)phenyl]amino]-1,2,4-thiadiazol-3-one;

lxiv) 2-[phenylethyl]-5-[[4-(trifluoromethyl)phenyl]amino]-1,2,4-thiadiazol-3-one;

lxv) 2-[(4-methoxyphenyl)methyl]-5-[[4-(trifluoromethoxy)phenyl]amino]-1,2,4-thiadiazol-3-one;

lxvi) 2-[(4-chlorophenyl)methyl]-5-[[4-(trifluoromethoxy)phenyl]amino]-1,2,4-thiadiazol-3-one;

lxvii) 2-[(3-fluorophenyl)methyl]-5-[[4-(trifluoromethoxy)phenyl]amino]-1,2,4-thiadiazol-3-one;

lxviii) 2-[phenylethyl]-5-[[4-(trifluoromethoxy)phenyl]amino]-1,2,4-thiadiazol-3-one; and

lxix) 4-[[2-[(3,4-difluorophenyl)methyl]-3-oxo-1,2,4-thiadiazol-5-yl]amino]benzonitrile.

15. A compound as defined in any one of Claims 1 to 14, or a pharmaceutically-acceptable salt or solvate, or a pharmaceutically functional derivative thereof, but without provisos (B) and (C), for use as a pharmaceutical.

16. A pharmaceutical formulation including a compound as defined in any one of Claims 1 to 14, 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.

17. A combination product comprising:

(A) a compound of formula I as defined in any one of Claims 1 to 14, 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.

18. A combination product as claimed in Claim 17 which comprises a pharmaceutical formulation including a compound of formula I as defined in any one of Claims 1 to 14, or a pharmaceutically-acceptable salt or solvate, or a pharmaceutically functional derivative thereof but without provisos (B) and (C); another therapeutic agent useful in the treatment of cancer; and a pharmaceutically-acceptable adjuvant, diluent or carrier.

19. A combination product as claimed in Claim 17, which comprises a kit of parts comprising components:

(a) a pharmaceutical formulation including a compound of formula I as defined in any one of Claims 1 to 14, 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; and

(b) a pharmaceutical formulation including another therapeutic agent useful in the treatment of cancer in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,

which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

20. A kit of parts as claimed in Claim 19, wherein components (A) and (B) are suitable for sequential, separate and/or simultaneous use in the treatment of cancer.

21. A combination product as claimed in any one of Claims 17 to 20, wherein the other therapeutic agent is selected from:

(xvii) a SIRT1 activator, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof; and/or

(xviii) salidroside, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof.

22. A combination product as claimed in Claim 21, wherein the other therapeutic agent is selected from cisplatin, doxorubicin, tamoxifen, anastrozole, letrozole, exemastane, herceptin, imatinib, gefitinib, erlotinib, canertinib, sunitinib, zactima, vatalanib, sorafenib, leflunomide, lapatinib, rosiglitazone, metformin, fluvastatin, simvastatin, rosuvastatin, pravastatin, atorvastatin, lovastatin and rapamycin.

23. A combination product as claimed in Claim 22, wherein the other therapeutic agent is selected from cisplatin, doxorubicin, tamoxifen and herceptin.

24. The use of a compound of formula I as defined in any one of Claims 1 to 14, 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 in any one of Claims 17 to 23, for the manufacture of a medicament for the treatment of cancer.

25. A compound as defined in any one of Claims 1 to 14, 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 in any one of Claims 17 to 23, for use in the treatment of cancer.

26. Use of a compound of formula I as defined in any one of Claims 1 to 14, 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 in any one of Claims 17 to 23, in the manufacture of medicament for inhibiting cell proliferation.

27. The kit of parts as claimed in Claim 20, the use as claimed in Claim 24 and 26, the compound or combination product as claimed in Claim 25, wherein the cancer is a solid tumor or a hematopoietic tumor.

28. The kit of parts, use, compound or combination as claimed in Claim 27, where the cancer is a solid tumor of the colon, the breast or the prostate.

29. The kit of parts, use, compound or combination as claimed in Claim 27, wherein the cancer is of the breast.

30. The kit of parts, use, compound or combination as claimed in Claim 27, where the cancer is a hematopoietic tumor that is a leukemia.

31. A kit of parts comprising:
(I) one of components (a) and (b) as defined in Claim 19, any one of Claims 20 to 23 or 27 to 30 (as dependent on Claim 19); together with
(II) instructions to use that component in conjunction with the other of the two components.

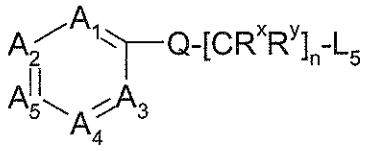
32. A method of making a kit of parts as defined in Claim 19, any one of Claims 20 to 23 or 27 to 30 (as dependent on Claim 19), which method comprises bringing a component (a) into association with a component (b), thus rendering the two components suitable for administration in conjunction with each other.

33. The use of a compound of formula I as defined in any one of Claims 1 to 14, or a pharmaceutically-acceptable salt or solvate, or a pharmaceutically functional derivative thereof but without provisos (B) and (C), for the manufacture of a medicament for the treatment of diabetes.

34. A compound as defined in any one of Claims 1 to 14, or a pharmaceutically acceptable salt or solvate, or a pharmaceutically functional derivative thereof but without provisos (B) and (C), for use in the treatment of diabetes.

35. The use as claimed in Claim 33 or a compound as claimed in Claim 34, wherein the diabetes is type 2 diabetes.

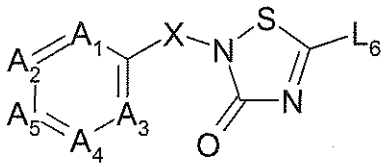
36. A process for the preparation of a compound of formula I as defined in any one of Claims 1 to 14,
(i) for compounds of formula I wherein A represents S, cyclisation of a compound of formula IIa,



VIII

wherein A_1 to A_5, n, R^x and R^y are as defined in Claim 1, L_5 is a suitable leaving group and Q is a bond, -O- or -S-;

(vi) for compounds of formula I wherein W is $-[CR^xR^y]_m-$, reaction of a compound of formula IX,



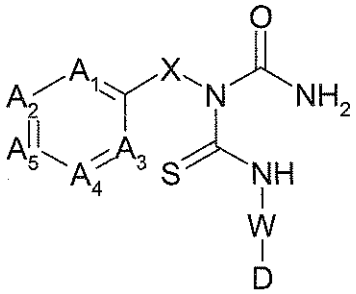
IX

wherein L_6 represents a suitable leaving group and A_1 to A_5 and X are as defined in Claim 1, with a compound of formula X,

$H_2N\text{-}W\text{-}D$ X

wherein W and D are as defined in Claim 1; and

vii) for compounds of formula I wherein B represents S, cyclisation of a compound of formula IIb,



IIb

wherein A_1 to A_5, X, W and D are as defined in Claim 1 above.

37. A process for the preparation of a pharmaceutical formulation as defined in Claim 16, which process comprises bringing into association a compound of formula I, as defined in any one of Claims 1 to 14, or a pharmaceutically-acceptable salt or solvate, or a pharmaceutically functional derivative thereof but without provisos (B) and (C), with a pharmaceutically-acceptable adjuvant, diluent or carrier.

38. A process for the preparation of a combination product as defined in any one of Claims 17 to 23, which process comprises bringing into association a compound of formula I, as defined in any one of Claims 1 to 14, or a pharmaceutically-acceptable salt

or solvate, or a pharmaceutically functional derivative thereof but without provisos (B) and (C), with the other therapeutic agent that is useful in the treatment of cancer.