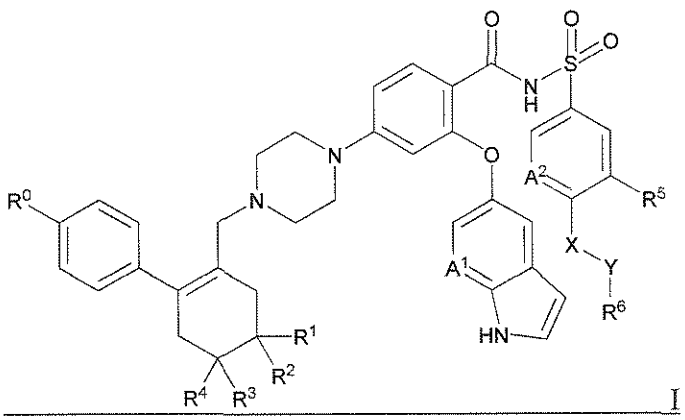
enable combination therapies with other chemotherapeutics.

SUMMARY

[0028a] In one aspect, there is provided a solid dispersion comprising, in essentially non-crystalline form, a compound of Formula I



I

where:

R^0 is halo;

R^1 and R^2 are H or are independently methyl or methoxy;

R^3 and R^4 are independently methyl or methoxy if R^1 and R^2 are H, or are H if R^1 and R^2 are independently methyl or methoxy;

A^1 and A^2 are each independently *CH* or N;

R^5 is C_{1-4} alkyl or haloalkyl, C_{1-4} alkylsulfonyl or haloalkylsulfonyl, halo, nitro or cyano;

X is –O– or –NH–;

Y is $-(CH_2)_n-$ where n is 0, 1, 2 or 3; and

R^6 is an unsubstituted or substituted 3- to 7-membered carbocyclic or heterocyclic ring as defined herein, or is NR^7R^8;

wherein, if R^6 is NR^7R^8, R^7 and R^8 are each independently H or $R^9-(CH_2)_m-$ groups, no more than one of R^7 and R^8 being H, where each R^9 is independently a 3- to 7-membered carbocyclic or heterocyclic ring, optionally substituted with no more than two Z^1 groups as defined below, and each m is independently 0 or 1; and

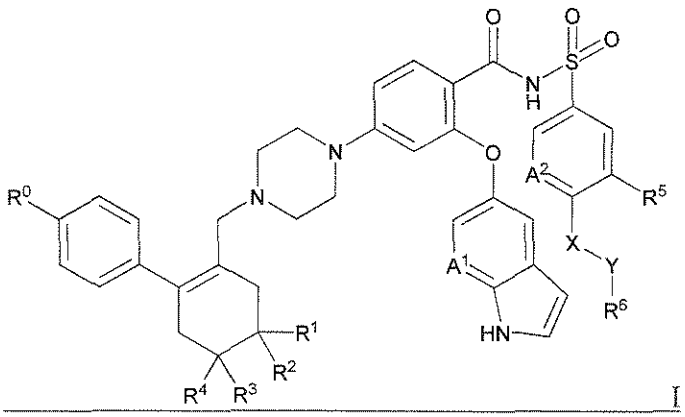
wherein, if R^6 is a substituted carbocyclic or heterocyclic ring, substituents thereon are no more than two Z^1 groups and/or no more than one Z^2 group, Z^1 groups being independently selected from (a) C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, C_{1-4} alkylsulfonyl, C_{1-4} alkylsulfonylamino, C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbonylamino and C_{1-4} alkylcarboxy, each

optionally substituted with one or more substituents independently selected from halo, hydroxy, C_{1-4} alkoxy, amino, C_{1-4} alkylamino, di-(C_{1-4} alkyl)amino and cyano, (b) halo, (e) hydroxy, (f) amino and (g) oxo groups, and Z^2 being (i) a further 3- to 6-membered carbocyclic or heterocyclic ring, optionally substituted with no more than two Z^1 groups as defined above, or (ii) NR^7R^8 where R^7 and R^8 are as defined above;

or a pharmaceutically acceptable salt thereof; dispersed in a solid matrix that comprises (a) at least one pharmaceutically acceptable water-soluble polymeric carrier and (b) at least one pharmaceutically acceptable surfactant.

[0028b] In one aspect, there is provided a process for preparing a solid dispersion, comprising:

(a) subjecting to elevated temperature (i) an active pharmaceutical ingredient (API) that comprises a compound of Formula I



I

where:

R^0 is halo;

R^1 and R^2 are H or are independently methyl or methoxy;

R^3 and R^4 are independently methyl or methoxy if R^1 and R^2 are H, or are H if R^1 and R^2 are independently methyl or methoxy;

A^1 and A^2 are each independently CH or N;

R^5 is C_{1-4} alkyl or haloalkyl, C_{1-4} alkylsulfonyl or haloalkylsulfonyl, halo, nitro or cyano;

X is –O– or –NH–;

Y is $-(CH_2)_n-$ where n is 0, 1, 2 or 3; and

R^6 is an unsubstituted or substituted 3- to 7-membered carbocyclic or heterocyclic ring as defined herein, or is NR^7R^8;

wherein, if R^6 is NR^7R^8, R^7 and R^8 are each independently H or R^9–$(CH_2)_m$– groups, no more than one of R^7 and R^8 being H, where each R^9 is independently a 3- to 7-membered carbocyclic or heterocyclic ring, optionally substituted with no more than two Z^1 groups as defined below, and each m is independently 0 or 1; and

wherein, if R^6 is a substituted carbocyclic or heterocyclic ring, substituents thereon are no more than two Z^1 groups and/or no more than one Z^2 group, Z^1 groups being independently selected from (a) C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, C_{1-4} alkylsulfonyl, C_{1-4} alkylsulfonylamino, C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbonylamino and C_{1-4} alkylcarboxy, each

optionally substituted with one or more substituents independently selected from halo, hydroxy, C_{1-4} alkoxy, amino, C_{1-4} alkylamino, di-(C_{1-4} alkyl)amino and cyano, (b) halo, (e) hydroxy, (f) amino and (g) oxo groups, and Z^2 being (i) a further 3- to 6-membered carbocyclic or heterocyclic ring, optionally substituted with no more than two Z^1 groups as defined above, or (ii) NR^7R^8 where R^7 and R^8 are as defined above;

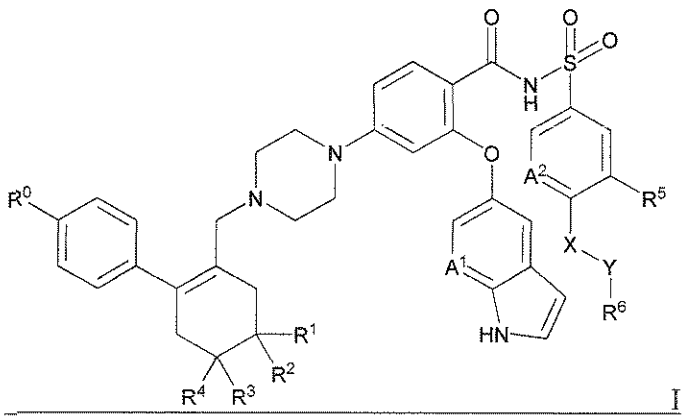
or a pharmaceutically acceptable salt thereof, (ii) a pharmaceutically acceptable water-soluble polymeric carrier and (iii) a pharmaceutically acceptable surfactant to provide an extrudable semi-solid mixture;

(b) extruding the semi-solid mixture; and

(c) cooling the resulting extrudate to provide a solid matrix comprising the polymeric carrier and the surfactant and having the compound or salt thereof dispersed in an essentially non-crystalline form therein.

[0028c] In one aspect, there is provided a process for preparing a solid dispersion, comprising:

(a) subjecting to elevated temperature (i) an active pharmaceutical ingredient (API) that comprises a compound of Formula I



I

where:

R^0 is halo;

R^1 and R^2 are H or are independently methyl or methoxy;

R^3 and R^4 are independently methyl or methoxy if R^1 and R^2 are H, or are H if R^1 and R^2 are independently methyl or methoxy;

A^1 and A^2 are each independently CH or N;

R^5 is C_{1-4} alkyl or haloalkyl, C_{1-4} alkylsulfonyl or haloalkylsulfonyl, halo, nitro or cyano;

X is –O– or –NH–;

Y is $-(CH_2)_n-$ where n is 0, 1, 2 or 3; and

R^6 is an unsubstituted or substituted 3- to 7-membered carbocyclic or heterocyclic ring as defined herein, or is NR^7R^8;

wherein, if R^6 is NR^7R^8, R^7 and R^8 are each independently H or $R^9-(CH_2)_m-$ groups, no more than one of R^7 and R^8 being H, where each R^9 is independently a 3- to 7-membered carbocyclic or heterocyclic ring, optionally substituted with no more than two Z^1 groups as defined below, and each m is independently 0 or 1; and

wherein, if R^6 is a substituted carbocyclic or heterocyclic ring, substituents thereon are no more than two Z^1 groups and/or no more than one Z^2 group, Z^1 groups being independently selected from (a) C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, C_{1-4} alkylsulfonyl, C_{1-4} alkylsulfonylamino, C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbonylamino and C_{1-4} alkylcarboxy, each optionally substituted with one or more substituents independently selected from halo, hydroxy, C_{1-4} alkoxy, amino, C_{1-4} alkylamino, di-(C_{1-4}

alkyl)amino and cyano, (b) halo, (e) hydroxy, (f) amino and (g) oxo groups, and Z^2 being (i) a further 3- to 6-membered carbocyclic or heterocyclic ring, optionally substituted with no more than two Z^1 groups as defined above, or (ii) NR^7R^8 where R^7 and R^8 are as defined above;

or a pharmaceutically acceptable salt thereof, (ii) a pharmaceutically acceptable water-soluble polymeric carrier and (iii) a pharmaceutically acceptable surfactant to provide an extrudable semi-solid mixture;

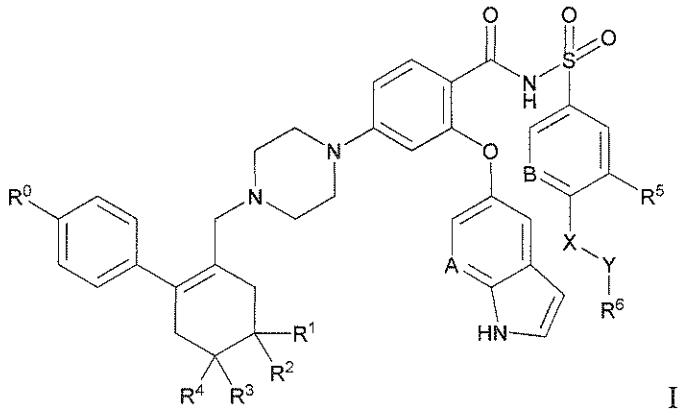
(b) extruding and calendering the semi-solid mixture; and

(c) cooling the resulting extrudate to provide a solid matrix comprising the polymeric carrier and the surfactant and having the compound or salt thereof dispersed in an essentially non-crystalline form therein.

[0028d] In one aspect, there is provided an orally deliverable pharmaceutical dosage form comprising the solid dispersion as defined herein.

[0028e] In one aspect, there is provided the use of a therapeutically effective amount of the solid dispersion as defined herein, in the manufacture of a medicament for treating a neoplastic, immune or autoimmune disease.

[0029] In one embodiment, there is~~There is now~~ provided a solid dispersion comprising, in essentially non-crystalline, for example amorphous, form, a compound of Formula I:



I

where:

R^0 is halo;

R^1 and R^2 are H or are independently methyl or methoxy;

R^3 and R^4 are independently methyl or methoxy if R^1 and R^2 are H, or are H if R^1 and R^2 are independently methyl or methoxy;

A and B are each independently CH or N;

R^5 is C_{1-4} alkyl or haloalkyl, C_{1-4} alkylsulfonyl or haloalkylsulfonyl, halo, nitro or cyano;

X is –O– or –NH–;

Y is $-(CH_2)_n-$ where n is 0, 1, 2 or 3; and

R^6 is an unsubstituted or substituted 3- to 7-membered carbocyclic or heterocyclic ring as defined herein, or is NR^7R^8;

wherein, if R^6 is NR^7R^8, R^7 and R^8 are each independently H or $R^9-(CH_2)_m-$ groups, no more than one of R^7 and R^8 being H, where each R^9 is independently a 3- to 7-membered carbocyclic or heterocyclic ring, optionally substituted with no more than two Z^1 groups as defined below, and each m is independently 0 or 1; and

wherein, if R^6 is a substituted carbocyclic or heterocyclic ring, substituents thereon are no more than two Z^1 groups and/or no more than one Z^2 group, Z^1 groups

are no more than two Z^1 groups and/or no more than one Z^2 group, Z^1 groups being independently selected from (a) C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, C_{1-4} alkylsulfonyl, C_{1-4} alkylsulfonylamino, C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbonylamino and C_{1-4} alkylcarboxy, each optionally substituted with one or more substituents independently selected from halo, hydroxy, C_{1-4} alkoxy, amino, C_{1-4} alkylamino, di-(C_{1-4} alkyl)amino and cyano, (b) halo, (e) hydroxy, (f) amino and (g) oxo groups, and Z^2 being (i) a further 3- to 6-membered carbocyclic or heterocyclic ring, optionally substituted with no more than two Z^1 groups as defined above, or (ii) NR^7R^8 where R^7 and R^8 are as defined above;

or a pharmaceutically acceptable salt thereof, (ii) a pharmaceutically acceptable water-soluble polymeric carrier and (iii) a pharmaceutically acceptable surfactant to provide an extrudable semi-solid mixture;

(b) extruding and calendering the semi-solid mixture; and

(c) cooling the resulting extrudate to provide a solid matrix comprising the polymeric carrier and the surfactant and having the compound or salt thereof dispersed in an essentially non-crystalline form therein.

42. The process of Claim 41, wherein API is 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide.

43. The process of claim 42, wherein the polymeric carrier is a copovidone.

44. The process of Claim 43, wherein the surfactant is a polysorbate.

45. An orally deliverable pharmaceutical dosage form comprising the solid dispersion of Claim 1.

46. Use of a therapeutically effective amount of the solid dispersion of Claim 1, in the manufacture of a medicament~~A method~~ for treating a neoplastic, immune or autoimmune disease~~, comprising orally administering to a subject having the disease a therapeutically effective amount of the solid dispersion of Claim 1~~.

47. The use~~method~~ of Claim 46, wherein the disease is a neoplastic disease.

48. The use~~method~~ of Claim 47, wherein the neoplastic disease is selected from the group consisting of cancer, mesothelioma, bladder cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, ovarian cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, bone cancer, colon cancer, rectal cancer, cancer of the anal region, stomach cancer, gastrointestinal (gastric, colorectal and/or duodenal) cancer, chronic lymphocytic leukemia, acute lymphocytic leukemia, esophageal cancer, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, testicular cancer, hepatocellular (hepatic and/or biliary duct) cancer, primary or secondary central nervous system tumor, primary or secondary brain tumor, Hodgkin's disease, chronic or acute leukemia, chronic myeloid leukemia, lymphocytic lymphoma, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, multiple myeloma, oral cancer, non-small-cell lung cancer, prostate cancer, small-cell lung cancer, cancer of the kidney and/or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system, primary central nervous system lymphoma, non-Hodgkin's lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, adrenocortical cancer, gall bladder cancer, cancer of the spleen, cholangiocarcinoma, fibrosarcoma, neuroblastoma, retinoblastoma and combinations thereof.

49. The use~~method~~ of Claim 47, wherein the neoplastic disease is a lymphoid malignancy.

50. The use~~method~~ of Claim 49, wherein the lymphoid malignancy is non-Hodgkin's lymphoma.

51. The use~~method~~ of Claim 47, wherein the neoplastic disease is chronic lymphocytic leukemia or acute lymphocytic leukemia.

52. The use~~method~~ of Claim 46, wherein the disease is an immune or autoimmune disease.

53. The use~~method~~ of Claim 46, wherein the solid dispersion is administered in a parent-compound-equivalent dose of about 50 to about 500 mg per day of the compound of

Formula I or salt thereof at an average treatment interval of about 3 hours to about 7 days.

54. The use~~method~~ of Claim 46, wherein the solid dispersion is administered once daily in a parent-compound-equivalent dose of about 50 to about 500 mg per day of the compound of Formula I or salt thereof.

55. The use~~method~~ of Claim 46, wherein the compound is selected from the group consisting of

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)-sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({4-[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

and pharmaceutically acceptable salts thereof.

56. The use~~method~~ of Claim 46, wherein the compound is 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide.