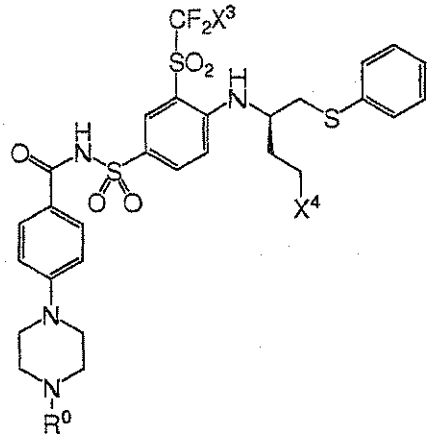
effective range. This can be achieved by daily parenteral, *e.g.*, intravenous (i.v.) or intraperitoneal (i.p.) administration. However, daily parenteral administration is often not practical in a clinical setting, particularly for outpatients. To enhance clinical utility of an apoptosis-promoting agent, for example as a chemotherapeutic in cancer patients, a solid dosage form with acceptable oral bioavailability would be highly desirable. Such a dosage form, and a regimen for oral administration thereof, would represent an important advance in treatment of many types of cancer, including NHL, and would more readily enable combination therapies with other chemotherapeutics.

SUMMARY OF THE DISCLOSUREINVENTION

There is now provided a solid dispersion comprising, in essentially non-crystalline, for example amorphous, form, a compound of Formula I:

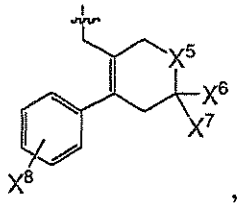


I

where:

X^3 is chloro or fluoro; and

(1) X^4 is azepan-1-yl, morpholin-4-yl, 1,4-oxazepan-4-yl, pyrrolidin-1-yl, $-N(CH_3)_2$, $-N(CH_3)(CH(CH_3)_2)$, 7-azabicyclo[2.2.1]heptan-7-yl or 2-oxa-5-azabicyclo[2.2.1] hept-5-yl; and R^0 is



,

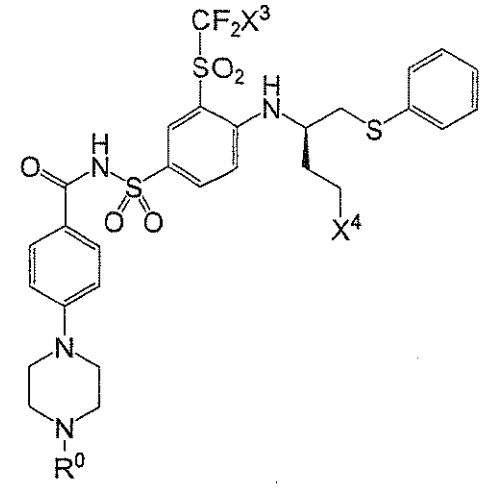
where

X^5 is $-CH_2-$, $-C(CH_3)_2-$ or $-CH_2CH_2-$;

X^6 and X^7 are both –H or both methyl; and

salt or *vice versa*. In a particular embodiment, the API is a salt, for example a crystalline salt, of a compound of Formula I, and the finished solid dispersion contains the compound in free base form. According to this embodiment, the process further comprises, prior to removing the solvent, adding a base for conversion of the salt to the free base, and optionally extracting a by-product of such conversion (*e.g.*, a salt by-product) from the resulting mixture.

In a first aspect, there is provided a process for preparing a solid dispersion, comprising: (a) dissolving an active pharmaceutical ingredient (API) comprising (i) a compound of Formula I

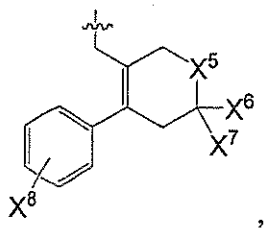


I

where

X^3 is chloro or fluoro; and

(1) X^4 is azepan-1-yl, morpholin-4-yl, 1,4-oxazepan-4-yl, pyrrolidin-1-yl, $-N(CH_3)_2$, $-N(CH_3)(CH(CH_3)_2)$, 7-azabicyclo[2.2.1]heptan-7-yl or 2-oxa-5-azabicyclo[2.2.1] hept-5-yl; and R^0 is



,

where

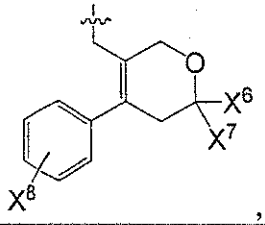
X^5 is $-CH_2-$, $-C(CH_3)_2-$ or $-CH_2CH_2-$;

X^6 and X^7 are both –H or both methyl; and

X^8 is fluoro, chloro, bromo or iodo;

or

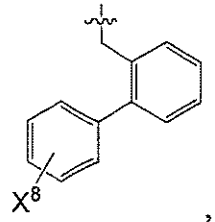
(2) X^4 is azepan-1-yl, morpholin-4-yl, pyrrolidin-1-yl, $-N(CH_3)(CH(CH_3)_2)$ or 7-azabicyclo[2.2.1]heptan-7-yl; and R^0 is



,

where X^6, X^7 and X^8 are as above; or

(3) X^4 is morpholin-4-yl or $-N(CH_3)_2$; and R^0 is



,

where X^8 is as above;

or a pharmaceutically acceptable salt, prodrug, salt of a prodrug or metabolite thereof, (ii) at least one pharmaceutically acceptable water-soluble polymeric carrier and (iii) at least one pharmaceutically acceptable surfactant in a suitable solvent; and

(b) removing the solvent to provide a solid matrix comprising the at least one polymeric carrier and the at least one surfactant and having the compound or a salt, prodrug, salt of a prodrug or metabolite thereof dispersed in an essentially non-crystalline form therein.

In a second aspect, there is provided an orally deliverable pharmaceutical dosage form comprising the solid dispersion as defined herein.

In a third aspect, there is provided the use of the solid dispersion as defined herein in the manufacture of a medicament for treating a disease characterized by apoptotic dysfunction and/or overexpression of an anti-apoptotic Bcl-2 family protein.

There is still further provided a solid dispersion prepared by the process described above.

There is still further provided a method for treating a disease characterized by apoptotic dysfunction and/or overexpression of an anti-apoptotic Bcl-2 family protein, comprising orally administering to a subject having the disease a therapeutically effective amount of a solid dispersion as described above, or one or more solid dosage forms comprising such a dispersion. Examples of such a disease include many neoplastic diseases including cancers. A specific illustrative type of cancer that can be treated according to the present method is non-Hodgkin's lymphoma (NHL). Another specific illustrative type of cancer that can be treated according to the present method is chronic lymphocytic leukemia. Yet another specific illustrative type of cancer that can be treated according to the present method is acute lymphocytic leukemia, for example in a pediatric patient.

According to any of the embodiments of the disclosure~~invention~~ described above, the compound of Formula I is illustratively ABT-263 or a pharmaceutically acceptable salt, prodrug, salt of a prodrug or metabolite thereof, for example ABT-263 free base or ABT-263 *bis*-hydrochloride salt (ABT-263 *bis*-HCl).

There is still further provided a method for maintaining in bloodstream of a human cancer patient, for example a patient having NHL, a therapeutically effective plasma concentration of ABT-263 and/or one or more metabolites thereof, comprising orally administering to the subject a solid dispersion of ABT-263 or a pharmaceutically acceptable salt, prodrug, salt of a prodrug or metabolite thereof (for example ABT-263 free base or ABT-263 *bis*-HCl) in essentially non-crystalline form in a matrix that comprises a pharmaceutically acceptable water-soluble polymeric carrier and a pharmaceutically acceptable surfactant, in a dosage amount equivalent to about 50 to about 500 mg ABT-263 free base equivalent per day, at an average dosage interval of about 3 hours to about 7 days.

Additional embodiments of the disclosure~~invention~~, including more particular aspects of those provided above, will be found in, or will be evident from, the detailed description that follows.

vacuum.

17. The process of any of Claims 10–16, wherein the solvent comprises methanol, ethanol or acetone.

18. An orally deliverable pharmaceutical dosage form comprising the solid dispersion of any of Claims 1–9.

19. Use of the solid dispersion of any of Claims 1-9 in the manufacture of a medicament for treating a disease characterized by apoptotic dysfunction and/or overexpression of an anti-apoptotic Bcl-2 family protein~~, by orally administering to a subject having the disease a therapeutically effective amount of the solid dispersion~~.

20. The use of Claim 19, wherein the disease is a neoplastic disease.

21. The use of Claim 20, 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.

22. The use of Claim 20, wherein the neoplastic disease is a lymphoid malignancy.