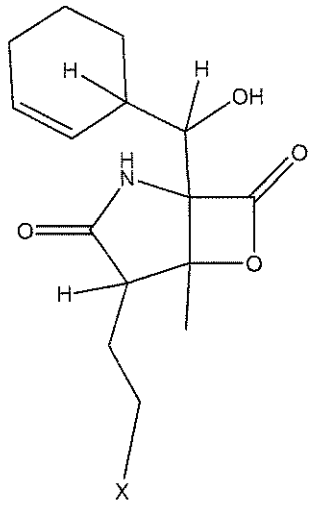
effects on MM biology by targeting: 1) cell-cycle regulatory proteins; 2) UPR pathway *via* modulating transcriptional activity of plasma cell differentiation factor X-box binding protein-1 (XBP-1); 3) p53-mediated apoptosis/MDM2; 4) DNA repair mechanisms; 5) classical stress-response pathways *via* both intrinsic (caspase-9 mediated) and extrinsic (caspase-8 mediated) cell death cascades. Specifically, Bortezomib activates JNK, which triggers mitochondrial apoptotic signaling: release of cytochrome-c (cyto-c) and second mitochondrial activator of caspases (Smac) from mitochondria to cytosol, followed by activation of caspase-9 and caspase-3. However, both intrinsic and acquired resistance has already been observed, and there are no therapies to overcome Bortezomib resistance at present.

Summary ~~of the Invention~~

[0004a] In a first aspect, there is provided a use of a compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof:

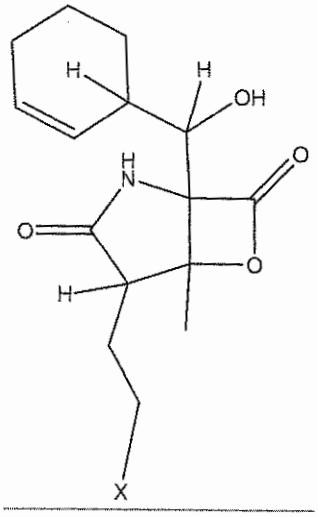


(I)

in the manufacture of a medicament for treating a neoplastic disease in a patient, wherein X is selected from the group consisting of fluorine, chlorine, bromine or iodine, and

wherein the neoplastic disease is resistant to at least one other chemotherapeutic agent selected from the group consisting of bortezomib, dexamethasone, and thalidomide.

[0004b] In a second aspect, there is provided a use of a compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof:

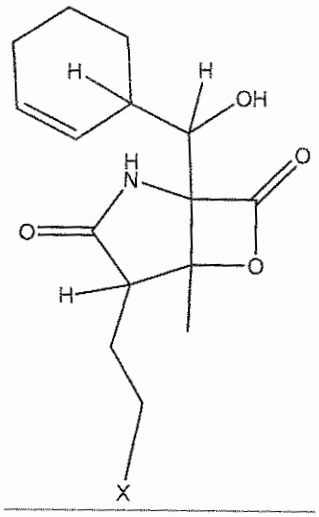


(I)

in the manufacture of a medicament for treating a neoplastic disease in a patient, wherein X is selected from the group consisting of fluorine, chlorine, bromine or iodine, in combination with at least one additional chemotherapeutic agent selected from the group consisting of bortezomib, dexamethasone, and thalidomide.

[0004c] In a third aspect, there is provided a pharmaceutical composition, comprising:

a compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof:

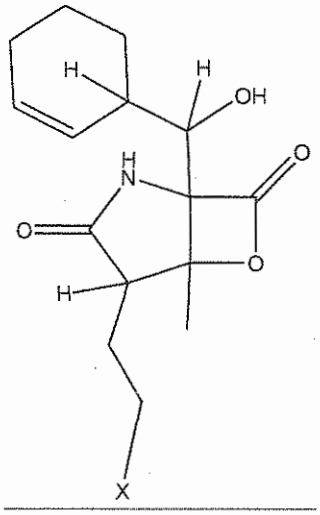


(I)

wherein X is selected from the group consisting of fluorine, chlorine, bromine or iodine; and

at least one additional chemotherapeutic agent selected from the group consisting of bortezomib, dexamethasone, and thalidomide.

[0004d] In a fourth aspect, there is provided a use of a synergistic combination of a proteosome inhibitor with a compound of formula (I)

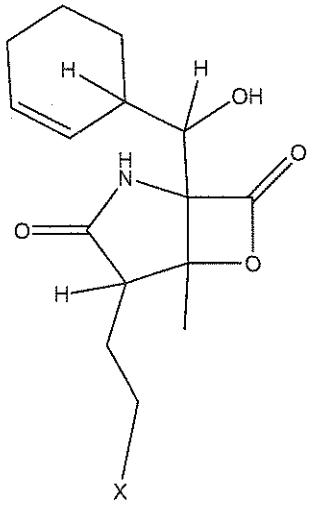


(I)

or a pharmaceutically ceptable salt thereof

wherein X is selected from the group consisting of fluorine, chlorine, bromine, or iodine, in the manufacture of a medicament for treating a neoplastic disease in a patient.

[0005] There is also provided ~~One aspect of the present invention is~~ a method of treating a neoplastic disease, comprising administering to a patient inflicted with the neoplastic disease a compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof:



(I)

[0006] wherein X is selected from the group consisting of fluorine, chlorine, bromine or iodine, and wherein the neoplastic disease is susceptible to resistance to at least one other chemotherapeutic agent.

[0007] There is also provided ~~Another aspect of the present invention is~~ a method of treating a neoplastic disease, comprising administering to a patient inflicted with the neoplastic disease a compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof wherein X

is selected from the group consisting of fluorine, chlorine, bromine or iodine, in combination with at least one additional chemotherapeutic agent.

[0008] There is also provided ~~Another aspect of the present invention is~~ a pharmaceutical composition, comprising a compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof, wherein X is selected from the group consisting of fluorine, chlorine, bromine or iodine, and at least one additional chemotherapeutic agent.

[0009] There is also provided ~~Another aspect of the present invention is~~ a method of treating a neoplastic disease, comprising administering to a patient inflicted with the neoplastic disease a synergistic combination of at least two proteosome inhibitors.

Brief Description of the Drawings

[0010] FIGURE 1 illustrates inhibition of chymotrypsin-like, caspase-like, and trypsin-like proteasome activities in human erythrocytes-derived 20S proteasome by NPI-0052.

[0011] FIGURE 2 illustrates the *in vivo* chymotrypsin-like activity of NPI-0052 in mice.

[0012] FIGURE 3 depicts the autoradiograph obtained after treating MM.1S multiple myeloma (MM) cells with NPI-0052 (7 nM) and incubating protein extracts with AdaY(^{125}I)Ahx$_3$L$_3$VS at 37°C.

[0013] FIGURE 4 depicts immunoblots obtained after treating MM.1S cells with NPI-0052 and then incubating with Dansyl-Ahx3L3VS.

[0014] FIGURE 5A illustrates cell viability of various multiple myeloma cell lines treated with indicated doses of NPI-0052 for 24h.

[0015] FIGURE 5B illustrates DNA fragmentation assays of apoptosis after treatment with NPI-0052 of MM cells obtained from patients.

[0016] FIGURE 6 illustrates DNA fragmentation assays of apoptosis after treatment with NPI-0052 of bone marrow stromal cells obtained from patients.

[0017] FIGURE 7 illustrates MTT assay of MM.1S cell viability after treatment with NPI-0052 or Dex in the presence or absence of IL-6 or IGF-I.

[0018] FIGURE 8 illustrates the effect of NPI-0052 on VEGF-induced migration of MM.1S cells.