

**Novel Spiro and cyclic bis-benzylidine proteasome inhibitor for the treatment of Cancer,
Diabetes and Neurological disorders**

BACKGROUND

[1] Ubiquitin-Proteasome System (UPS) play a vital role in cellular homeostasis, cell cycle progression and signaling pathways that are altered in many diseases. Modulating UPS function with small molecules that directly bind to the proteasomal proteins can be useful to treat wide variety of diseases specifically cancers, diabetes and neurological disorders. Targeting the aberrant metabolism of cancer cells is an emerging approach for cancer therapy. Indeed, despite early skepticism that inhibiting protein degradation with a proteasome inhibitor would provide a sufficient therapeutic index for cancer therapy, over the last decade three proteasome inhibitors that target the catalytic function of the 20S proteasome were approved by FDA to treat multiple myeloma and mantle cell lymphoma. However, their limited efficacy against solid tumors, toxicities and the emergence of resistant multiple myeloma has driven search for alternative proteasome inhibitors with distinct and complementary mechanisms of action.

SUMMARY

[2] Provided herein are spiro and cyclic bis-benzylidine small molecules (Up I, II and III, Up compounds hereafter), a new type of proteasome inhibitor, that inhibit the proteasome function through either ubiquitin receptor ADRM1/RPN13 or proteasome DUB enzymes (USP14, UCH37 and RPN11) can be used for the treatment of cancers/diabetes/neurological disorders. The Up compounds bind to the 19S regulatory particle of the proteasome which triggers a rapid and toxic accumulation of high molecular weight poly-ubiquitinated protein aggregates, reflecting inhibition of deubiquitinase activity and substrate recognition by the proteasome.

BRIEF DESCRIPTION OF THE DRAWINGS

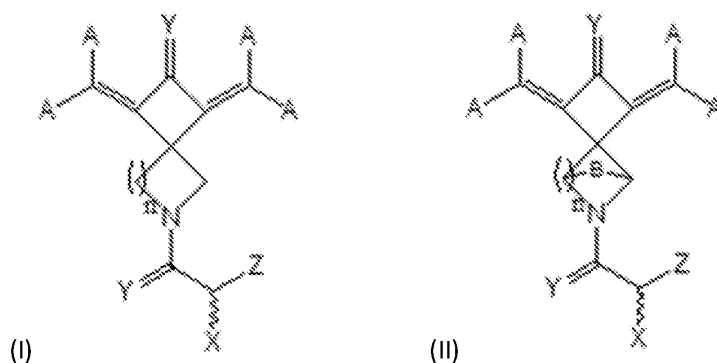
[3] Figure 1: Up109 and Up117 stabilized proteasome-targeted firefly luciferase reporter.

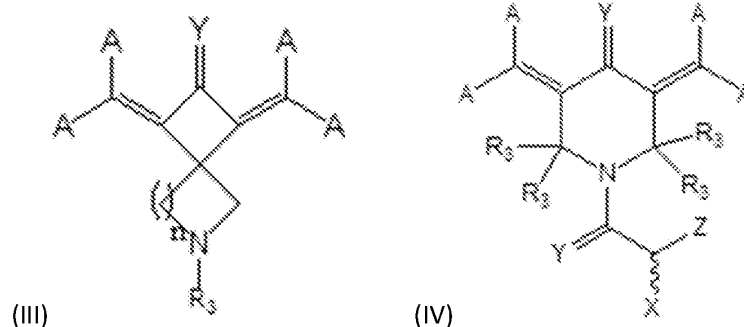
[4] Figure 2: Up109 and Up117 accumulated poly ubiquitin tagged proteins.

- [5] Figure 3: Up109 and Up117 inhibited NFκB signaling.
- [6] Figure 4: Up109 and Up117 binds to RPN13.
- [7] Figure 5: Accumulation of PolyUB proteins with the treatment of compounds: (A) HeLa cells treated with Up compounds (1 μM) for 4 h and immunoblotted with K48 linked anti-Ub antibody; (B) OV2008 cells treated with Up compounds (1 μM) for 12 h and immunoblotted with anti-Ub antibody; (C) LNCaP cells treated with Up compounds for 4 h and immunoblotted with anti-Ub antibody.
- [8] Figure 6: Stabilization of 4UBFL reporter protein with Up109 treatment.
- [9] Figure 7: Up109 binds to RPN13.
- [10] Figure 8: (A) CHOP-10 quantification in ES2 cells treated with Up109 for 12 h; (B) Annexin-V staining by FACS analysis of ES2 cells treated with Up109 and Bortezomib for 12 h.
- [11] Figure 9: BALB/C mice were electroporated with 4UBFL gene and treated with Up109 and the IVIS imaging was used to quantify luciferase activity.
- [12] Figure 10: In vivo efficacy of Up109 against ES2Lu tumor growth.

DETAILED DESCRIPTION

- [13] Provided herein are compounds having the structure of formula either I, or II, or III, or IV, shown below





- wherein each pair of A is one of:
 - (i) phenyl, optionally substituted with 1-5 substituents selected from the group consisting of R1, OR1, NR1R2, S(O)qR1, SO₂NR1R2, NR1SO₂R2, C(O)R1, C(O)OR1, C(O)NR1R2, NR1C(O)R2, NR1C(O)OR2, CF₃, and OCF₃;
 - (ii) naphthyl, optionally substituted with 1-5 substituents selected from the consisting of R1, OR1, NR1R2, S(O)qR1, SO₂NR1R2, NR1SO₂R2, C(O)R1, C(O)OR1, C(O)NR1R2, NR1C(O)R2, NR1C(O)OR2, CF₃, and OCF₃;
 - (iii) a 5 or 6 membered monocyclic heteroaryl group, having 1-3 heteroatoms selected from the group consisting of O, N, and S, optionally substituted with 1-3 substituents selected from the group consisting of R1, OR1, NR1R2, S(O)qR1, SO₂NR1R2, NR1SO₂R2, C(O)R1, C(O)OR1, C(O)NR1R2, NR1C(O)R2, NR1C(O)OR2, CF₃, and OCF₃; and
 - (iv) an 8 to 10 membered bicyclic heteroaryl group containing 1-3 heteroatoms selected from the group consisting of O, N, and S; and the second ring is fused to the first ring using 3 to 4 carbon atoms, and the bicyclic hetero aryl group is optionally substituted with 1-3 substituents selected from the group consisting of R1, OR1, NR1R2, S(O)qR1, SO₂NR1R2, NR1SO₂R2, C(O)R1, C(O)OR1, C(O)NR1 R2, NR1 C(O)R2, NR1C(O)OR2, CF₃, and OCF₃;
 - (v) any group belongs to R1 or R2
- wherein n represents number of atoms ranging from 0-4 (0,1,2,3,4) and can be a Carbon, Nitrogen or Oxygen. In the case of nitrogen, it can be NH, NR1 or NR2;

- wherein X is Hydrogen, OR1 or NP, wherein P is selected from the group consisting of R1, C(O)R1, C(O)OR1, C(O)NR1R2, S-N(R1)COOR1, and S-N(R1), wherein Y is selected from the group consisting of O, S, NR1 and CR1R2, and wherein R1 and R2 are selected from the group consisting of hydrogen, nitro, hydroxyl, carboxy, amino, halogen, cyano and C1-C14 linear or branched alkyl groups, that are optionally substituted with 1-3 substituents selected from the group consisting of C1-C4 linear or branched alkyl, up to perhalo substituted C1-C14 linear or branched alkyl, C1-C4 alkoxy, hydrogen, nitro, hydroxyl, carboxy, amino, C1-C14 alkylamino, C1-C-n dialkylamino, halogen, and cyano;
- wherein Z is selected from the group consisting of hydrogen; C1 to C14 linear, branched, or cyclic alkyls; alkenyls, phenyl; benzyl, 1-5 substituted benzyl, C1 to C3 alkyl-phenyl, wherein the alkyl moiety is optionally substituted with halogen up to perhalo; up to perhalo substituted C1 to C14 linear or branched alkyls; -(CH2)q-K, where K is a 5 or 6 membered monocyclic heterocyclic ring, containing 1 to 4 atoms selected from oxygen, nitrogen and sulfur, which is saturated, partially saturated, or aromatic, or an 8 to 10 membered bicyclic heteroaryl having 1-4 heteroatoms selected from the group consisting of O, N and S, wherein said alkyl moiety is optionally substituted with halogen up to perhalo, and wherein the variable q is an integer ranging from 0 to 4;
- wherein B is (i) R1, C(O)R1, C(O)OR1, C(O)NR1R2, S-N(R)COOR1, S-N(R1)COO(B), S(B); and wherein each R1-R2, other than perhalo substituted C1-C14 linear or branched alkyl, is optionally substituted with 1-3 substituents independently selected from the group consisting of C1-C14 linear or branched alkyl, up to perhalo substituted C1-C14 linear or branched alkyl, C1-C3 alkoxy, hydroxyl, carboxy, amino, C1-C3 alkylamino, C1-C6 dialkylamino, halogen, cyano; and
- where in R3 is H, C1-6-alkyl, C2-6-alkenyl; C1-3-alkoxy-C1-6-alkyl-; C1-3-alkoxy-C2-6-alkenyl-; aryl-C0-6-alkyl-; heteroaryl-C0-6-alkyl-; heterocyclyl-C0-6-alkyl-; cycloalkyl-C0-6-alkyl-; ---C1-6-alkyl-COOC1-6-alkyl; ---C2-6-alkyl-aryloxy; C1-6-alkyl-heteroaryl; C1-6-alkyl-heterocyclyl; C1-6-alkyl-cycloalkyl; C1-6-alkyl-aryl; COR⁴, where R⁴ is selected from: C1-6-alkyl; C2-6-alkenyl; C1-6-alkoxy; C1-3-alkoxy-C1-6-alkyl-; C1-3-alkoxy-C2-6-alkenyl-; aryl-C0-

₆-alkyl-; heteroaryl-C₀₋₆-alkyl-; heterocyclyl-C₀₋₆-alkyl-; cycloalkyl-C₀₋₆-alkyl-; ---C₁₋₆-alkyl-COOC₁₋₆-alkyl; NH₂;---NHC₁₋₆-alkyl; ---N(C₁₋₆-alkyl)₂; ----C₀₋₆-alkyl-aryloxy.

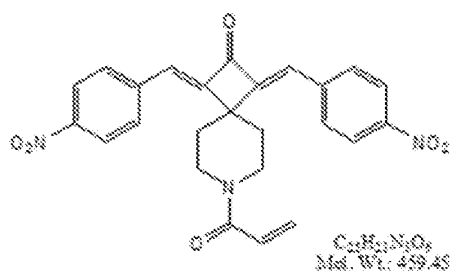
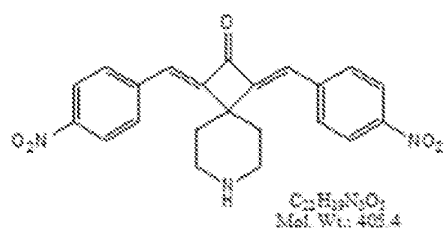
[14] The compounds described herein bind to proteasomal proteins as either DUB inhibitor or proteasome receptor inhibitor.

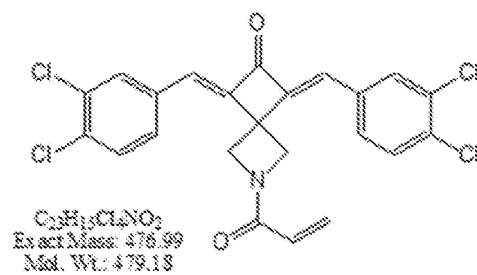
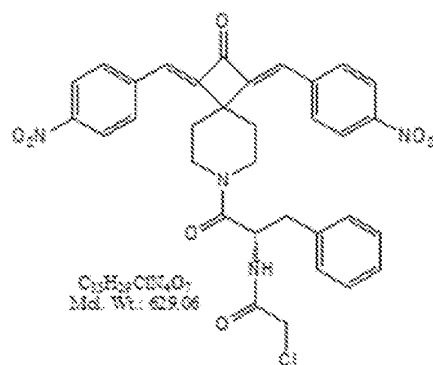
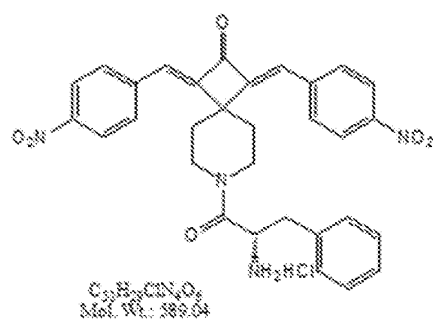
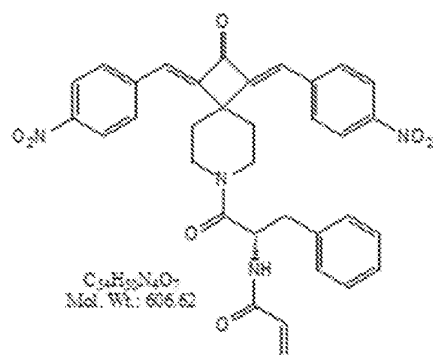
[15] Also provided herein is a method of inhibiting proteasomes in a mammal by administering an effective amount of the compound disclosed herein to the mammal. As used herein, the term “mammal” includes, for example, humans, dogs, and cats.

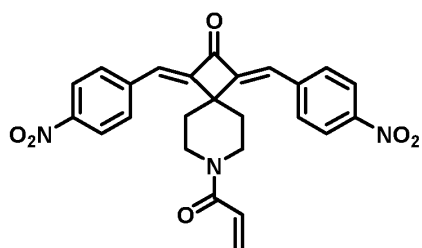
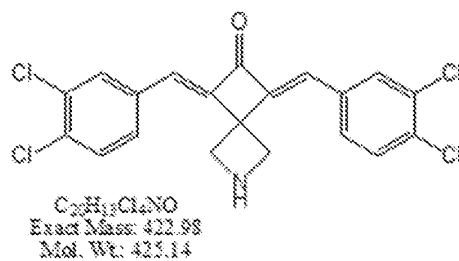
[16] Also provided herein are methods of treating a disease in a mammal by administering to the mammal a therapeutically effective dose of a compound as described herein. The disease to be treated may be, for example, cancer, or diabetes, or neurological disorders.

[17] The compounds disclosed herein may be usefully administered alone or in combination with at least one other therapeutic agent or radiation, as can be determined by a medical professional.

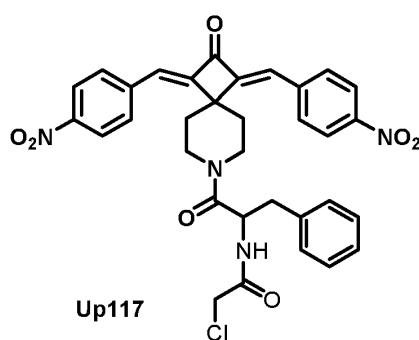
[18] Exemplary compounds which meet the requirements described herein include the following:



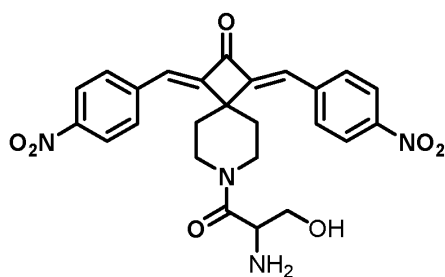




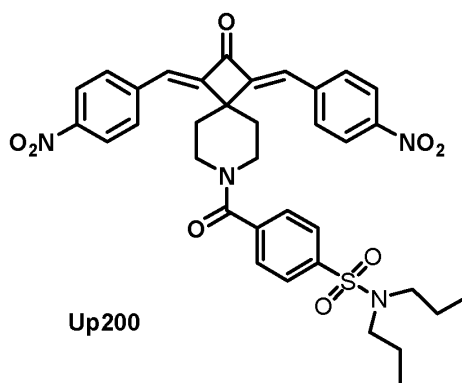
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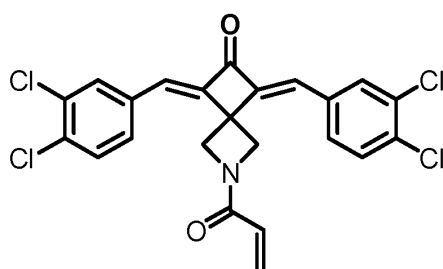
Up117



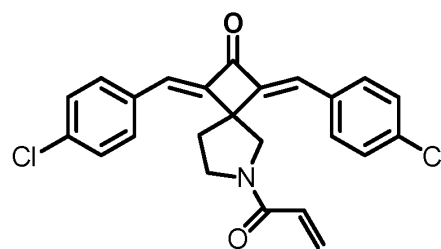
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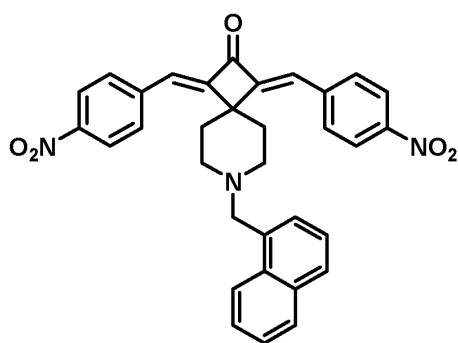
Up200



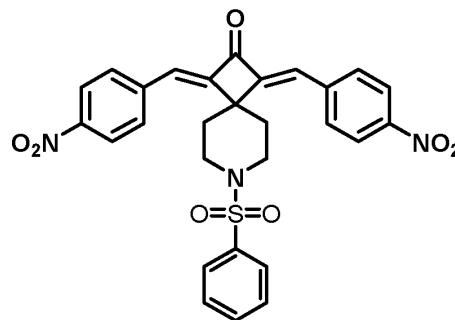
Up111



Up171



Up201



Up188

EXAMPLES**Example 1: Inhibition of cancer cell proliferation and colony formation by Up Therapeutics Compounds (Up compounds)**

[19] Treatment of cancer cells with Up compounds inhibited cell proliferation as indicated by MTT assay. Briefly cancer cells incubated with Up compounds for the period of 24 or 48 or 72 hours and the cell viability was measured using MTT assay. IC₅₀ of compounds listed in Table1. Also Up109 and Up117 also significantly blocked colony formation in OV2008 and A2780 cancer cells corresponding to their IC₅₀ values. Both compounds were similarly active in SKOV3 and its taxol resistant line (SKOV3-TR) whereas Taxol show 7-fold difference.

Table1: IC₅₀ values of selected Up Therapeutics compounds (in μ M)

Cell Line				
Name	Type			
		Up101	Up109	Up117
MM.1S	Multiple Myeloma		0.035	0.042
RPMI8226	Multiple Myeloma		0.123	0.14
RPMI8226-R	Multiple Myeloma		0.061	0.078
LNCaP	Prostate Cancer		0.065	0.087
PC-3	Prostate Cancer		0.057	0.074
DU145	Prostate Cancer		0.077	0.13
ES2	Ovarian Cancer	0.453	0.022	0.041
OVCAR3	Ovarian Cancer	0.761	0.021	

OVCAR5	Ovarian Cancer	0.592	0.019	0.037
SKOV3	Ovarian Cancer	>1.25	0.045	0.157
SKOV3-TR	Ovarian Cancer	>1.25	0.058	0.202
A2780	Ovarian Cancer	0.365	0.013	0.022
OV2008	Ovarian Cancer	0.968	0.034	0.047
HS578T	Triple Negative Breast Cancer		0.017	0.032
MDA-MB-231	Triple Negative Breast Cancer		0.038	0.056
HCC1806	Triple Negative Breast Cancer		0.042	0.071
HeLa	Cervical Cancer		0.075	0.089
HepG2	Liver Cancer		0.118	0.447
HFF(primary human foreskin fibroblast)	Normal Cell line	>1.25	>1.25	>1.25

Example 2

[20] To measure proteasome function in live cells, we utilized an engineered ubiquitin-firefly (4Ub-FL) reporter in which four copies of mutant ubiquitin (ubiquitin G76V) gene are fused to the N-terminus of the firefly luciferase (FL) gene. The results of this experiment, shown in Figure 1, reveal that the 4Ub-FL reporter protein is rapidly degraded by the proteasome. Importantly, treatment of 293TT cells expressing 4Ub-FL gene with proteasome inhibitors results in its stabilization and an increase in luciferase activity. Interestingly, treatment of Up109 and Up117 produced a greater increase in the 4Ub-FL bioluminescence than RA190 in a dose dependent manner. Up109 shows thirteen-fold increase in bioluminescence whereas eleven and fivefold increase was observed with Up117 and RA190 respectively compared to before treatment.

Example 3

[21] Accumulation of poly ubiquitinated proteins is a general phenomenon of proteasome inhibition. We examined the impact of these compounds on the levels of polyubiquitinated proteins in HeLa cells by anti-K48-linked ubiquitin immunoblot analysis. The results of this experiment, shown in Figure 2, reveal that treatment of HeLa cells with Up109 or Up117 (4 hr) dramatically increased the levels of K48-linked polyubiquitinated proteins similarly to RA190. However, accumulated K48 polyubiquitinated proteins observed following exposure to

compounds exhibited a higher molecular weight than that seen in Bortezomib-treated cells and occurred more rapidly. These results suggest that the toxicity exerted by Up109 and Up117 in cervical cancer cells is associated with a prior accumulation of high-molecular-weight polyubiquitinated proteins and occurs by a mechanism distinct to Bortezomib.

Example 4

[22] NF κ B is constitutively activated in many cancers including high grade cervical intraepithelial neoplasia (CIN) and cervical cancer. Stimulation of 293 cells carrying an NF κ B reporter construct with human TNF- α leads to increased reporter activity, and Up109, Up117 and RA190 produced a significant dose-dependent decrease of reporter activity after stimulation with TNF- α (Figure 3). Stabilization of I κ B - α was observed in HeLa cells post treatment with Up109 and Up117 in the presence of TNF- α .

Example 5

[23] To identify the cellular target, a competition assay was performed using RA190B probe. Earlier we showed that biotinylated RA190 (RA190B) covalently binds to RPN13. We used RA190B as a probe to determine the Up compound binding to RPN13. HeLa cell lysate was pretreated with Up109 or Up117 and then subsequently treated with RA190B. Lysate was denatured under reduced conditions and proteins were separated on a gel and probed with HRPStreptavidin. Figure 4 shows that disappearance of RA190B labeling of the 42kDa protein in the presence of Up109 and UP117 indicates competition with RA190B for binding to RPN13.

Example 6: Up compounds accumulated Poly Ubiquitinated proteins *in vitro*

[24] Accumulation of poly ubiquitinated proteins is a general phenomenon of proteasome inhibition. We examined the impact of these compounds on the levels of polyubiquitinated proteins cancer cells by anti-ubiquitin immunoblot analysis. Cancer cell lines (HeLa, OV2008 and LNCaP) treated with Up compounds for the period of indicated time and the cells were lysed and subjected to Westernblot Analysis. Immunoblot with anti-Ubiquitin antibody show the accumulation of polyUbiquitinated proteins in treated cells (Figure 5). HeLa cells were probed

with K48-linked anti-Ub antibody which recognizes the proteins tagged with ubiquitin through K-48 linkage. K48-linked polyubiquitin chains attached to substrate proteins often serve as a recognition sequence for targeting and destruction of the substrate by the 26S Proteasome. OV2008 and LNCaP cells were probed with anti-Ub antibody.

Example 7: Up109 stabilized proteasome dependent reporter protein

[25] To measure proteasome function in live cells, we utilized an engineered ubiquitin-firefly (4Ub-FL) reporter in which four copies of mutant ubiquitin (ubiquitin G76V) gene are fused to the N-terminus of the firefly luciferase (FL) gene. The 4Ub-FL reporter protein is rapidly degraded by the proteasome (Figure 6). Importantly, treatment of 293TT cells expressing 4Ub-FL gene with Up109 results in its stabilization and an increase in luciferase activity. Treatment of Up109 produced a greater increase in the 4Ub-FL bioluminescence in a dose dependent manner.

Example 8: Up109 and Up117 binds to RPN13

[26] To identify the cellular target, a competition assay was performed using RA190B probe. Earlier we showed that biotinylated RA190 (RA190B) covalently binds to RPN13. We used RA190B as a probe to determine the Up compounds binding to RPN13. OV2008 cell lysate was pretreated with Up compounds (25 μ M) and then subsequently treated with RA190B (5 μ M). Lysate was denatured under reduced conditions and proteins were separated on a gel and probed with HRP Streptavidin. Disappearance of RA190B labeling of the RPN13 protein in the presence of Up109 and UP117 indicates competition with RA190B for binding to RPN13 (Figure 7).

Example 9: Up109 elevated ER stress and apoptosis

[27] Accumulation of unfolded proteins upon the inhibition of proteasome function rapidly induces endoplasmic reticulum (ER) stress. ER stress triggers an evolutionarily conserved series of signal-transduction events, which constitute the unfolded protein response (UPR). The UPR attempts to restore protein homeostasis by eliminating the accumulated unfolded proteins in

the ER; however, if protein homeostasis cannot be restored, apoptosis is triggered. C/EBP homologous protein (CHOP) is elevated at the onset of UPR-induced programmed cell death. Up109 treatment of ES2 cells rapidly up-regulated *CHOP-10* mRNA expression (Figure 8A). Annexin-V positive cells indicate the elevation of apoptosis by Up109 treatment (Figure 8B).

Example 10: Up109 stabilized 4UBFL in vivo:

[28] To test for proteasome inhibition by Up109 *in vivo*, muscle cells of live Balb/c mice transduced with the 4UbFL reporter DNA construct by electroporation. After i.p. injection of luciferin, the enzymic activity of luciferase in the transfected muscle tissue was visualized as bioluminescence using an IVIS imager. At two days post electroporation of the 4UbFL DNA, mice were imaged and base line luminescence recorded. The control group (n = 5) of mice was treated i.p. with vehicle alone and another group (n = 5) treated i.p with Up109 (40 mg/Kg). After 4h, 24h and 48h post treatment mice were again imaged and luminescence was quantified (Figure 9). This result indicates (1) Up109 has good accessibility to solid tissue; (2) Up109 could potentially be dosed every other day.

Example 11: Dose limiting toxicity studies

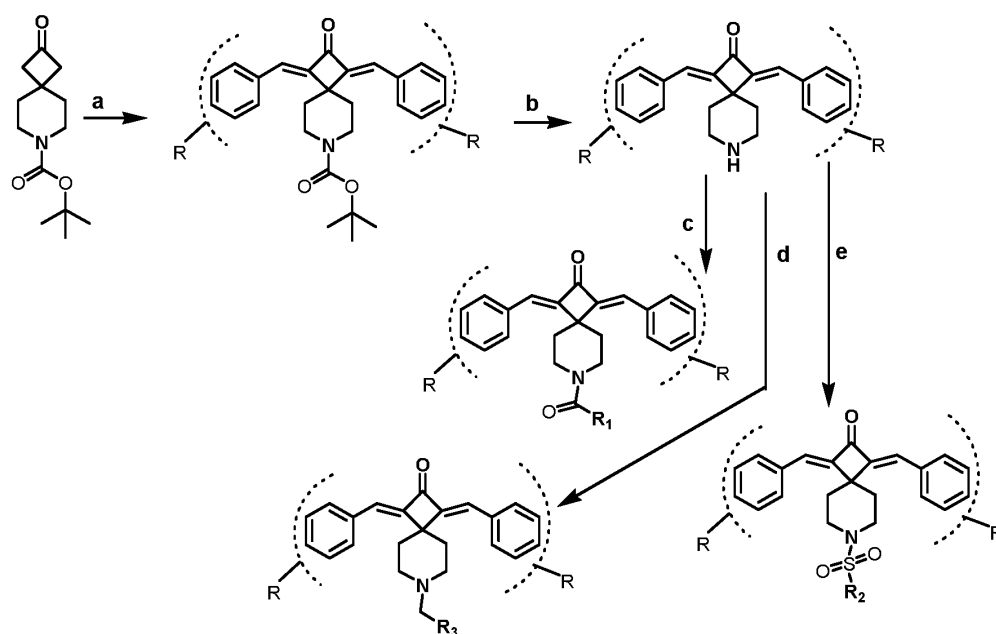
[29] To identify the optimal dose that induces a clinical effect and operates with acceptable toxicity a set of experiments has been performed on female Balb/C strain mice with Up109. Individual groups of mice (n = 3) were injected i.p. with increasing single doses of Up109 (3, 10, 20, 40 and 100mg/Kg) and the endpoint evaluations included clinical observations and body weights. No clinically apparent sign of adverse effect was found with Up109. Another experiment was done with repeated i.p. doses of Up109 (40mg/Kg, n = 5) every other day for two weeks. No observable toxicities/weight loss were found.

Example 12: In Vivo efficacy of Up109 against ES2 ovarian tumor growth

[30] To test the efficacy of Up109 to treat the human ovarian cancer ES2 xenograft model, the luciferase-expressing ES2 cells (ES2-Lu) were inoculated into peritoneal cavity of nude female mice (i.e. orthotopically). Two days after inoculation the mice were imaged for their

basal luminescence activity and then randomized into two groups (n= 10). First group was treated with the vehicle and the second group was treated with Up109 (10 mg/Kg) on alternate days for two weeks. Mice were imaged after the first and second week of treatment for their luciferase activity. As indicated in Figure 6, Up109 significantly reduced the tumor burden compared to the vehicle and there was no weight loss and any observable side effects. Tumor burden in the vehicle group mice was excessive and sacrificed at the end of the treatment (Figure 10).

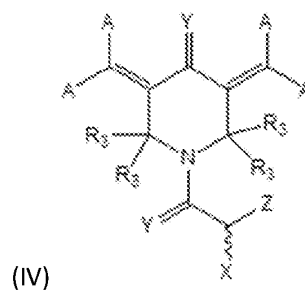
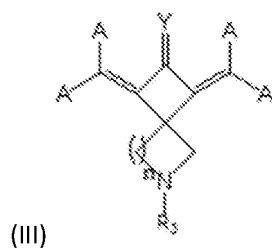
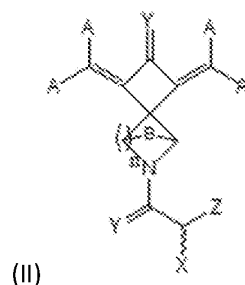
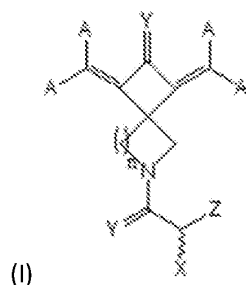
Example 13: Up compounds general synthetic scheme



[31] Reaction conditions: (a) substituted aldehydes, NaOH, Ethanol; (b) 4 M HCl in dioxane; (c) acid chloride, DCM, triethyl amine or acid, HOBt, HBTU, DMF, DIPEA; (d) alkyl bromide, acetone, K₂CO₃; (e) sulfonyl chloride, DCM, triethyl amine. R = different substituents on the aromatic ring.

What is claimed is:

1. Compounds having the structure of formula either I, or II, or III, or IV



wherein each pair of A is one of:

- (i) phenyl, optionally substituted with 1-5 substituents selected from the group consisting of R₁, OR₁, NR₁R₂, S(O)_qR₁, SO₂NR₁R₂, NR₁SO₂R₂, C(O)R₁, C(O)OR₁, C(O)NR₁R₂, NR₁C(O)R₂, NR₁C(O)OR₂, CF₃, and OCF₃;
 - (ii) naphthyl, optionally substituted with 1-5 substituents selected from the consisting of R₁, OR₁, NR₁R₂, S(O)_qR₁, SO₂NR₁R₂, NR₁SO₂R₂, C(O)R₁, C(O)OR₁, C(O)NR₁R₂, NR₁C(O)R₂, NR₁C(O)OR₂, CF₃, and OCF₃;
 - (iii) a 5 or 6 membered monocyclic heteroaryl group, having 1-3 heteroatoms selected from the group consisting of O, N, and S, optionally substituted with 1-3 substituents selected from the group consisting of R₁, OR₁, NR₁R₂, S(O)_qR₁, SO₂NR₁R₂, NR₁SO₂R₂, C(O)R₁, C(O)OR₁, C(O)NR₁R₂, NR₁C(O)R₂, NR₁C(O)OR₂, CF₃, and OCF₃;
- and

- (iv) an 8 to 10 membered bicyclic heteroaryl group containing 1-3 heteroatoms selected from the group consisting of O, N, and S; and the second ring is fused to the first ring using 3 to 4 carbon atoms, and the bicyclic hetero aryl group is optionally substituted with 1-3 substituents selected from the group consisting of R1, OR1, NR1R2, S(O)_qR1, SO₂NR1R2, NR1SO₂R2, C(O)R1, C(O)OR1, C(O)NR1 R2, NR1 C(O)R2, NR1C(O)OR2, CF₃, and OCF₃;
- (v) any group belongs to R1 or R2

wherein n represents number of atoms ranging from 0-4 (0,1,2,3,4) and can be C, N, or O, wherein when n is N, it can be NH, NR1 or NR2;

wherein X is Hydrogen, OR1 or NP, wherein P is selected from the group consisting of R1, C(O)R1, C(O)OR1, C(O)NR1 R2, S- N(R1)COOR1, and S-N(R1), wherein Y is selected from the group consisting of O, S, NR1 and CR1 R2, and wherein R1 and R2 are selected from the group consisting of hydrogen, nitro, hydroxyl, carboxy, amino, halogen, cyano and C1-C14 linear or branched alkyl groups, that are optionally substituted with 1-3 substituents selected from the group consisting of Ci-C 4 linear or branched alkyl, up to perhalo substituted C 1-C14 linear or branched alkyl, Ci-Ci4 alkoxy, hydrogen, nitro, hydroxyl, carboxy, amino, C1 -C14 alkylamino, C-i-C-n dialkylamino, halogen, and cyano;

wherein Z is selected from the group consisting of hydrogen; C1 to C14 linear, branched, or cyclic alkyls; alkenyls, phenyl; benzyl, 1-5 substituted benzyl, Ci to C3 alkyl-phenyl, wherein the alkyl moiety is optionally substituted with halogen up to perhalo; up to perhalo substituted Ci to C14 linear or branched alkyls; -(CH₂)_q-K, where K is a 5 or 6 membered monocyclic heterocyclic ring, containing 1 to 4 atoms selected from oxygen, nitrogen and sulfur, which is saturated, partially saturated, or aromatic, or an 8 to 10 membered bicyclic heteroaryl having 1-4 heteroatoms selected from the group consisting of O,N and S, wherein said alkyl moiety is optionally substituted with halogen up to perhalo, and wherein the variable q is an integer ranging from 0 to 4;

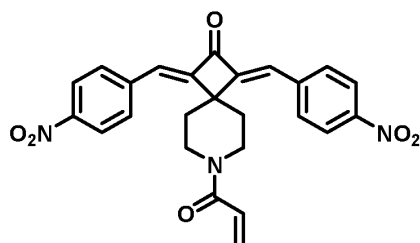
wherein B is (i) R1, C(O)R1, C(O)OR1, C(O)NR1R2, S-N(R)COOR1, S- N(R1)COO(B), S(B); and wherein each R1-R2, other than per-halo substituted C1-C14 linear or branched alkyl, is

optionally substituted with 1-3 substituents independently selected from the group consisting of C-1-C14 linear or branched alkyl, up to perhalo substituted C1-C14 linear or branched alkyl, C1-C3 alkoxy, hydroxyl, carboxy, amino, C1-C3 alkylamino, C1-C6 dialkylamino, halogen, cyano; and

wherein R_3 is H, C₁₋₆-alkyl, C₂₋₆-alkenyl; C₁₋₃-alkoxy-C₁₋₆-alkyl; C₁₋₃-alkoxy-C₂₋₆-alkenyl; aryl-C₀₋₆-alkyl; heteroaryl-C₀₋₆-alkyl; heterocyclyl-C₀₋₆-alkyl; cycloalkyl-C₀₋₆-alkyl; ---C₁₋₆-alkyl-COOC₁₋₆-alkyl; ---C₂₋₆-alkyl-aryloxy; C₁₋₆-alkyl-heteroaryl; C₁₋₆-alkyl-heterocyclyl; C₁₋₆-alkyl-cycloalkyl; C₁₋₆-alkyl-aryl; COR⁴, wherein R⁴ is selected from: C₁₋₆-alkyl; C₂₋₆-alkenyl; C₁₋₆-alkoxy; C₁₋₃-alkoxy-C₁₋₆-alkyl; C₁₋₃-alkoxy-C₂₋₆-alkenyl; aryl-C₀₋₆-alkyl; heteroaryl-C₀₋₆-alkyl; heterocyclyl-C₀₋₆-alkyl; cycloalkyl-C₀₋₆-alkyl; -C₁₋₆-alkyl-COOC₁₋₆-alkyl; NH₂; -NHC₁₋₆-alkyl; -N(C₁₋₆-alkyl)₂; -C₀₋₆-alkyl-aryloxy.

2. A compound according to claim 1 which binds to proteasomal proteins as either DUB inhibitor or proteasome receptor inhibitor.

3. The compound according to claim 1, wherein the compound has the formula



3. A method of inhibiting proteasomes in a mammal by administering to the mammal an effective amount of the compound of claim 1.

4. A method of treating or a disease in a mammal by administering to the mammal a therapeutically effective dose of the compound of claim 1.

5. The method of claim 4 wherein the mammal is a human, or a dog, or a cat.

6. The method of claim 4 wherein the disease is a type of cancer or diabetes or neurological disorders.
7. The method of claim 4 wherein the compound of claim 1 is administered alone or in combination with at least one other therapeutic agent or radiation.