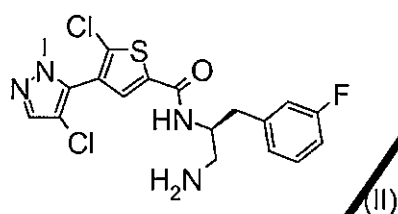


We claim:

1. A combination comprising:

(i) a proteasome inhibiting compound; and

(ii) a compound of Structure (II):

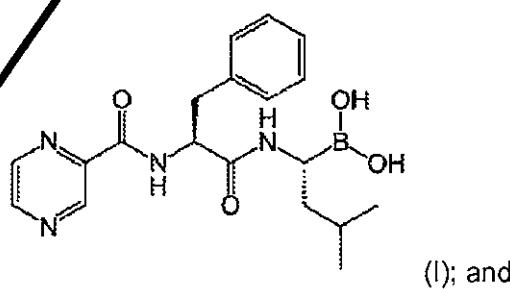


or a pharmaceutically acceptable salt thereof; and

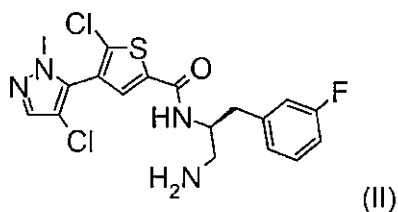
(iii) optional additional antineoplastic agents.

2. A combination comprising:

(i) a compound of Structure (I):



(ii) a compound of Structure (II):



in the form of a monohydrochloride salt.

3. A combination kit comprising a combination according to claim 1 or claim 2 together with a pharmaceutically acceptable carrier or carriers.

4. A combination according to any one of claims 1 to 3 where the amount of the compound of Structure (II) is an amount selected from 5mg to 500mg, and that amount is administered once per day.

5. Use of a combination according to any of claims 1 to 4 in the manufacture of a medicament or medicaments for the treatment of cancer.

6. A method of treating cancer in a human in need thereof which comprises the in vivo administration of a therapeutically effective amount of a combination of bortezomib, and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide, or a pharmaceutically acceptable salt thereof, to such human,

wherein the combination is administered within a specified period, and

wherein the combination is administered for a duration of time.

7. A method according to claim 6 wherein the amount of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide, or a pharmaceutically acceptable salt thereof, is selected from about 50mg to about 300mg, and that amount is administered once per day.

8. A method according to claim 7 wherein the amount of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide, or a pharmaceutically acceptable salt thereof, is selected from about 60mg to about 300mg, and that amount is administered once per day, and bortezomib is administered intravenously once or twice a week in an amount selected from 0.5 to 1.3mg/m².

9. A method according to claim 8 wherein bortezomib and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride are administered within 12 hours of each other for 1 or 2 days during a seven day period and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride is administered alone for the remaining days of the 7 day period, optionally followed by one or more cycles of repeat dosing.

10. A method treating a cancer selected from: brain (gliomas), glioblastomas, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, inflammatory breast cancer, Wilm's tumor, Ewing's sarcoma, Rhabdomyosarcoma, ependymoma, medulloblastoma, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma, osteosarcoma, giant cell tumor of bone, thyroid,

Lymphoblastic T cell leukemia, Chronic myelogenous leukemia, Chronic lymphocytic leukemia, Hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, Chronic neutrophilic leukemia, Acute lymphoblastic T cell leukemia, Plasmacytoma, Immunoblastic large cell leukemia, Mantle cell leukemia, Multiple myeloma Megakaryoblastic leukemia, multiple myeloma, acute megakaryocytic leukemia, promyelocytic leukemia, Erythroleukemia,

malignant lymphoma, hodgkins lymphoma, non-hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma,

neuroblastoma, bladder cancer, urothelial cancer, lung cancer, vulval cancer, cervical cancer, endometrial cancer, renal cancer, mesothelioma, esophageal cancer, salivary gland cancer, hepatocellular cancer, gastric cancer, nasopharyngeal cancer,

buccal cancer, cancer of the mouth, GIST (gastrointestinal stromal tumor) and testicular cancer;

in a human in need thereof which comprises the in vivo administration of a therapeutically effective amount of a combination of bortezomib, and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide or a pharmaceutically acceptable salt thereof, to such human, wherein the combination is administered within a specified period, and wherein the combination is administered for a duration of time.

11. A method according to claim 10 wherein the amount of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide, or a pharmaceutically acceptable salt thereof, is selected from about 50mg to about 300mg, and that amount is administered once per day.

12. A method according to claim 11 wherein the amount of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide or a pharmaceutically acceptable salt thereof, is selected from about 60mg to about 300mg, and that amount is administered once per day, and bortezomib is administered intravenously once or twice a week in an amount selected from 0.5 to 1.3mg/m².

13. A method according to claim 12 wherein bortezomib and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride are administered within 12 hours of each other for 1 or 2 days during a seven day period and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride is administered alone for the remaining days of the 7 day period, optionally followed by one or more cycles of repeat dosing.

14. A method according to claim 10 wherein the cancer is multiple myeloma.

15. A method according to claim 11 wherein the cancer is multiple myeloma.

16. A method according to claim 12 wherein the cancer is multiple myeloma.

17. A method according to claim 13 wherein the cancer is multiple myeloma.

18. A method treating a cancer selected from: brain (gliomas), glioblastomas, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, inflammatory breast cancer, Wilm's tumor, Ewing's sarcoma, Rhabdomyosarcoma, ependymoma, medulloblastoma, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma, osteosarcoma, giant cell tumor of bone, thyroid,

Lymphoblastic T cell leukemia, Chronic myelogenous leukemia, Chronic lymphocytic leukemia, Hairy-cell leukemia, Acute lymphoblastic leukemia, acute myelogenous leukemia, Chronic neutrophilic leukemia, Acute lymphoblastic T cell leukemia, Plasmacytoma, Immunoblastic large cell leukemia, Mantle cell leukemia, Multiple myeloma Megakaryoblastic leukemia, multiple myeloma, acute megakaryocytic leukemia, promyelocytic leukemia, Erythroleukemia,

malignant lymphoma, hodgkins lymphoma, non-hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma,

neuroblastoma, bladder cancer, urothelial cancer, lung cancer, vulval cancer, cervical cancer, endometrial cancer, renal cancer, mesothelioma, esophageal cancer, salivary gland cancer, hepatocellular cancer, gastric cancer, nasopharyngeal cancer, buccal cancer, cancer of the mouth, GIST (gastrointestinal stromal tumor) and testicular cancer;

in a human in need thereof which comprises the in vivo administration of a therapeutically effective amount of a combination of bortezomib, and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide, or a pharmaceutically acceptable salt thereof, to such human,

wherein the compounds of the combination are administered sequentially.

19. A method according to claim 18 wherein the amount of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide, or a pharmaceutically acceptable salt thereof, is selected from about 50mg to about 300mg, and that amount is administered once per day.

20. A method according to claim 19 wherein the amount of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide, or a pharmaceutically acceptable salt thereof, is selected from about 60mg to about 300mg, and that amount is administered once per day, and bortezomib is administered intravenously once or twice a week in an amount selected from 0.5 to 1.3mg/m².

21. A method according to claim 20 wherein bortezomib is administered for from 1 to 30 consecutive days, followed by an optional drug holiday of from 1 to 14 days, followed by administration of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride for from 1 to 30 days.

22. A method according to claim 18 wherein the cancer is multiple myeloma.

23. A method according to claim 19 wherein the cancer is multiple myeloma.

24. A method according to claim 20 wherein the cancer is multiple myeloma.

25. A method according to claim 21 wherein the cancer is multiple myeloma.

26. A method according to claim 21 wherein bortezomib is administered for from 1 to 21 consecutive days, followed by a drug holiday of from 3 to 10 days, followed

by administration of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride for from 1 to 21 days.

27. A method according to claim 26 wherein the cancer is multiple myeloma.

28. A method according to claim 8 wherein bortezomib and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride are administered within 12 hours of each other for 2 days over a 7 day period, and during the other days of the 7 day period bortezomib is administered alone, optionally followed by one or more cycles of repeat dosing.

29. A method according to claim 12 wherein bortezomib and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride are administered within 12 hours of each other for 2 days over a 7 day period, and during the other days of the 7 day period bortezomib is administered alone, optionally followed by one or more cycles of repeat dosing.

30. A method according to claim 8 wherein bortezomib and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride are administered within 12 hours of each other for 5 consecutive days followed by administration of bortezomib for 2 consecutive days, optionally followed by one or more cycles of repeat dosing.

31. A method according to claim 12 wherein bortezomib and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride are administered within 12 hours of each other for 5 consecutive days followed by administration of bortezomib for 2 consecutive days, optionally followed by one or more cycles of repeat dosing.

32. A method according to claim 21 bortezomib and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide hydrochloride are administered within 12 hours of each other for 5 consecutive days followed by administration of bortezomib once a week, optionally followed by one or more cycles of repeat dosing.

1 A method treating a cancer selected from: brain (gliomas), glioblastomas, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, inflammatory breast cancer, Wilm's tumor, Ewing's sarcoma, Rhabdomyosarcoma, ependymoma, medulloblastoma, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma, osteosarcoma, giant cell tumor of bone, thyroid,

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malignant lymphoma, hodgkins lymphoma, non-hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma,

neuroblastoma, bladder cancer, urothelial cancer, lung cancer, vulval cancer, cervical cancer, endometrial cancer, renal cancer, mesothelioma, esophageal cancer, salivary gland cancer, hepatocellular cancer, gastric cancer, nasopharyngeal cancer, buccal cancer, cancer of the mouth, GIST (gastrointestinal stromal tumor) and testicular cancer;

in a human in need thereof which comprises the in vivo administration of a therapeutically effective amount of a combination of bortezomib, and *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-

thiophenecarboxamide or a pharmaceutically acceptable salt thereof, to such human,

wherein the combination is administered within a specified period, and

wherein the combination is administered for a duration of time,

wherein the cancer is multiple myeloma.