on the therapeutic agent and clinical setting. Therefore it is desirable to develop a mode of cancer treatment that would prevent drug resistance in cancer patients.

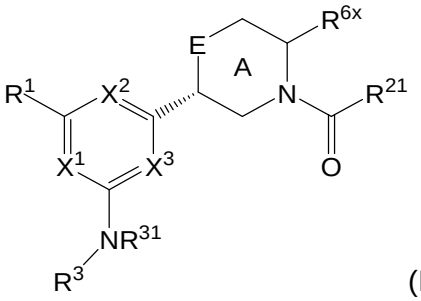
Phenotypic, signalling, transcriptional, and metabolic plasticity as well as the acquisition of novel genetic alterations have been found to be a driving factor in the development of resistance to cancer treatment including molecularly targeted inhibitors and immunotherapies. There is a need to avoid development of resistance to treatment.

Thus, an objective of the present invention is to provide novel compounds which are able to treat cancer or to prevent the development of resistance. Furthermore, it is an objective of the present invention to provide improved treatment options for cancer patients using the compounds of the invention alone or in combination therapy.

SUMMARY

The present inventors have surprisingly found that compounds of the formula (I), optionally in the form of a pharmaceutically acceptable salt, solvate, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof, have activity against cancer.

The present invention refers to subject matter as defined in the attached set of claims. In one example, there is described a compound of formula (I), or a pharmaceutically acceptable salt, solvate, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof



(I)

wherein

R^1 is selected from halogen, unsubstituted or substitutedhydrocarbon group which contains from 1 to 20 carbon atoms and unsubstituted or substituted hydrocarbon group which contains from 1 to 20 carbon atoms and 1 to 15 heteroatoms selected from O, N and S;

R^{21} is selected from hydrogen, unsubstituted or substituted $C_{1–6}$ alkyl, unsubstituted or substituted C_{1-6} alkyl which contains one to three oxygen atoms between carbon atoms, and unsubstituted or substituted $C_{3–6}$ cycloalkyl;

R^3 is selected from unsubstituted or substituted heterocyclyl, unsubstituted or substituted carbocyclyl, unsubstituted or substituted $C_{1–6}$ alkylene-(heterocyclyl), unsubstituted or substituted C_{1-6} alkylene-(substituted heterocyclyl),unsubstituted

unsubstituted or substituted –$C_{1–6}$ alkylene–(substituted heterocyclyl), unsubstituted or substituted –O–($C_{1–6}$ alkylene)–(carbocyclyl), unsubstituted or substituted –O–($C_{1–6}$ alkylene)–(substituted carbocyclyl), unsubstituted or substituted –O–($C_{1–6}$ alkylene)–(heterocyclyl), and unsubstituted or substituted –O–($C_{1–6}$ alkylene)–(substituted heterocyclyl), and

wherein the substituent of the substituted hydrocarbon group, substituted $C_{3–6}$ cycloalkyl, substituted heterocyclyl, substituted heterocycle, substituted carbocyclyl, substituted carbocycle and substituted $C_{1–6}$ alkylene is independently selected from –C_{1-6} alkyl, –$C_{1–6}$ alkyl substituted with one or more halogen, –halogen, –CN, –NO_2, oxo, –C(O)R*, –COOR*, –C(O)NR*R*, –NR*R*, –N(R*)–C(O)R*, –N(R*)–C(O)–OR*, –N(R*)–C(O)–NR*R*, –N(R*)–$S(O)_2$R*, –OR*, –O–C(O)R*, –O–C(O)–NR*R*, –SR*, –S(O)R*, –$S(O)_2$R*, –$S(O)_2$–NR*R*, –N(R*)–$S(O)_2$–NR*R*, heterocyclyl, heterocyclyl substituted with halogen or C_{1-6} alkyl, carbocyclyl, and carbocyclyl substituted with halogen or C_{1-6} alkyl; wherein each R* is independently selected from H, C_{1-6} alkyl, $C_{1–6}$ alkyl substituted with halogen, heterocyclyl, heterocyclyl substituted with halogen or C_{1-6} alkyl, carbocyclyl, and carbocyclyl substituted with halogen or C_{1-6} alkyl; wherein any two R* connected to the same nitrogen atom are either separate substituents or linked with each other, and

wherein the substituent of the substituted $C_{1–6}$ alkyl and of the substituted $C_{1–6}$ alkylene is independently selected from –halogen, –CN, –NO_2, oxo, –C(O)R**, –COOR**, –C(O)NR**R**, –NR**R**, –N(R**)–C(O)R**, –N(R**)–C(O)–OR**, –N(R**)–C(O)–NR**R**, –N(R**)–$S(O)_2$R**, –OR**, –O–C(O)R**, –O–C(O)–NR**R**, –SR**, –S(O)R**, –$S(O)_2$R**, –$S(O)_2$–NR**R**, and –N(R**)–$S(O)_2$–NR**R**; wherein R** is independently selected from H, $C_{1–6}$ alkyl, $C_{1–6}$ alkyl substituted with halogen, heterocyclyl, heterocyclyl substituted with halogen or C_{1-6} alkyl, carbocyclyl and carbocyclyl substituted with halogen or C_{1-6} alkyl; wherein any two R** connected to the same nitrogen atom are either separate substituents or linked with each other.

In another example, there is described a pharmaceutical composition comprising: a compound having the formula (I) as defined herein, or a pharmaceutically acceptable salt, solvate, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof, and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

In yet another example, there is describeda use of a compound having the formula (I) as defined herein, or a pharmaceutically acceptable salt, solvate, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof, and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s), or a pharmaceutical composition as defined herein, in the manufacture of a medicament for the treatment or

amelioration of cancer, wherein preferably the cancer is selected from melanoma, non-small cell lung cancer, prostate cancer, bile duct cancer, bladder cancer, pancreatic cancer, thyroid cancer, ovarian cancer, colorectal tumor, hairy cell leukemia, acute myeloid leukemia, multiple myeloma, liver cancer, breast cancer, esophageal cancer, head and neck cancer and glioma, in particular multiple myeloma, acute myeloid leukemia, prostate cancer, melanoma and non-small cell lung cancer.

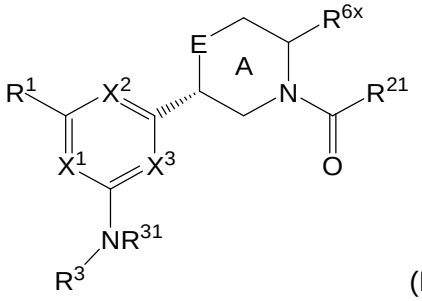
In yet another example, there is describeda use of a compound having the formula (I) as defined herein, or a pharmaceutically acceptable salt, solvate, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof, and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s), or a pharmaceutical composition as defined herein, and a second therapeutic agent in the manufacture of a medicament for combination therapy for the treatment or amelioration of cancer, wherein preferably said second therapeutic agent is an anti-cancer agent, and wherein preferably the cancer is selected from melanoma, non-small cell lung cancer, prostate cancer, bile duct cancer, bladder cancer, pancreatic cancer, thyroid cancer, ovarian cancer, colorectal tumor, hairy cell leukemia, acute myeloid leukemia, multiple myeloma, liver cancer, breast cancer, esophageal cancer, head and neck cancer and glioma, in particular multiple myeloma, acute myeloid leukemia, prostate cancer, melanoma and non-small cell lung cancer.

In a further example, there is describeda use of a compound having the formula (I) as defined herein, or in the form of a pharmaceutically acceptable salt, solvate, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof, and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s), or a pharmaceutical composition as defined herein in the manufacture of a first medicament and use of a second therapeutic agent in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy for the treatment or amelioration of cancer, wherein preferably said second therapeutic agent is an anti-cancer agent, and wherein preferably the cancer is selected from melanoma, non-small cell lung cancer, prostate cancer, bile duct cancer, bladder cancer, pancreatic cancer, thyroid cancer, ovarian cancer, colorectal tumor, hairy cell leukemia, acute myeloid leukemia, multiple myeloma, liver cancer, breast cancer, esophageal cancer, head and neck cancer and glioma, in particular multiple myeloma, acute myeloid leukemia, prostate cancer, melanoma and non-small cell lung cancer.

In a further example, there is describeda use of a compound having the formula (I) as defined herein, or in the form of a pharmaceutically acceptable salt, solvate, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof, and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s), or a pharmaceutical composition as defined herein in the manufacture of a medicament for use in combinatorial

CLAIMS

1. A compound of formula (I), or a pharmaceutically acceptable salt, solvate, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof



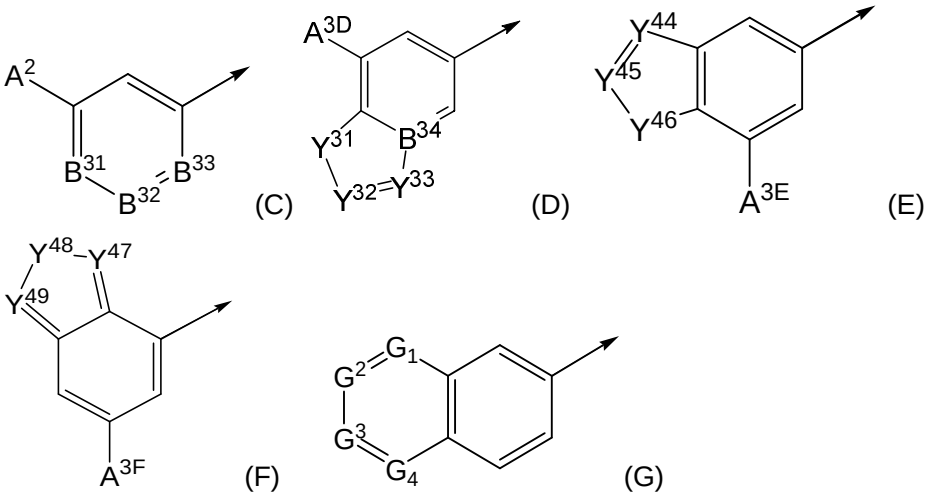
(I)

wherein

R^1 is selected from phenyl, a 5- or 6-membered monocyclic heteroaryl and a 8-10 membered bicyclic heteroaryl, each independently comprising one or more ring heteroatoms independently selected from O, S and N, and wherein said phenyl, said 5- or 6-membered monocyclic heteroaryl and said 8-10 membered bicyclic heteroaryl is independently unsubstituted or substituted with one or more substituents selected from halogen, $–C_{1–6}$ alkyl, $C_{1–6}$ haloalkyl, $–O–(C_{1–6}$ alkyl), $–O–(C_{1–6}$ haloalkyl), –OH, $–(C_{1–2}$alkylene)–O–$(C_{1–4}$alkylene)–OR*, $–(C_{1–2}$alkylene)–OR*, $–O–(C_{1–4}$alkylene)–OR*, $–(C_{1–2}$alkylene)–O–$(C_{1–4}$alkylene)–$N(R°°)_2$, $–O–(C_{1–4}$alkylene)–$N(R°°)_2$, $–O–(C_{1–4}$alkylene)–$C(O)N(R°°)_2$, –CN, =O, –C(O)R*, –COOR*, –C(O)NR*R*, –NR*R*, –N(R*)–C(O)R*, –N(R*)–C(O)–OR*, –N(R*)–C(O)–NR*R*, –O–C(O)R*, –O–C(O)–NR*R*, and 3-6 membered monocyclic carbocyclyl and 3-6 membered monocyclic heterocyclyl comprising 1 to 4 heteroatoms selected from O, S and N, each monocyclic carbocyclyl and heterocyclyl independently unsubstituted or substituted with one or more substituents independently selected from halogen, $–C_{1–4}$ alkyl, $C_{1–4}$ haloalkyl, $–O–(C_{1–4}$ alkyl), $–O–(C_{1–4}$ haloalkyl), –OH, =O, –C(O)R* and –C(O)NR*R*; wherein each R* is independently selected from H, $C_{1–4}$ alkyl, $C_{1–4}$ haloalkyl, and wherein each R°° is independently selected from H, C_{1-4} alkyl, or together with the nitrogen atom to which they are attached form a six-membered monocyclic heterocyclyl; and/or wherein each monocyclic heterocyclyl is independently unsubstituted or substituted with one bivalent substituent selected from C_{1-3} alkylene, C_{1-3} alkylene substituted with 1 to 4 F, $-CH_2-O-CH_2-$ and $-CH_2-NH-CH_2-$;

R^{21} is selected from hydrogen, $C_{1–2}$ alkyl, $C_{1–2}$ haloalkyl, $C_{1–2}$ alkyl substituted with one or two OH, $C_{3–4}$ cycloalkyl, and $C_{3–4}$ cycloalkyl substituted with one or more R^{22}, wherein R^{22} is selected from -Cl, -F, and -OH;

R^3 is selected from formula (C), formula (D), formula (E), formula (F), and formula (G)



wherein the arrow denotes the bond in the compounds of formula (I);

B^{31} is N, CH or C(A^{31}), wherein A^{31} is selected from $–C_{1–2}$ alkyl, $C_{1–2}$ haloalkyl, –F, –Cl, $–O(C_{1–2}alkyl)$, –OH, and $–NHC(O)(C_{1–2}alkyl)$;

B^{32} is N, CH or C(A^{32}), wherein A^{32} is selected from $–C_{1–2}$ alkyl, $C_{1–2}$ haloalkyl, –F, –Cl, $–O(C_{1–2}alkyl)$, =O, –OH, $–NHC(O)(C_{1–2}alkyl)$, $–NHC(O)–C_{1-2}alkylene–OH$, $–NHC(O)–C_{1-2}alkylene–O(C_{1–2}alkyl)$, $–C(O)NH(C_{1–2}alkyl)$, $–C(O)N(C_{1–2}alkyl)_2$, –NHC(O)(cyclopropyl), –NHC(O)(phenyl), 3-6 membered monocyclic carbocyclyl, and 3-6 membered monocyclic heterocyclyl comprising 1 to 4 heteroatoms selected from O, B, S and N, each monocyclic carbocyclyl and heterocyclyl independently unsubstituted or substituted with one or two substituents independently selected from halogen, tetrahydropyranyl, cyclopropyl, $–C_{1–4}$ alkyl, $C_{1–4}$ haloalkyl, $–O–(C_{1–4}$ alkyl), $–O–(C_{1–4}$ haloalkyl), –OH, =O, $–C_{1-3}alkylene–OR^*$, $–C(O)R^*$ and $–C(O)NR^*R^*$; wherein each R* is independently selected from H, $C_{1–4}$ alkyl, $C_{1–4}$ haloalkyl, and phenyl, and/or wherein each monocyclic heterocyclyl is independently unsubstituted or substituted with one bivalent substituent selected from C_{1-3} alkylene, C_{1-3} alkylene substituted with 1 to 4 F, $-CH_2-O-CH_2-$ and $-CH_2-NH-CH_2-$;

B^{33} is N, CH or C(A^{33}), wherein A^{33} is selected from $–C_{1–2}$ alkyl, $C_{1–2}$ haloalkyl, –F, –Cl, $–O(C_{1–2}alkyl)$, –OH, and $–NHC(O)(C_{1–2}alkyl)$;

A^2 is selected from hydrogen, $–C_{1–2}$ alkyl, $C_{1–2}$ haloalkyl, –F, –Cl, $–O(C_{1–2}alkyl)$, =O, –OH, $–NHC(O)(C_{1–2}alkyl)$, $–NHC(O)–C_{1-2}alkylene–OH$, $–NHC(O)–C_{1-2}alkylene–O(C_{1–2}alkyl)$, $–C(O)NH(C_{1–2}alkyl)$, $–C(O)N(C_{1–2}alkyl)_2$, –

NHC(O)(cyclopropyl), –NHC(O)(phenyl), 3-6 membered monocyclic carbocyclyl, and 3-6 membered monocyclic heterocyclyl comprising 1 to 4 heteroatoms selected from O, B, S and N, each monocyclic carbocyclyl and heterocyclyl independently unsubstituted or substituted with one or two substituents independently selected from halogen, tetrahydropyranyl, cyclopropyl, $–C_{1–4}$ alkyl, $C_{1–4}$ haloalkyl, $–O–(C_{1–4}$ alkyl), $–O–(C_{1–4}$ haloalkyl), –OH, =O, $–C_{1-3}$alkylene–OR*, –C(O)R* and –C(O)NR*R*; wherein each R* is independently selected from H, $C_{1–4}$ alkyl, $C_{1–4}$ haloalkyl, and phenyl, and/or wherein each monocyclic heterocyclyl is independently unsubstituted or substituted with one bivalent substituent selected from C_{1-3} alkylene, C_{1-3} alkylene substituted with 1 to 4 F, $-CH_2-O-CH_2-$ and $-CH_2-NH-CH_2-$;

Y^{31} is N, CH or $C(A^{31})$, wherein A^{31} is selected from methyl and ethyl;

Y^{32} is N, CH or $C(A^{32})$, wherein A^{32} is selected from methyl and ethyl;

Y^{33} is N, CH or $C(A^{33})$, wherein A^{33} is selected from methyl and ethyl;

B^{34} is N;

A^{3D} is selected from hydrogen, $–C_{1–2}$ alkyl, $C_{1–2}$ haloalkyl, –F, –Cl, $–O(C_{1–2}$alkyl), =O, –OH, $–NHC(O)(C_{1–2}$alkyl), $–C(O)NH(C_{1–2}$alkyl), $–C(O)N(C_{1–2}$alkyl$)_2$, and –NHC(O)(phenyl);

Y^{44} is N, NH, $N(A^{44})$, C(O), CH or $C(A^{44})$, wherein A^{44} is independently selected from methyl and ethyl;

Y^{45} is N, NH, $N(A^{45})$, C(O), CH or $C(A^{45})$, wherein A^{45} is independently selected from methyl and ethyl;

Y^{46} is N, NH, $N(A^{46})$, O, C(O), CH or $C(A^{46})$, wherein A^{46} is independently selected from methyl and ethyl; and wherein at least one of said Y^{44}, Y^{45} and Y^{46} is NH, $N(CH_3)$ or $N(C_2H_5)$; and wherein

A^{3E} is selected from hydrogen, $–C_{1–2}$ alkyl, $C_{1–2}$ haloalkyl, –F, –Cl, $–O(C_{1–2}$alkyl), =O, –OH, $–NHC(O)(C_{1–2}$alkyl), $–C(O)NH(C_{1–2}$alkyl), $–C(O)N(C_{1–2}$alkyl$)_2$, and –NHC(O)(phenyl);

Y^{47} is N, NH, $N(A^{47})$, C(O), CH or $C(A^{47})$, wherein A^{47} is independently selected from methyl and ethyl;

Y^{48} is N, NH, $N(A^{48})$, C(O), CH or $C(A^{48})$, wherein A^{48} is independently selected from methyl and ethyl;

Y^{49} is N, NH, $N(A^{49})$, O, C(O), CH or $C(A^{49})$, wherein A^{49} is independently selected from methyl and ethyl; and wherein at least one of said Y^{47}, Y^{48} and Y^{49} is NH, $N(CH_3)$ or $N(C_2H_5)$;

A^{3F} is selected from hydrogen, $–C_{1–2}$ alkyl, $C_{1–2}$ haloalkyl, –F, –Cl, $–O(C_{1–2}$alkyl), =O, –OH, $–NHC(O)(C_{1–2}$alkyl), $–C(O)NH(C_{1–2}$alkyl), $–C(O)N(C_{1–2}$alkyl$)_2$, and –NHC(O)(phenyl);

and wherein

G^1, G^2, G^3, G^4 is independently selected from N, CH, C(O), NH or N($C_{1–2}$ alkyl;

X^2 and X^3 are N; and

X^1 is selected from N, CH and CR^x;

R^{31} is selected from –hydrogen, –C_{1-6}-alkyl, and –C_{1-6}-alkyl substituted with one or more F; and

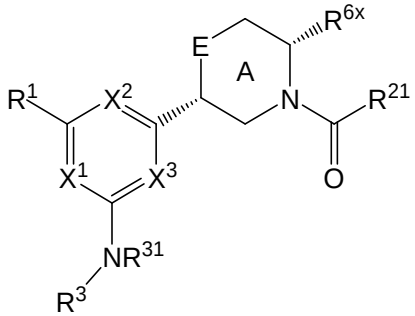
E is either absent or is selected from –CH_2–, –CHR^x–, –CR^x_2–, –NH–, –NR^x–, –O–, –L^1–L^2– and –L^2–L^1–, wherein L^1 is selected from –CH_2–, –CHR^x–, –CR^x_2–, –NH–, –NR^x– and –O– and L^2 is selected from –CH_2–, –CHR^x– and –CR^x_2–;

R^{6x} is $C_{1–3}$ alkyl, $C_{1–2}$ haloalkyl, and $C_{1–3}$ alkyl substituted with one or more OH;

wherein Ring A is further unsubstituted or substituted with one or more groups R^x, wherein

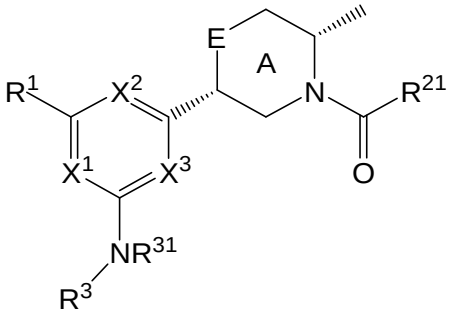
each R^x is independently selected from –halogen, –OH, –O–$C_{1–2}$ alkyl, –O–$C_{1–2}$ alkyl substituted with one or more R^{xa}, –NH–$C_{1–2}$ alkyl, –NH–$C_{1–2}$ alkyl substituted with one or more R^{xa}, –N($C_{1–2}$ alkyl)$_2$, –N($C_{1–2}$ alkyl substituted with one or more R^{xa})$_2$, =O, $C_{1–3}$ alkyl, $C_{1–3}$ alkyl substituted with one or more R^{xa}, $C_{1–2}$ haloalkyl, –W–(monocyclic carbocyclyl), –W–(monocyclic carbocyclyl substituted with one or more R^{xa}), –W–(monocyclic heterocyclyl), –W–(monocyclic heterocyclyl substituted with one or more R^{xa}), and wherein –W– is absent, –($C_{1–2}$ alkylene)– or –O–($C_{1–2}$ alkylene)–, and wherein monocyclic carbocyclyl is selected from phenyl and $C_{3–6}$ cycloalkyl, and wherein monocyclic heterocyclyl is selected from thiophenyl, pyridyl, pyrazinyl and pyrimidinyl, and wherein said R^{xa} is independently selected from –Cl, -F, and –OH.

2. The compound according to claim 1, wherein the compound of formula (I) is a compound of formula (V)



(V),

3. The compound according to claim 1 or claim 2, wherein the compound of formula (I) is a compound of formula (VI)



(VI)

4. The compound according to any one of the preceding claims, wherein X^1 is CH.

5. The compound according to any one of the preceding claims, wherein R^{21} is $–CH_3$ or $–CH_2CH_3$, and wherein preferably R^{21} is $–CH_3$.

6. The compound according to any one of the preceding claims, wherein R^{31} is selected from –hydrogen and $–C_{1\text{-}2}$-alkyl, and wherein preferably R^{31} is –hydrogen.

7. The compound according to any one of the preceding claims, wherein E is selected from $–CH_2–$, –O–, $–CH_2–O–$ and $–CH_2–CH_2–$, and wherein preferably E is $–CH_2–$.

8. The compound according to any one of the preceding claims, wherein the number of groups R^x in Ring A is 0, 1, or 2.

9. The compound according to any one of the preceding claims, wherein the compound of formula (I) is active on the bromodomain of p300 and/or the bromodomain of CBP with an EC50 of 10000 nM or less.

10. A pharmaceutical composition comprising:
a compound having the formula (I) as defined in any of claims 1 to 9, or a pharmaceutically acceptable salt, solvate, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof,
and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

11. Use of a compound having the formula (I) as defined in any of claims 1 to 9, or a pharmaceutically acceptable salt, solvate, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof, and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s), or a pharmaceutical

composition of claim 10, in the manufacture of a medicament for the treatment or amelioration of cancer, wherein preferably the cancer is selected from melanoma, non-small cell lung cancer, prostate cancer, bile duct cancer, bladder cancer, pancreatic cancer, thyroid cancer, ovarian cancer, colorectal tumor, hairy cell leukemia, acute myeloid leukemia, multiple myeloma, liver cancer, breast cancer, esophageal cancer, head and neck cancer and glioma, in particular multiple myeloma, acute myeloid leukemia, prostate cancer, melanoma and non-small cell lung cancer.

12. Use of a compound having the formula (I) as defined in any of claims 1 to 9, or a pharmaceutically acceptable salt, solvate, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof, and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s), or a pharmaceutical composition of claim 10, and a second therapeutic agent in the manufacture of a medicament for combination therapy for the treatment or amelioration of cancer, wherein preferably said second therapeutic agent is an anti-cancer agent,
and wherein preferably the cancer is selected from melanoma, non-small cell lung cancer, prostate cancer, bile duct cancer, bladder cancer, pancreatic cancer, thyroid cancer, ovarian cancer, colorectal tumor, hairy cell leukemia, acute myeloid leukemia, multiple myeloma, liver cancer, breast cancer, esophageal cancer, head and neck cancer and glioma, in particular multiple myeloma, acute myeloid leukemia, prostate cancer, melanoma and non-small cell lung cancer.

13. Use of a compound having the formula (I) as defined in any of claims 1 to 9, or in the form of a pharmaceutically acceptable salt, solvate, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof, and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s), or a pharmaceutical composition of claim 10 in the manufacture of a first medicament and use of a second therapeutic agent in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy for the treatment or amelioration of cancer,
wherein preferably said second therapeutic agent is an anti-cancer agent,
and wherein preferably the cancer is selected from melanoma, non-small cell lung cancer, prostate cancer, bile duct cancer, bladder cancer, pancreatic cancer, thyroid cancer, ovarian cancer, colorectal tumor, hairy cell leukemia, acute myeloid leukemia, multiple myeloma, liver cancer, breast cancer, esophageal cancer, head and neck cancer and glioma, in particular multiple myeloma, acute myeloid leukemia, prostate cancer, melanoma and non-small cell lung cancer.

14. Use of a compound having the formula (I) as defined in any of claims 1 to 9, or in the form of a pharmaceutically acceptable salt, solvate, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof, and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s), or a pharmaceutical composition of claim 10 in the manufacture of a medicament for use in combinatorial therapy for the treatment or amelioration of cancer, wherein said medicament is to be administered in combination with a second therapeutic agent, wherein preferably said second therapeutic agent is an anti-cancer agent,
and wherein preferably the cancer is selected from melanoma, non-small cell lung cancer, prostate cancer, bile duct cancer, bladder cancer, pancreatic cancer, thyroid cancer, ovarian cancer, colorectal tumor, hairy cell leukemia, acute myeloid leukemia, multiple myeloma, liver cancer, breast cancer, esophageal cancer, head and neck cancer and glioma, in particular multiple myeloma, acute myeloid leukemia, prostate cancer, melanoma and non-small cell lung cancer.