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.

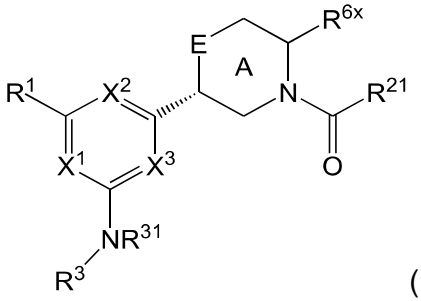
Phenotypic, signalling, transcriptional, and metabolic plasticity as well as the acquisition of novel genetic alterations have been found to be a driving factor in the development of resistance to cancer treatment including molecularly targeted inhibitors and immunotherapies. There is a need to avoid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

In one aspect, the present disclosure provides 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

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

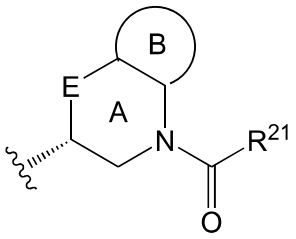
each of $X^1$, $X^2$ and $X^3$ is independently selected from N, CH and $CR^x$, wherein at least one of said $X^1$, $X^2$ and $X^3$ is N;

$R^{31}$ is selected from –hydrogen, $–C_{1-6}$-alkyl, and $–C_{1-6}$-alkyl substituted with one or more F; wherein $R^3$ and any $R^{31}$ are separate substituents or linked with each other; 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 –halogen, –OH, =O, $C_{1–6}$ alkyl, $C_{1–6}$ haloalkyl, $C_{1–6}$ alkyl substituted with one or more OH, monocyclic aryl unsubstituted or substituted with one or more $R^{xb}$, monocyclic heteroaryl unsubstituted or substituted with one or more $R^{xb}$, monocyclic cycloalkyl unsubstituted or substituted with one or more $R^{xb}$, monocyclic heterocycloalkyl unsubstituted or substituted with one or more $R^{xb}$, monocyclic cycloalkenyl unsubstituted or substituted with one or more $R^{xb}$, monocyclic heterocycloalkenyl unsubstituted or substituted with one or more $R^{xb}$, wherein said $R^{xb}$ is independently selected from –halogen, –OH, =O, $C_{1–4}$ alkyl, $C_{1–2}$ haloalkyl, $C_{1–2}$ alkyl substituted with one or two OH;

wherein Ring A is further unsubstituted or substituted with one or more groups $R^x$, wherein any two $R^x$ groups at ring A are separate substituents or linked with each other, and/or any $R^x$ group at ring A is a separate substituent or linked with $R^{21}$; and/or wherein Ring A is further substituted with one group $R^x$ so as to form together with $R^{6x}$ a bicyclic moiety having the following partial structure:




wherein Ring B is an unsubstituted or substituted heterocycle or unsubstituted or substituted carbocycle;

each $R^x$ is independently selected from –halogen, –OH, unsubstituted or substituted $–O–C_{1–6}$ alkyl, unsubstituted or substituted $–NH–$ $C_{1–6}$ alkyl, unsubstituted or substituted $–N(C_{1–6}$ alkyl$)_2$, =O, unsubstituted or substituted – $C_{1–6}$ alkyl, unsubstituted or substituted carbocyclyl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted $–C_{1–6}$ alkylene–(carbocyclyl), unsubstituted or substituted $–C_{1–6}$ alkylene–(substituted carbocyclyl), unsubstituted or substituted $–C_{1–6}$ alkylene–(heterocyclyl),

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 aspect, the present disclosure provides 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 aspect, the present disclosure provides a 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.

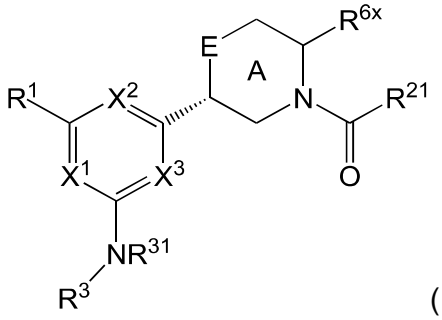
In yet another aspect, the present disclosure provides a use of a compound having the formula (I) as defined herein, or a pharmaceutically acceptable salt, solvate, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof, and optionally one or more pharmaceutically acceptable excipient(s) 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 aspect, the present disclosure provides a 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 aspect, the present disclosure provides a 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

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.

Thus, in a first example, the present disclosure provides a compound of formula (I), optionally in the form of a pharmaceutically acceptable salt, solvate, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof




(I)

wherein

$R^1$ is selected from halogen and –(optionally substituted hydrocarbon group which contains from 1 to 20 carbon atoms and optionally 1 to 15 heteroatoms selected from O, N and S);

$R^{21}$ is selected from hydrogen, –(optionally substituted $C_{1–6}$ alkyl) which may contain one to three oxygen atoms between carbon atoms, and –(optionally substituted $C_{3–6}$ cycloalkyl);

$R^3$ is selected from –(optionally substituted heterocyclyl), –(optionally substituted carbocyclyl), –(optionally substituted $C_{1–6}$ alkylene)–(optionally substituted heterocyclyl) and –(optionally substituted $C_{1–6}$ alkylene)–(optionally substituted carbocyclyl);

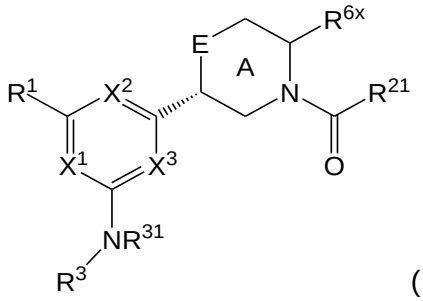
substituted $C_{1–6}$ alkylene is independently selected from –($C_{1–6}$ alkyl which is optionally substituted with one or more halogen), –halogen, –CN, –$NO_2$, oxo, –C(O)R*, –COOR*, –C(O)NR*R*, –NR*R*, –N(R*)–C(O)R*, –N(R*)–C(O)–OR*, –N(R*)–C(O)–NR*R*, –N(R*)–$S(O)_2$R*, –OR*, –O–C(O)R*, –O–C(O)–NR*R*,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

The type of cancer that can be treated with the compounds and compositions of the present disclosure is not specifically limited and can be selected from non-melanoma skin cancer, esophagogastric adenocarcinoma, glioblastoma, bladder cancer, bladder urothelial carcinoma, esophagogastric cancer, melanoma, non-small cell lung cancer, endometrial cancer, cervical adenocarcinoma, esophageal squamous cell carcinoma, breast cancer, head and neck squamous cell carcinoma, germ cell tumor, small cell lung cancer, ovarian cancer, soft tissue sarcoma, hepatocellular carcinoma, colorectal adenocarcinoma, cervical squamous cell carcinoma, cholangiocarcinoma, prostate cancer, upper tract urothelial carcinoma, diffuse glioma, colorectal cancer, ampullary carcinoma, adrenocortical carcinoma, head and neck cancer, renal clear cell carcinoma, hepatobiliary cancer, glioma, non-Hodgkin lymphoma, mesothelioma, salivary gland cancer, renal non-clear cell carcinoma, miscellaneous neuroepithelial tumor, pheochromocytoma, thymic tumor, multiple myeloma, renal cell carcinoma, bone cancer, pancreatic cancer, leukemia, peripheral nervous system tumors, thyroid cancer, B-lymphoblast leukemia, monoclonal B-cell lymphocytosis, lymphoma, hairy cell leukemia, acute myeloid leukemia, Wilms tumor, in particular multiple myeloma, acute myeloid leukemia, melanoma and non-small cell lung cancer.

Further examples of the present disclosure will be become apparent as this description continues.

## 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 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 or substituted $C_{1–6}$ alkylene-(carbocyclyl), and unsubstituted or substituted $C_{1-6}$ alkylene-(substituted carbocyclyl);

each of $X^1$, $X^2$ and $X^3$ is independently selected from N, CH and $CR^x$, wherein at least one of said $X^1$, $X^2$ and $X^3$ is N;

$R^{31}$ is selected from –hydrogen, $–C_{1-6}$-alkyl, and $–C_{1-6}$-alkyl substituted with one or more F; wherein $R^3$ and any $R^{31}$ are separate substituents or linked with each other; and

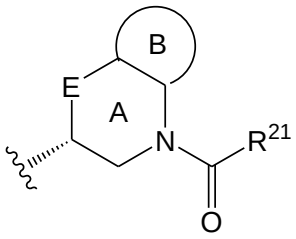
E is either absent or is selected from $–CH_2–$, $–CHR^x–$, $–CR^x{}_2–$, –NH–, $–NR^x–$,

–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 –halogen, –OH, =O, $C_{1–6}$ alkyl, $C_{1–6}$ haloalkyl, $C_{1–6}$ alkyl substituted with one or more OH, monocyclic aryl unsubstituted or substituted with one or

more $R^{xb}$, monocyclic heteroaryl unsubstituted or substituted with one or more $R^{xb}$, monocyclic cycloalkyl unsubstituted or substituted with one or more $R^{xb}$, monocyclic heterocycloalkyl unsubstituted or substituted with one or more $R^{xb}$, monocyclic cycloalkenyl unsubstituted or substituted with one or more $R^{xb}$, monocyclic heterocycloalkenyl unsubstituted or substituted with one or more $R^{xb}$, wherein said $R^{xb}$ is independently selected from –halogen, –OH, =O, $C_{1–4}$ alkyl, $C_{1–2}$ haloalkyl, $C_{1–2}$ alkyl substituted with one or two OH;

wherein Ring A is further unsubstituted or substituted with one or more groups $R^x$, wherein any two $R^x$ groups at ring A are separate substituents or linked with each other, and/or any $R^x$ group at ring A is a separate substituent or linked with $R^{21}$; and/or wherein Ring A is further substituted with one group $R^x$ so as to form together with $R^{6x}$ a bicyclic moiety having the following partial structure:




wherein Ring B is an unsubstituted or substituted heterocycle or unsubstituted or substituted carbocycle;

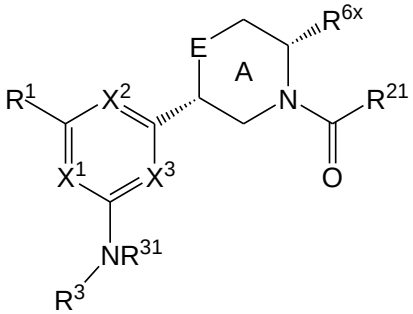
each $R^x$ is independently selected from –halogen, –OH, unsubstituted or substituted –O–$C_{1–6}$ alkyl, unsubstituted or substituted –NH– $C_{1–6}$ alkyl, unsubstituted or substituted –N($C_{1–6}$ alkyl)$_2$, =O, unsubstituted or substituted –$C_{1–6}$ alkyl, unsubstituted or substituted carbocyclyl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted –$C_{1–6}$ alkylene–(carbocyclyl), unsubstituted or substituted –$C_{1–6}$ alkylene–(substituted carbocyclyl), unsubstituted or substituted –$C_{1–6}$ alkylene–(heterocyclyl), 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

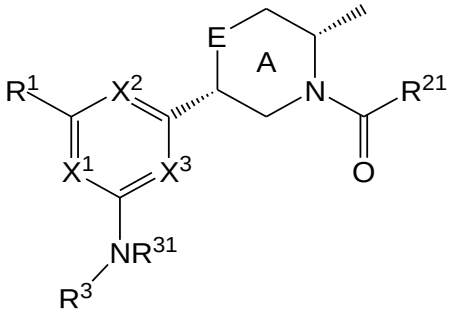
wherein the substituent of the substituted $C_{1–6}$ alkyl and of the substituted $C_{1–6}$ alkylene is independently selected from –halogen, –CN, –$NO_2$, oxo, –C(O)R**, –COOR**, –C(O)NR**R**, –NR**R**, –N(R**)–C(O)R**, –N(R**)–C(O)–OR**, –N(R**)–C(O)–NR**R**, –N(R**)–$S(O)_2$R**, –OR**, –O–C(O)R**, –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.

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 $X^2$ and $X^3$ are N, and wherein preferably $X^1$ 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 $–C_{1-2}$-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 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.

10. The compound according to any one of the preceding claims, wherein $R^1$ is selected from unsubstituted or substituted heterocyclyl and unsubstituted or substituted carbocyclyl, and wherein preferably $R^1$ 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/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 $-CH_2-NH-CH_2-$.

11. The compound according to any one of the preceding claims, wherein $R^3$ is selected from phenyl, a 6-membered monocyclic heteroaryl and a 8-10 membered bicyclic heteroaryl, each independently comprising one or more ring heteroatoms independently selected from O, B, S and N, and wherein said phenyl, said 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, –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, B, S and N, each monocyclic carbocyclyl and heterocyclyl independently unsubstituted or substituted with one or more substituents independently selected from halogen, 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, cyclopropyl, cyclobutyl, oxetanyl, $–C_{1-2}$alkylene–OH, $–C_{1-2}$alkylene–$O(C_{1–2}$alkyl), phenyl, and wherein each R** is independently selected from H, $C_{1–4}$ alkyl, $C_{1–4}$ haloalkyl, and/or wherein each monocyclic heterocyclyl is independently unsubstituted or substituted with one bivalent substituent selected from $C_{1-3}$ alkylene such as -$CH_2$-$CH_2$- and -$CH_2$-$CH_2$-$CH_2$-, $C_{1-3}$ alkylene substituted with 1 to 4 F, -$CH_2$-O-$CH_2$- and -$CH_2$-NH-$CH_2$-.

12. 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.

13. A pharmaceutical composition comprising:
a compound having the formula (I) as defined in any of claims 1 to 12, 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).

14. Use of a compound having the formula (I) as defined in any of claims 1 to 12, 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 13, 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.

15. Use of a compound having the formula (I) as defined in any of claims 1 to 12, 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 13, 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.

16. Use of a compound having the formula (I) as defined in any of claims 1 to 12, 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 13 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.

17. Use of a compound having the formula (I) as defined in any of claims 1 to 12, 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 13 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.