well known and these have been shown to have activity towards a number of cancer cell lines, with some assemblies used to encapsulate and target *cis*-platin delivery.[21]

[0004] In spite of the advances discussed above, there remains a need for new compounds useful in the treatment of proliferative disorders, in particular cancer.

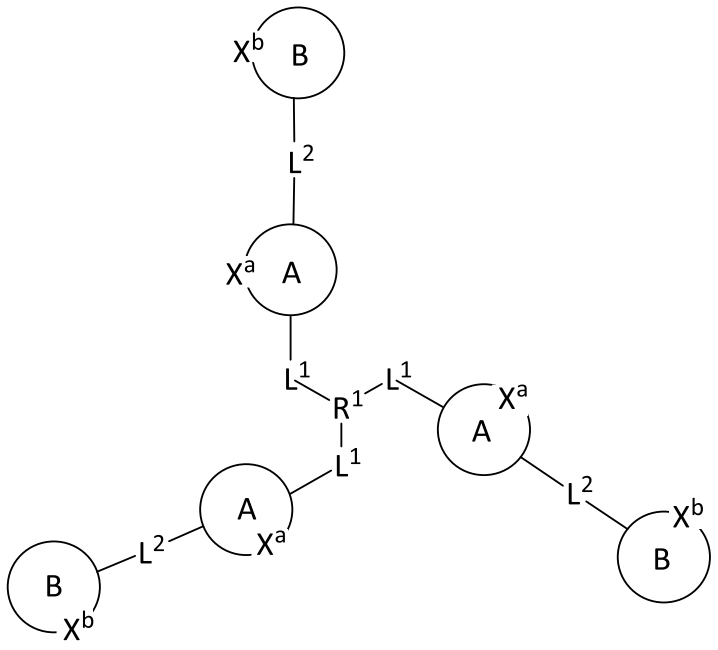
[0005] The present invention was devised with the foregoing in mind.

SUMMARY ~~OF THE INVENTION~~

[0006] The inventors have surprisingly discovered that compounds of Formula I described herein function as tripodal ligands that are able to self-assemble in the presence of certain metals and anions to form mono- and trinuclear complexes (the compounds of Formula II and III described herein). Interestingly, the complexes demonstrate phosphatase activity, whereby encapsulated organo-phosphate dianions (i.e. $ROPO_3^{2-}$) are readily hydrolysed to phosphate (i.e. PO_4^{3-}).

[0007] In cell studies, the complexes are highly toxic to a range of human cancer cell lines as well as a glioblastoma cancer stem cell model.[22,23] As well as potency, the complexes show remarkable selective activity towards cancer cells compared to healthy, non-cancerous cells (by up to 2000 fold; ARPE19,[24] MCF10a,[25] and NP1[22,23] non-cancer cell models). Encapsulation of certain anions (notably phosphate or sulfate anions) further modulates potency and selectivity. Mechanism of action studies show that the complexes have selective phosphatase activity towards phospho-serine, phospho-tyrosine and phospho-threonine amino acids resulting in the selective inhibition of multiple kinases, cancer cell ATP depletion, autophagy and cancer cell toxicity. Kinase inhibition by certain complexes is postulated to occur through binding to phospho-amino acids rather than dephosphorylation. These represent highly novel mechanisms of action with the ability to target multiple kinases whilst retaining selective cancer cell toxicity a feature that would be predicted to suppress the emergence of resistant cancer cell sub-populations.

[0007a] In a first aspect of the present disclosure, there is provided a compound having a structure according to Formula I shown below, or a pharmaceutically acceptable salt, hydrate or solvate thereof, for use as a medicament:



Formula I

wherein

R^1 is selected from the group consisting of N, CR^2, aryl, heteroaryl, carbocyclyl and heterocyclyl, where any aryl, heteroaryl, carbocyclyl or heterocyclyl in R^1 is optionally substituted with one or more R^3;

each R^3 is independently selected from the group consisting of hydroxy, cyano, halogen, (1-4C)alkyl, (1-4C)haloalkyl, (2-4C)alkenyl, (2-4C)alkynyl, aryl, aryl(1-3C)alkyl, heteroaryl, heteroaryl(1-3C)alkyl, carbocyclyl, carbocyclyl(1-3C)alkyl, heterocyclyl, heterocyclyl(1-3C)alkyl, $-OR^{3a}$, $-NR^{3a}R^{3b}$, $-C(O)-R^{3a}$, $-C(O)-OR^{3a}$, $-O-C(O)-R^{3a}$, $-C(O)-NR^{3a}R^{3b}$, $-N(R^{3a})C(O)-R^{3b}$ and $-S(O)_{0-2}R^{3a}$, where any (1-4C)alkyl, (1-4C)haloalkyl, (2-4C)alkenyl, (2-4C)alkynyl, aryl, aryl(1-3C)alkyl, heteroaryl, heteroaryl(1-3C)alkyl, carbocyclyl, carbocyclyl(1-3C)alkyl, heterocyclyl or heterocyclyl(1-3C)alkyl in R^3 is optionally substituted with one or more R^{3c};

R^{3a} and R^{3b} are each independently selected from the group consisting of hydrogen, (1-3C)alkyl and (1-3C)haloalkyl;

each R^{3c} is independently selected from the group consisting of hydroxy, halogen, cyano, amino, (1-3C)alkyl, (1-3C)alkoxy and (1-3C)haloalkyl;

R^2 is selected from the group consisting of hydrogen, hydroxy, cyano, halogen, (1-4C)alkyl, (1-4C)haloalkyl, (2-4C)alkenyl, (2-4C)alkynyl, aryl, aryl(1-3C)alkyl, heteroaryl, heteroaryl(1-3C)alkyl, carbocyclyl, carbocyclyl(1-3C)alkyl, heterocyclyl, heterocyclyl(1-3C)alkyl, $-OR^{2a}$, $-NR^{2a}R^{2b}$, $-C(O)-R^{2a}$, $-C(O)-OR^{2a}$, $-O-C(O)-R^{2a}$, $-C(O)-NR^{2a}R^{2b}$, $-N(R^{2a})C(O)-R^{2b}$ and $-S(O)_{0-2}R^{9a}$, where any (1-4C)alkyl, (1-4C)haloalkyl, (2-4C)alkenyl, (2-4C)alkynyl, aryl, aryl(1-3C)alkyl,

heteroaryl, heteroaryl(1-3C)alkyl, carbocyclyl, carbocyclyl(1-3C)alkyl, heterocyclyl or heterocyclyl(1-3C)alkyl in R^2 is optionally substituted with one or more R^{2c};

R^{2a} and R^{2b} are each independently selected from the group consisting of hydrogen, (1-3C)alkyl and (1-3C)haloalkyl;

each R^{2c} is independently selected from the group consisting of hydroxy, halogen, cyano, amino, (1-3C)alkyl, (1-3C)alkoxy and (1-3C)haloalkyl;

each L^1 is a group:

$$-(W)_n-(X)_m-(Y)_o-(Z)_p-$$

in which

n and o are each independently 0, 1 or 2, and m and p are each independently 0 or 1, with the provisos that when m and p are both 1, o is not 0;

each W is selected from the group consisting of (1-3C)alkylene, (2-3C)alkenylene, (2-3C)alkynylene, arylene, heteroarylene, carbocyclylene and heterocyclylene, where any (1-3C)alkylene, (2-3C)alkenylene, (2-3C)alkynylene, arylene, heteroarylene, carbocyclylene or heterocyclylene in W is optionally substituted with one or more W^a, where each W^a is independently selected from the group consisting of hydroxy, cyano, halogen, amino, (1-2)alkoxy and (1-2C)haloalkyl;

X is selected from the group consisting of -O-, -C(O)-, -C(O)-O-, -O-C(O)-, $-S(O)_{0-2}-$, $-C(O)-N(R^x)-$, $-N(R^x)-C(O)-$, $-NR^x-$, $-N(R^x)-C(O)-NR^x-$, $-SO_2N(R^x)-$, and $-N(R^x)SO_2$, where each R^x is independently selected from the group consisting of hydrogen, hydroxy, cyano, (1-4C)alkyl, (2-4C)alkenyl and (2-4C)alkynyl;

each Y is selected from the group consisting of (1-3C)alkylene, (2-3C)alkenylene, (2-3C)alkynylene, arylene, heteroarylene, carbocyclylene and heterocyclylene, where any (1-3C)alkylene, (2-3C)alkenylene, (2-3C)alkynylene, arylene, heteroarylene, carbocyclylene or heterocyclylene in Y is optionally substituted with one or more Y^a, where each Y^a is independently selected from the group consisting of hydroxy, cyano, halogen, amino, (1-2)alkoxy and (1-2C)haloalkyl;

Z is selected from the group consisting of -O-, -C(O)-, -C(O)-O-, -O-C(O)-, $-S(O)_{0-2}-$, $-C(O)-N(R^z)-$, $-N(R^z)-C(O)-$, $-NR^z-$, $-N(R^z)-C(O)-NR^z-$, $-SO_2N(R^z)-$, and $-N(R^z)SO_2$, where each R^z is independently selected from the group consisting of hydrogen, hydroxy, cyano, (1-4C)alkyl, (2-4C)alkenyl and (2-4C)alkynyl;

X^a is a ring heteroatom located within ring A and is selected from N and O;

each ring A is a monocyclic heteroaryl, bicyclic heteroaryl, monocyclic heterocycle or bicyclic heterocycle, any one of which is optionally substituted with one or more R^4, where each R^4 is independently selected from the group consisting of hydroxy, cyano, halogen, (1-6C)alkyl, (1-6C)haloalkyl, (2-6C)alkenyl, (2-6C)alkynyl, aryl, aryl(1-3C)alkyl, heteroaryl, heteroaryl(1-3C)alkyl, carbocyclyl, carbocyclyl(1-3C)alkyl, heterocyclyl, heterocyclyl(1-3C)alkyl, $-R^{4a}-OR^{4b}$, $-R^{4a}-NR^{4b}R^{4c}$, $-R^{4a}-C(O)-R^{4b}$, $-R^{4a}-C(O)-OR^{4b}$, $-R^{4a}-O-C(O)-R^{4b}$, $-R^{4a}-C(O)-NR^{4b}R^{4c}$, $-R^{4a}-N(R^{4b})C(O)-R^{4c}$ and $-R^{4a}-S(O)_{0-2}R^{4b}$, where any (1-6C)alkyl, (1-6C)haloalkyl, (2-6C)alkenyl, (2-6C)alkynyl, aryl, aryl(1-3C)alkyl, heteroaryl, heteroaryl(1-3C)alkyl, carbocyclyl, carbocyclyl(1-3C)alkyl, heterocyclyl or heterocyclyl(1-3C)alkyl in R^4 is optionally substituted with one or more R^{4d};

R^{4a} is absent or is (1-3C)alkylene that is optionally substituted with one or substituents selected from group consisting of hydroxy, halo and amino;

R^{4b} and R^{4c} are each independently selected from the group consisting of hydrogen, (1-3C)alkyl and (1-3C)haloalkyl;

each R^{4d} is independently selected from the group consisting of hydroxy, halogen, cyano, amino, (1-3C)alkyl, (1-3C)alkoxy and (1-3C)haloalkyl;

X^b is a ring heteroatom located within ring B and is selected from N and O

each ring B is a monocyclic heteroaryl, bicyclic heteroaryl, monocyclic heterocycle or bicyclic heterocycle, any one of which is optionally substituted with one or more R^5, where each R^5 is independently selected from the group consisting of hydroxy, cyano, halogen, (1-6C)alkyl, (1-6C)haloalkyl, (2-6C)alkenyl, (2-6C)alkynyl, aryl, aryl(1-3C)alkyl, heteroaryl, heteroaryl(1-3C)alkyl, carbocyclyl, carbocyclyl(1-3C)alkyl, heterocyclyl, heterocyclyl(1-3C)alkyl, $-R^{5a}-OR^{5b}$, $-R^{5a}-NR^{5b}R^{5c}$, $-R^{5a}-C(O)-R^{5b}$, $-R^{5a}-C(O)-OR^{5b}$, $-R^{5a}-O-C(O)-R^{5b}$, $-R^{5a}-C(O)-NR^{5b}R^{5c}$, $-R^{5a}-N(R^{5b})C(O)-R^{5c}$ and $-R^{5a}-S(O)_{0-2}R^{5b}$, where any (1-6C)alkyl, (1-6C)haloalkyl, (2-6C)alkenyl, (2-6C)alkynyl, aryl, aryl(1-3C)alkyl, heteroaryl, heteroaryl(1-3C)alkyl, carbocyclyl, carbocyclyl(1-3C)alkyl, heterocyclyl or heterocyclyl(1-3C)alkyl in R^5 is optionally substituted with one or more R^{5d};

R^{5a} is absent or is (1-3C)alkylene that is optionally substituted with one or substituents selected from group consisting of hydroxy, halo and amino;

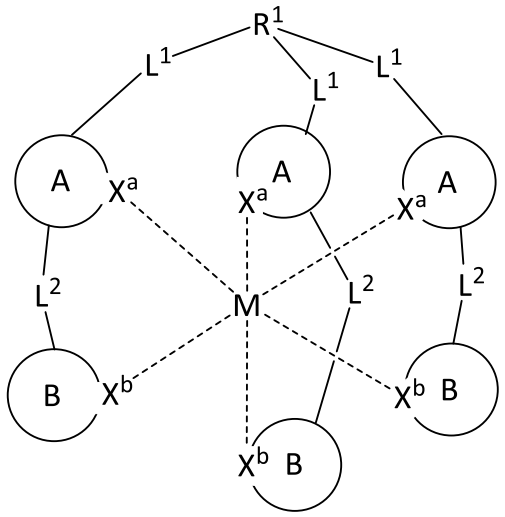
R^{5b} and R^{5c} are each independently selected from the group consisting of hydrogen, (1-5C)alkyl (e.g. (1-3C)alkyl) and (1-3C)haloalkyl;

each R^{5d} is independently selected from the group consisting of hydroxy, halogen, cyano, amino, (1-3C)alkyl, (1-3C)alkoxy and (1-3C)haloalkyl; and

each L^2 is selected from the group consisting of absent (in which case ring A is bonded directly to ring B), (1-2C)alkylene, ethenylene and ethynylene, where any (1-2C)alkylene, ethenylene and ethynylene in L^2 is optionally substituted with one or more substituents selected form the group consisting of hydroxy, halogen, cyano, amino, (1-3C)alkyl, (1-3C)alkoxy and (1-3C)haloalkyl;

and wherein the compound of Formula I, or the pharmaceutically acceptable salt, hydrate or solvate thereof, is for use in combination with a source of M, wherein M is selected from the group consisting of Zn^{2+}, Mn^{2+}, Cu^{2+}, Fe^{2+}, Co^{2+} and Ni^{2+}.

[0007b] In another aspect of the present disclosure, there is provided a compound having a structure according to Formula II shown below, or a pharmaceutically acceptable salt, hydrate or solvate thereof, for use as a medicament:

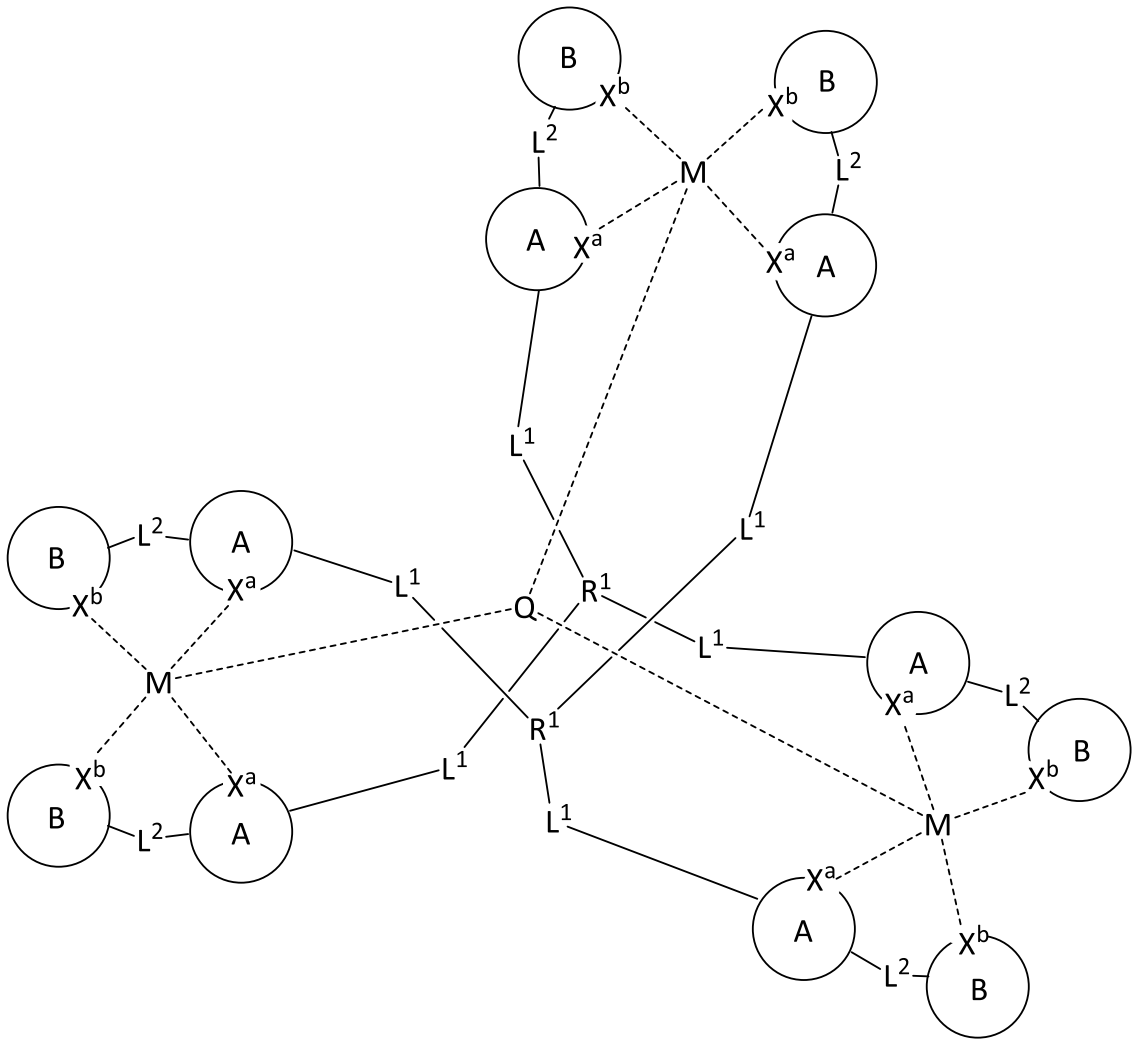


Formula II

wherein

M, R^1, L^1, A, X^a, L^2, B, X^b and any associated subgroups are as disclosed herein.

[0007c] In yet another aspect of the present disclosure, there is provided a compound having a structure according to Formula III shown below, or a pharmaceutically acceptable salt, hydrate or solvate thereof, for use as a medicament:



Formula III

wherein

M, Q, R^1, L^1, A, X^a, L^2, B, X^b and any associated subgroups are as disclosed herein.

[0007d] In a further aspect of the present disclosure, there is provided the compound, pharmaceutically acceptable salt, hydrate or solvate for use as disclosed herein, wherein the medicament is for the treatment of a proliferative disorder (e.g. cancer).

[0007e] In another aspect of the present disclosure, there is provided a use of the compound, pharmaceutically acceptable salt, hydrate or solvate as disclosed herein, in the manufacture of a medicament for treatment of a proliferative disorder (e.g. cancer).

[0008] Thus, according to a first ~~aspect~~example of the present ~~invention~~disclosure there is provided a compound having a structure according to Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, with the proviso that the compound is not Compound Ia defined herein or a pharmaceutically acceptable salt, hydrate or solvate thereof.

[0009] According to a further ~~aspect~~example of the present ~~invention~~disclosure there is provided a compound having a structure according to Formula II as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof. Suitably, the compound not Compound IIa defined herein or a pharmaceutically acceptable salt, hydrate or solvate thereof. More suitably, M is selected from the group consisting of Zn^{2+}, Mn^{2+}, Fe^{2+}, Co^{2+} and Ni^{2+}.

[0010] According to a further ~~aspect~~example of the present ~~invention~~disclosure there is provided a compound having a structure according to Formula III as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, with the proviso that the compound does not have a structure according to Formula IIIa defined herein. Suitably, M is selected from the group consisting of Zn^{2+}, Mn^{2+}, Fe^{2+}, Co^{2+} and Ni^{2+}.

[0011] According to a further ~~aspect~~example of the present ~~invention~~disclosure there is provided a pharmaceutical composition comprising a compound having a structure according to Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, a source of M as defined herein, and one or more pharmaceutically acceptable diluents, excipients or carriers. Suitably, the pharmaceutical composition further comprises a source of Q as defined herein.

[0012] According to a further ~~aspect~~example of the present ~~invention~~disclosure there is provided a pharmaceutical composition comprising a compound having a structure according to Formula II as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, and one or more pharmaceutically acceptable diluents, excipients or carriers. Suitably, the pharmaceutical composition further comprises a source of Q as defined herein.

[0013] According to a further ~~aspect~~example of the present ~~invention~~disclosure there is provided a pharmaceutical composition comprising a compound having a structure according to Formula III as defined herein or a pharmaceutically acceptable salt, hydrate or solvate thereof, and one or more pharmaceutically acceptable diluents, excipients or carriers.

[0014] According to a further ~~aspect~~example of the present ~~invention~~disclosure there is provided a kit of parts comprising a compound having a structure according to Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, and a source of M as defined herein.

[0015] According to a further ~~aspect~~example of the present ~~invention~~disclosure there is provided a kit of parts comprising a compound having a structure according to Formula II as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, and a source of Q as defined herein

[0016] According to a further ~~aspect~~example of the present ~~invention~~disclosure there is provided a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in combination with a source of M as defined herein, for use as a medicament. Suitably, the compound of Formula I and the source of M are in further combination with a source of Q as defined herein.

[0017] According to a further ~~aspect~~example of the present ~~invention~~disclosure there is provided a compound of Formula II as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, for use as a medicament. Suitably, the compound of Formula II is in combination with a source of Q as defined herein.

[0018] According to a further ~~aspect~~example of the present ~~invention~~disclosure there is provided a compound of Formula III as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, for use as a medicament.

[0019] According to a further ~~aspect~~example of the present ~~invention~~disclosure there is provided a pharmaceutical composition as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, for use as a medicament.

[0020] According to a further ~~aspect~~example of the present ~~invention~~disclosure there is provided a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in combination with a source of M as defined herein, for use in the treatment of a proliferative disorder (e.g. cancer). Suitably, the compound of Formula I and the source of M are in further combination with a source of Q as defined herein.

[0021] According to a further ~~aspect~~example of the present ~~invention~~disclosure there is provided a compound of Formula II as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, for use in the treatment of a proliferative disorder (e.g. cancer). Suitably, the compound of Formula II is in combination with a source of Q as defined herein.

[0022] According to a further ~~aspect~~example of the present ~~invention~~disclosure there is provided a compound of Formula III as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, for use in the treatment of a proliferative disorder (e.g. cancer).

[0023] According to a further ~~aspect~~example of the present ~~invention~~disclosure there is provided a pharmaceutical composition as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, for use in the treatment of a proliferative disorder (e.g. cancer).

[0024] According to a further ~~aspect~~example of the present ~~invention~~disclosure there is provided a method of treating a proliferative disorder (e.g. cancer) in a patient in need of such treatment, the method comprising administering to the patient a therapeutically effective amount of a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in combination with a source of M as defined herein. Suitably, the compound of Formula I and the source of M are administered in combination with a source of Q.

[0025] According to a further ~~aspect~~example of the present ~~invention~~disclosure there is provided a method of treating a proliferative disorder (e.g. cancer) in a patient in need of such treatment, the method comprising administering to the patient a therapeutically effective amount of a compound of Formula II as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof. Suitably, the compound of Formula II is administered in combination with a source of Q.

[0026] According to a further ~~aspect~~example of the present ~~invention~~disclosure there is provided a method of treating a proliferative disorder (e.g. cancer) in a patient in need of such treatment, the method

comprising administering to the patient a therapeutically effective amount of a compound of Formula III as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof.

[0027] According to a further ~~aspect~~example of the present ~~invention~~disclosure there is provided a method of treating a proliferative disorder (e.g. cancer) in a patient in need of such treatment, the method comprising administering to the patient a therapeutically effective amount of a pharmaceutical composition as defined herein.

[0028] According to a further ~~aspect~~example of the present ~~invention~~disclosure there is provided the use of a compound of Formula I, II or III, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in the manufacture of a medicament. Suitably, the medicament is for the treatment of a proliferative disorder (e.g. cancer).

[0029] In the above-outlined ~~aspect~~examples of the ~~invention~~disclosure, the proliferative disorder is suitably cancer, and the cancer is suitably a human cancer. In particular, the compounds of the present ~~invention~~disclosure will be useful for the treatment of any cancer in which a mis-match repair inhibition is beneficial. Any suitable cancer may be targeted (e.g. adenoid cystic carcinoma, adrenal gland tumor, amyloidosis, anal cancer, appendix cancer, astrocytoma, ataxia-telangiectasia, Beckwith-Wiedemann Syndrome, bile duct cancer (cholangiocarcinoma), Birt-Hogg-Dubé Syndrome, bladder cancer, bone cancer, brain stem glioma, brain tumor, breast cancer, Carney Complex, central nervous system tumors, cervical cancer, colorectal cancer, Cowden Syndrome, craniopharyngioma, desmoplastic infantile ganglioglioma, ependymoma, esophageal cancer, Ewing sarcoma, eye cancer, eyelid cancer, familial adenomatous polyposis, familial GIST, familial malignant melanoma, familial non-VHL clear cell renal cell carcinoma, familial pancreatic cancer, gallbladder cancer, gastrointestinal stromal tumor – GIST, germ cell tumor, gestational trophoblastic disease, head and neck cancer, hereditary breast and ovarian cancer, hereditary diffuse gastric cancer, hereditary leiomyomatosis and renal cell cancer, hereditary mixed polyposis syndrome, hereditary pancreatitis, hereditary papillary renal carcinoma, juvenile polyposis syndrome, kidney cancer, lacrimal gland tumor, laryngeal and hypopharyngeal cancer, leukemia (acute lymphoblastic leukamia (ALL), acute myeloid leukemia (AML), B-cell prolymphocytic leukemia, hairy cell leukemia, chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), chronic T-cell lymphocytic leukemia, eosinophilic leukemia), Li-Fraumeni Syndrome, liver cancer, lung cancer (non-small cell lung cancer, small cell lung cancer), Lymphoma (Hodgkin, non-Hodgkin), Lynch Syndrome, mastocytosis, medulloblastoma, melanoma, meningioma, mesothelioma, multiple endocrine neoplasia Type 1 & 2, multiple myeloma, MUTYH (or MYH)-associated polyposis, myelodysplastic syndromes (MDS), nasal cavity and paranasal sinus Cancer, nasopharyngeal Cancer, neuroblastoma, neuroendocrine tumors (e.g. of the gastrointestinal tract, lung or pancreas), neurofibromatosis Type 1 & 2, nevoid basal cell carcinoma syndrome, oral and oropharyngeal cancer, osteosarcoma, ovarian /

fallopian tube / peritoneal cancer, pancreatic cancer, parathyroid cancer, penile cancer, Peutz-Jeghers Syndrome, pheochromocytoma, paraganglioma, pituitary gland tumor, pleuropulmonary blastoma, prostate cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcoma (e.g. Kaposi or soft tissue), skin cancer, small bowel cancer, stomach cancer, testicular cancer, thymoma and thymic carcinoma, thyroid cancer, tuberous sclerosis complex, uterine cancer, vaginal cancer, Von Hippel-Lindau syndrome, vulvar cancer, Waldenstrom's macroglobulinemia, Werner syndrome, Wilms Tumor and xeroderma pigmentosum). Particular cancers of interest include haematological cancers such as lymphomas (including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), Burkitt lymphoma (BL) and angioimmunoblastic T-cell lymphoma (AITL)), leukaemias (including acute lymphoblastic leukaemia (ALL) and chronic myeloid leukaemia (CML)), multiple myeloma, breast cancer, non-small cell lung cancer (NSCLC), colorectal cancer, endometrial cancer, gastro-oesophageal cancer, neuroendocrine cancers, osteosarcomas, prostate cancer, pancreatic cancer, small intestine cancer, bladder cancer, rectal cancer, cholangiocarcinoma, CNS cancer, thyroid cancer, head and neck cancer, oesophageal cancer, and ovarian cancer.

[0030] Components used *in combination with* one another (e.g. the compounds of Formula I, II or III, and sources of M and Q) may be administered simultaneously, separately or sequentially. In one ~~aspect~~example of the ~~invention~~disclosure *in combination with* refers to simultaneous administration. In another ~~aspect~~example of the ~~invention~~disclosure *in combination with* refers to separate administration. In a further ~~aspect~~example of the ~~invention~~disclosure *in combination with* refers to sequential administration. Where the administration is sequential or separate, the delay in administering the second (and any subsequent) component should not be such as to lose the beneficial effect of the combination.

[0031] Features, including optional, suitable, and preferred features in relation to one ~~aspect~~example of the ~~invention~~disclosure may also be features, including optional, suitable and preferred features in relation to any other ~~aspect~~example of the ~~invention~~disclosure.

DETAILED DESCRIPTION OF THE INVENTION

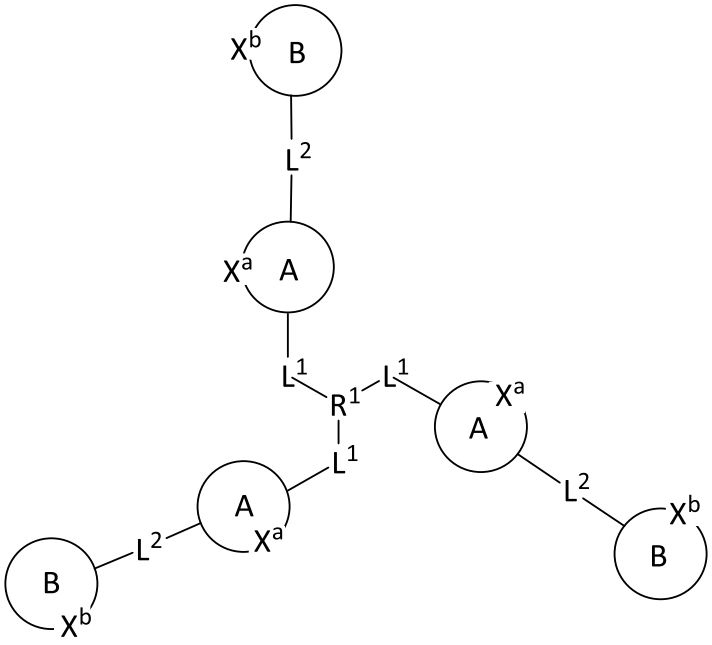
Definitions

[0032] Unless otherwise stated, the following terms used in the specification and claims have the following meanings set out below.

[0033] It is to be appreciated that references to "treating" or "treatment" include prophylaxis as well as the alleviation of established symptoms of a condition. "Treating" or "treatment" of a state, disorder or condition therefore includes: (1) preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a human that may be afflicted with or

CLAIMS

1. A compound having a structure according to Formula I shown below, or a pharmaceutically acceptable salt, hydrate or solvate thereof, for use as a medicament:



Formula I

wherein

R^1 is selected from the group consisting of N, CR^2, aryl, heteroaryl, carbocyclyl and heterocyclyl, where any aryl, heteroaryl, carbocyclyl or heterocyclyl in R^1 is optionally substituted with one or more R^3;

each R^3 is independently selected from the group consisting of hydroxy, cyano, halogen, (1-4C)alkyl, (1-4C)haloalkyl, (2-4C)alkenyl, (2-4C)alkynyl, aryl, aryl(1-3C)alkyl, heteroaryl, heteroaryl(1-3C)alkyl, carbocyclyl, carbocyclyl(1-3C)alkyl, heterocyclyl, heterocyclyl(1-3C)alkyl, $-OR^{3a}$, $-NR^{3a}R^{3b}$, $-C(O)-R^{3a}$, $-C(O)-OR^{3a}$, $-O-C(O)-R^{3a}$, $-C(O)-NR^{3a}R^{3b}$, $-N(R^{3a})C(O)-R^{3b}$ and $-S(O)_{0-2}R^{3a}$, where any (1-4C)alkyl, (1-4C)haloalkyl, (2-4C)alkenyl, (2-4C)alkynyl, aryl, aryl(1-3C)alkyl, heteroaryl, heteroaryl(1-3C)alkyl, carbocyclyl, carbocyclyl(1-3C)alkyl, heterocyclyl or heterocyclyl(1-3C)alkyl in R^3 is optionally substituted with one or more R^{3c};

R^{3a} and R^{3b} are each independently selected from the group consisting of hydrogen, (1-3C)alkyl and (1-3C)haloalkyl;

each R^{3c} is independently selected from the group consisting of hydroxy, halogen, cyano, amino, (1-3C)alkyl, (1-3C)alkoxy and (1-3C)haloalkyl;

R^2 is selected from the group consisting of hydrogen, hydroxy, cyano, halogen, (1-4C)alkyl, (1-4C)haloalkyl, (2-4C)alkenyl, (2-4C)alkynyl, aryl, aryl(1-3C)alkyl, heteroaryl, heteroaryl(1-3C)alkyl, carbocyclyl, carbocyclyl(1-3C)alkyl, heterocyclyl, heterocyclyl(1-3C)alkyl, $-OR^{2a}$, $-NR^{2a}R^{2b}$, $-C(O)-R^{2a}$, $-C(O)-OR^{2a}$, $-O-C(O)-R^{2a}$, $-C(O)-NR^{2a}R^{2b}$, $-N(R^{2a})C(O)-R^{2b}$ and $-S(O)_{0-2}R^{9a}$, where any (1-4C)alkyl, (1-4C)haloalkyl, (2-4C)alkenyl, (2-4C)alkynyl, aryl, aryl(1-3C)alkyl, heteroaryl, heteroaryl(1-3C)alkyl, carbocyclyl, carbocyclyl(1-3C)alkyl, heterocyclyl or heterocyclyl(1-3C)alkyl in R^2 is optionally substituted with one or more R^{2c};

R^{2a} and R^{2b} are each independently selected from the group consisting of hydrogen, (1-3C)alkyl and (1-3C)haloalkyl;

each R^{2c} is independently selected from the group consisting of hydroxy, halogen, cyano, amino, (1-3C)alkyl, (1-3C)alkoxy and (1-3C)haloalkyl;

each L^1 is a group:

$$-(W)_n-(X)_m-(Y)_o-(Z)_p-$$

in which

n and o are each independently 0, 1 or 2, and m and p are each independently 0 or 1, with the provisos that when m and p are both 1, o is not 0;

each W is selected from the group consisting of (1-3C)alkylene, (2-3C)alkenylene, (2-3C)alkynylene, arylene, heteroarylene, carbocyclylene and heterocyclylene, where any (1-3C)alkylene, (2-3C)alkenylene, (2-3C)alkynylene, arylene, heteroarylene, carbocyclylene or heterocyclylene in W is optionally substituted with one or more W^a, where each W^a is independently selected from the group consisting of hydroxy, cyano, halogen, amino, (1-2)alkoxy and (1-2C)haloalkyl;

X is selected from the group consisting of -O-, -C(O)-, -C(O)-O-, -O-C(O)-, -$S(O)_{0-2}$-, -C(O)-$N(R^x)$-, -$N(R^x)$-C(O)-, -NR^x-, -$N(R^x)$-C(O)-NR^x-, -$SO_2N(R^x)$-, and -$N(R^x)SO_2$, where each R^x is independently selected from the group consisting of hydrogen, hydroxy, cyano, (1-4C)alkyl, (2-4C)alkenyl and (2-4C)alkynyl;

each Y is selected from the group consisting of (1-3C)alkylene, (2-3C)alkenylene, (2-3C)alkynylene, arylene, heteroarylene, carbocyclylene and heterocyclylene, where any (1-3C)alkylene, (2-3C)alkenylene, (2-3C)alkynylene, arylene, heteroarylene, carbocyclylene or heterocyclylene in Y is optionally substituted with one or more Y^a, where each Y^a is independently selected from the group consisting of hydroxy, cyano, halogen, amino, (1-2)alkoxy and (1-2C)haloalkyl;

Z is selected from the group consisting of -O-, -C(O)-, -C(O)-O-, -O-C(O)-, -$S(O)_{0-2}$-, -C(O)-$N(R^z)$-, -$N(R^z)$-C(O)-, -NR^z-, -$N(R^z)$-C(O)-NR^z-, -$SO_2N(R^z)$-, and -$N(R^z)SO_2$, where each R^z is independently selected from the group consisting of hydrogen, hydroxy, cyano, (1-4C)alkyl, (2-4C)alkenyl and (2-4C)alkynyl;

X^a is a ring heteroatom located within ring A and is selected from N and O;

each ring A is a monocyclic heteroaryl, bicyclic heteroaryl, monocyclic heterocycle or bicyclic heterocycle, any one of which is optionally substituted with one or more R^4, where each R^4 is independently selected from the group consisting of hydroxy, cyano, halogen, (1-6C)alkyl, (1-6C)haloalkyl, (2-6C)alkenyl, (2-6C)alkynyl, aryl, aryl(1-3C)alkyl, heteroaryl, heteroaryl(1-3C)alkyl, carbocyclyl, carbocyclyl(1-3C)alkyl, heterocyclyl, heterocyclyl(1-3C)alkyl, -R^{4a}-OR^{4b}, -R^{4a}-$NR^{4b}R^{4c}$, -R^{4a}-C(O)-R^{4b}, -R^{4a}-C(O)-OR^{4b}, -R^{4a}-O-C(O)-R^{4b}, -R^{4a}-C(O)-$NR^{4b}R^{4c}$, -R^{4a}-$N(R^{4b})$C(O)-R^{4c} and -R^{4a}-$S(O)_{0-2}R^{4b}$, where any (1-6C)alkyl, (1-6C)haloalkyl, (2-6C)alkenyl, (2-6C)alkynyl, aryl, aryl(1-3C)alkyl, heteroaryl, heteroaryl(1-3C)alkyl, carbocyclyl, carbocyclyl(1-3C)alkyl, heterocyclyl or heterocyclyl(1-3C)alkyl in R^4 is optionally substituted with one or more R^{4d};

R^{4a} is absent or is (1-3C)alkylene that is optionally substituted with one or substituents selected from group consisting of hydroxy, halo and amino;

R^{4b} and R^{4c} are each independently selected from the group consisting of hydrogen, (1-3C)alkyl and (1-3C)haloalkyl;

each R^{4d} is independently selected from the group consisting of hydroxy, halogen, cyano, amino, (1-3C)alkyl, (1-3C)alkoxy and (1-3C)haloalkyl;

X^b is a ring heteroatom located within ring B and is selected from N and O

each ring B is a monocyclic heteroaryl, bicyclic heteroaryl, monocyclic heterocycle or bicyclic heterocycle, any one of which is optionally substituted with one or more R^5, where each R^5 is independently selected from the group consisting of hydroxy, cyano, halogen, (1-6C)alkyl, (1-6C)haloalkyl, (2-6C)alkenyl, (2-6C)alkynyl, aryl, aryl(1-3C)alkyl, heteroaryl, heteroaryl(1-3C)alkyl, carbocyclyl, carbocyclyl(1-3C)alkyl, heterocyclyl, heterocyclyl(1-3C)alkyl, $-R^{5a}-OR^{5b}$, $-R^{5a}-NR^{5b}R^{5c}$, $-R^{5a}-C(O)-R^{5b}$, $-R^{5a}-C(O)-OR^{5b}$, $-R^{5a}-O-C(O)-R^{5b}$, $-R^{5a}-C(O)-NR^{5b}R^{5c}$, $-R^{5a}-N(R^{5b})C(O)-R^{5c}$ and $-R^{5a}-S(O)_{0-2}R^{5b}$, where any (1-6C)alkyl, (1-6C)haloalkyl, (2-6C)alkenyl, (2-6C)alkynyl, aryl, aryl(1-3C)alkyl, heteroaryl, heteroaryl(1-3C)alkyl, carbocyclyl, carbocyclyl(1-3C)alkyl, heterocyclyl or heterocyclyl(1-3C)alkyl in R^5 is optionally substituted with one or more R^{5d};

R^{5a} is absent or is (1-3C)alkylene that is optionally substituted with one or substituents selected from group consisting of hydroxy, halo and amino;

R^{5b} and R^{5c} are each independently selected from the group consisting of hydrogen, (1-5C)alkyl (e.g. (1-3C)alkyl) and (1-3C)haloalkyl;

each R^{5d} is independently selected from the group consisting of hydroxy, halogen, cyano, amino, (1-3C)alkyl, (1-3C)alkoxy and (1-3C)haloalkyl; and

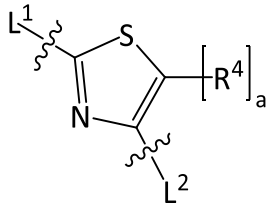
each L^2 is selected from the group consisting of absent (in which case ring A is bonded directly to ring B), (1-2C)alkylene, ethenylene and ethynylene, where any (1-2C)alkylene, ethenylene and ethynylene in L^2 is optionally substituted with one or more substituents selected form the group consisting of hydroxy, halogen, cyano, amino, (1-3C)alkyl, (1-3C)alkoxy and (1-3C)haloalkyl;

and wherein the compound of Formula I, or the pharmaceutically acceptable salt, hydrate or solvate thereof, is for use in combination with a source of M, wherein M is selected from the group consisting of Zn^{2+}, Mn^{2+}, Cu^{2+}, Fe^{2+}, Co^{2+} and Ni^{2+}.

2. The compound, pharmaceutically acceptable salt, hydrate or solvate for use according to claim 1, wherein each ring A is a 5-6 membered monocyclic heteroaryl containing 1, 2 or 3 ring heteroatoms in total independently selected from N, O and S, or a 5-6 membered monocyclic heterocycle containing 1, 2 or 3 ring heteroatoms in total independently selected from N, O and S, wherein each ring A is optionally substituted with one or more R^4, and
X^a is located immediately adjacent the carbon atom bonded to L^1;

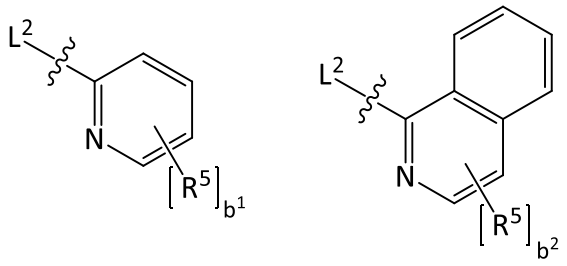
3. The compound, pharmaceutically acceptable salt, hydrate or solvate for use according to claim 1 or 2, wherein each ring B is:
i) a 5-6 membered monocyclic heterocycle containing 1, 2 or 3 ring heteroatoms in total that are independently selected from N, O and S;
ii) a 5-6 membered monocyclic heteroaryl containing 1, 2 or 3 ring heteroatoms in total that are independently selected from N, O and S;
iii) a 9-10 membered bicyclic heterocycle containing 1, 2 or 3 ring heteroatoms in total that are independently selected from N, O and S; or
iv) a 9-10 membered bicyclic heteroaryl containing 1, 2 or 3 ring heteroatoms in total that are independently selected from N, O and S,
wherein any ring in B is optionally substituted with one or more R^5, and
X^b is located immediately adjacent the carbon atom bonded to L^2.

4. The compound, pharmaceutically acceptable salt, hydrate or solvate for use according to claim 1, 2 or 3, wherein each ring A is group:



wherein a is 0 or 1.

5. The compound, pharmaceutically acceptable salt, hydrate or solvate for use according to any preceding claim, wherein each ring B is any of the following:



wherein:
b^1 is 0, 1 or 2, and
b^2 is 0, 1, 2 or 3.

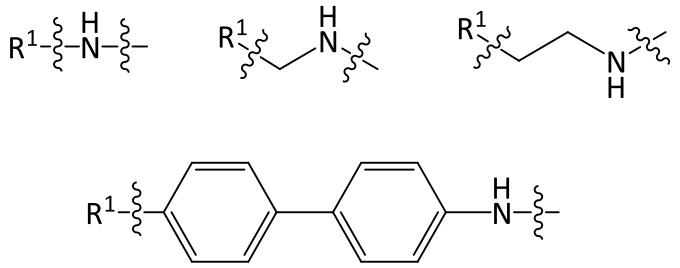
6. The compound, pharmaceutically acceptable salt, hydrate or solvate for use according to any preceding claim, wherein
each W is selected from the group consisting of (1-3C)alkylene or phenylene, where any (1-3C)alkylene or phenylene in W is optionally substituted with one or more W^a;
X is selected from the group consisting of -C(O)-N(R^x)-, -N(R^x)-C(O)- and -NR^x-;
each Y is selected from the group consisting of (1-3C)alkylene or phenylene, where any (1-3C)alkylene or phenylene in Y is optionally substituted with one or more Y^a; and
Z is selected from the group consisting of -C(O)-N(R^z)-, -N(R^z)-C(O)- and -NR^z-.

7. The compound, pharmaceutically acceptable salt, hydrate or solvate for use according to any preceding claim, wherein:
n is 0 or 1 and W is selected from the group consisting of (1-3C)alkylene or phenylene, where any (1-3C)alkylene or phenylene in W is optionally substituted with one or more W^a, where each W^a is independently selected from the group consisting of hydroxy, halogen, (1-2)alkoxy and (1-2C)haloalkyl;
m is 0;
o is 0 or 1 and Y is selected from the group consisting of (1-3C)alkylene or phenylene, where any (1-3C)alkylene or phenylene in Y is optionally substituted with one or more Y^a, where each Y^a is independently selected from the group consisting of hydroxy, halogen, (1-2)alkoxy and (1-2C)haloalkyl; and
p is 1 and Z is -NR^z-, where R^z is hydrogen.

8. The compound, pharmaceutically acceptable salt, hydrate or solvate for use according to any preceding claim, wherein:
n is 0 or 1 and W is selected from the group consisting of (1-3C)alkylene or phenylene, where any (1-3C)alkylene or phenylene in W is optionally substituted with one or more W^a,

where each W^a is independently selected from the group consisting of hydroxy, halogen, (1-2)alkoxy and (1-2C)haloalkyl;
m is 0;
o is 0 or 1 and Y is selected from the group consisting of (1-3C)alkylene or phenylene, where any (1-3C)alkylene or phenylene in Y is optionally substituted with one or more Y^a, where each Y^a is independently selected from the group consisting of hydroxy, halogen, (1-2)alkoxy and (1-2C)haloalkyl; and
p is 1 and Z is $-NR^z-$, where R^z is hydrogen.

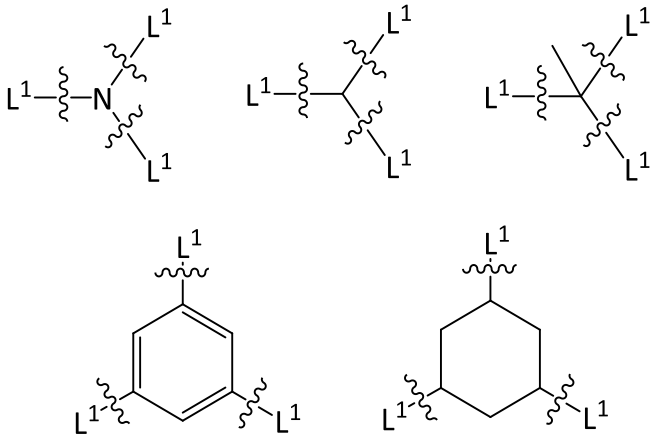
9. The compound, pharmaceutically acceptable salt, hydrate or solvate for use according to any preceding claim, wherein L^1 has a structure according to any one of the following:



10. The compound, pharmaceutically acceptable salt, hydrate or solvate for use according to any preceding claim, wherein L^2 is selected from the group consisting of absent and (1-2C)alkylene, where any (1-2C)alkylene in L^2 is optionally substituted with one or more substituents selected form the group consisting of hydroxy, halogen and (1-2C)haloalkyl.

11. The compound, pharmaceutically acceptable salt, hydrate or solvate for use according to any preceding claim, wherein
R^1 is selected from the group consisting of N, CR^2, phenyl and cyclohexyl, where any phenyl or cyclohexyl in R^1 is optionally substituted with one or more R^3;
each R^3 is independently selected from the group consisting of hydroxy, halogen, (1-4C)alkyl, (1-4C)haloalkyl and $-OR^{3a}$, where any (1-4C)alkyl or (1-4C)haloalkyl in R^3 is optionally substituted with one or more R^{3c};
R^2 is selected from the group consisting of hydrogen, and (1-3C)alkyl, where any (1-4C)alkyl in R^2 is optionally substituted with one or more R^{2c}.

12. The compound, pharmaceutically acceptable salt, hydrate or solvate for use according to any preceding claim, wherein R^1 has a structure according to any one of the following:



13. The compound, pharmaceutically acceptable salt, hydrate or solvate for use according to any preceding claim, wherein R^{5b} and R^{5c} are each independently selected from the group consisting of hydrogen, (1-3C)alkyl and (1-3C)haloalkyl.

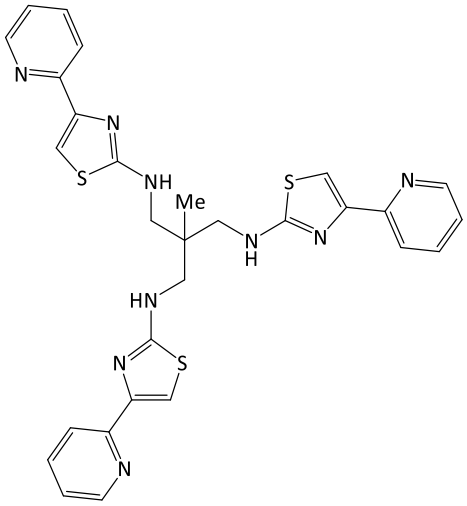
14. The compound, pharmaceutically acceptable salt, hydrate or solvate for use according to any preceding claim, wherein M is selected from the group consisting of Zn^{2+}, Cu^{2+}, Mn^{2+} and Fe^{2+}.

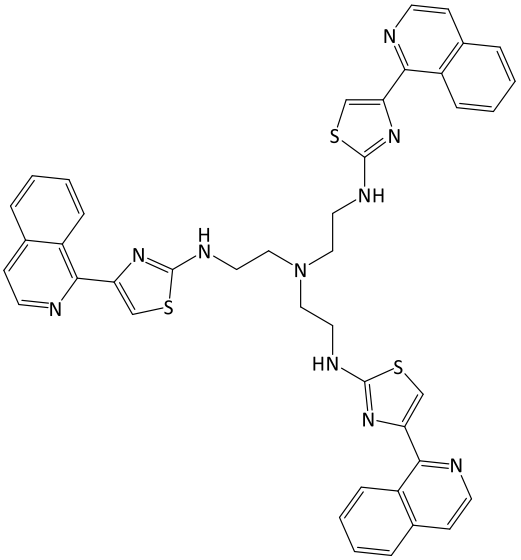
15. The compound, pharmaceutically acceptable salt, hydrate or solvate for use according to any preceding claim, wherein the compound of Formula I, or a pharmaceutically acceptable salt, hydrate or solvate thereof, is in further combination with a source of Q, wherein Q is an anion selected from the group consisting of spherical monoanionic anions, trigonal planar anions, dianionic tetrahedral anions, trianionic tetrahedral anions, dianionic octahedral anions and trianionic octahedral anions.

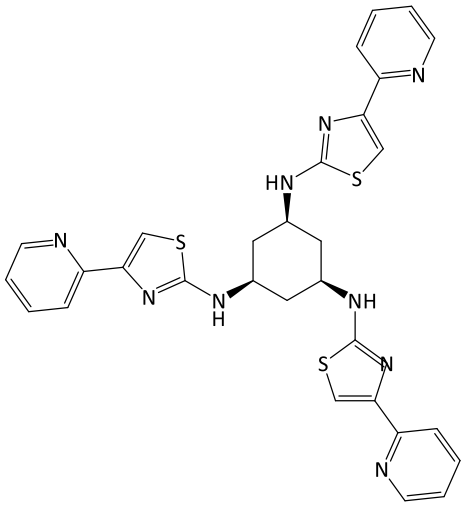
16. The compound, pharmaceutically acceptable salt, hydrate or solvate for use according to claim 15, wherein Q is an anion selected from the group consisting of dianionic tetrahedral oxoanions and trianionic tetrahedral oxoanions.

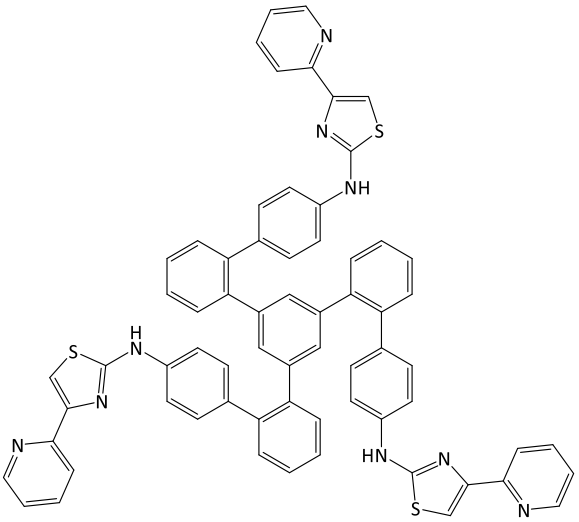
17. The compound, pharmaceutically acceptable salt, hydrate or solvate for use according to claim 15 or 16, wherein Q is sulfate (SO_4^{2-}), phosphate (PO_4^{3-}) or organophosphate (such as monophenylphosphate).

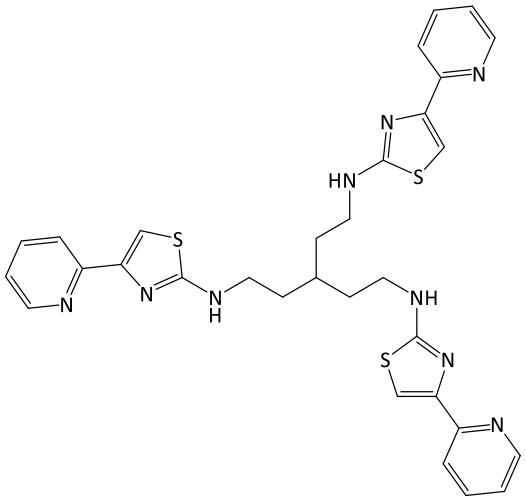
18. The compound, pharmaceutically acceptable salt, hydrate or solvate for use according to any preceding claim, wherein the compound of Formula I has a structure according to any one of the following:

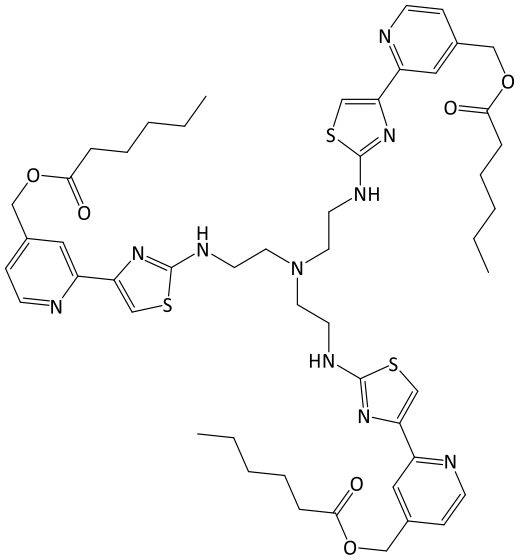


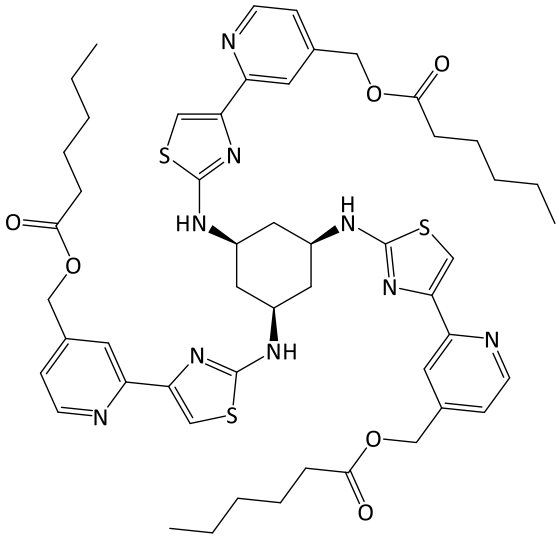


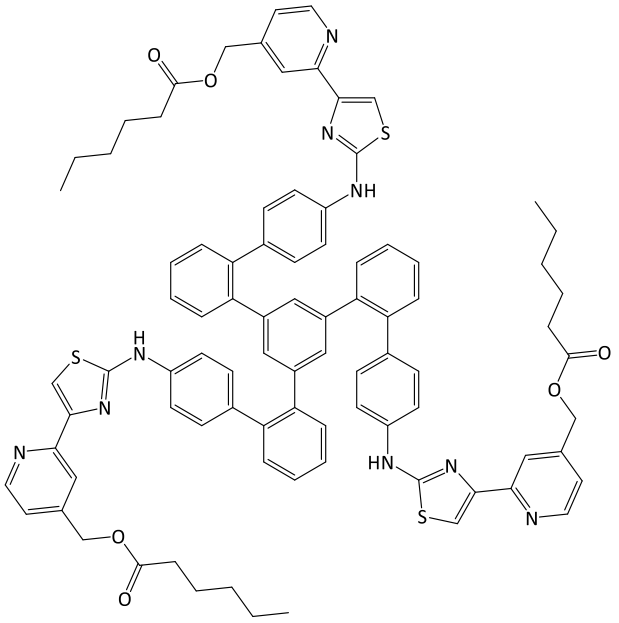


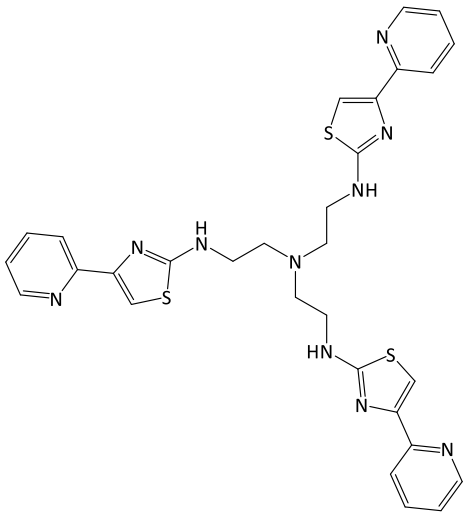






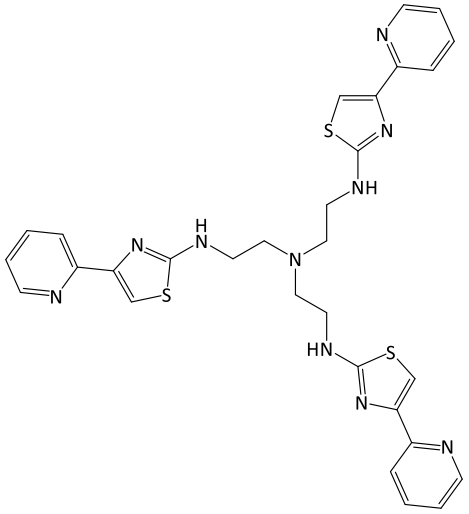






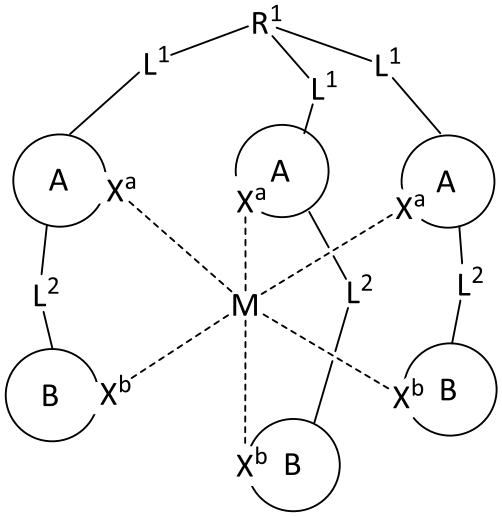
or a pharmaceutically-acceptable salt, hydrate and/or solvate thereof.

19. The compound, pharmaceutically acceptable salt, hydrate or solvate for use according to any preceding claim, wherein the compound of Formula I has the structure:



or a pharmaceutically-acceptable salt, hydrate and/or solvate thereof.

20. A compound having a structure according to Formula II shown below, or a pharmaceutically acceptable salt, hydrate or solvate thereof, for use as a medicament:



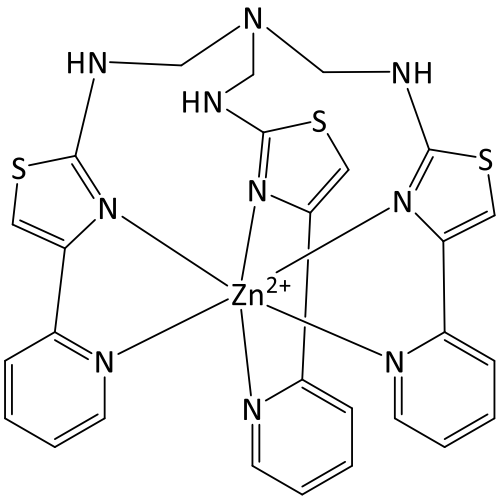
Formula II

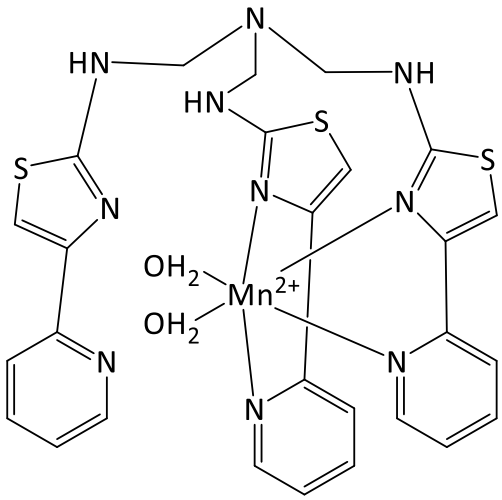
wherein

M, R^1, L^1, A, X^a, L^2, B, X^b and any associated subgroups are as defined in any preceding claim.

21. The compound, pharmaceutically acceptable salt, hydrate or solvate for use according to claim 20, wherein the compound of Formula II, or a pharmaceutically acceptable salt, hydrate or solvate thereof, is in further combination with a source of Q as defined in any one of claims 15, 16 and 17.

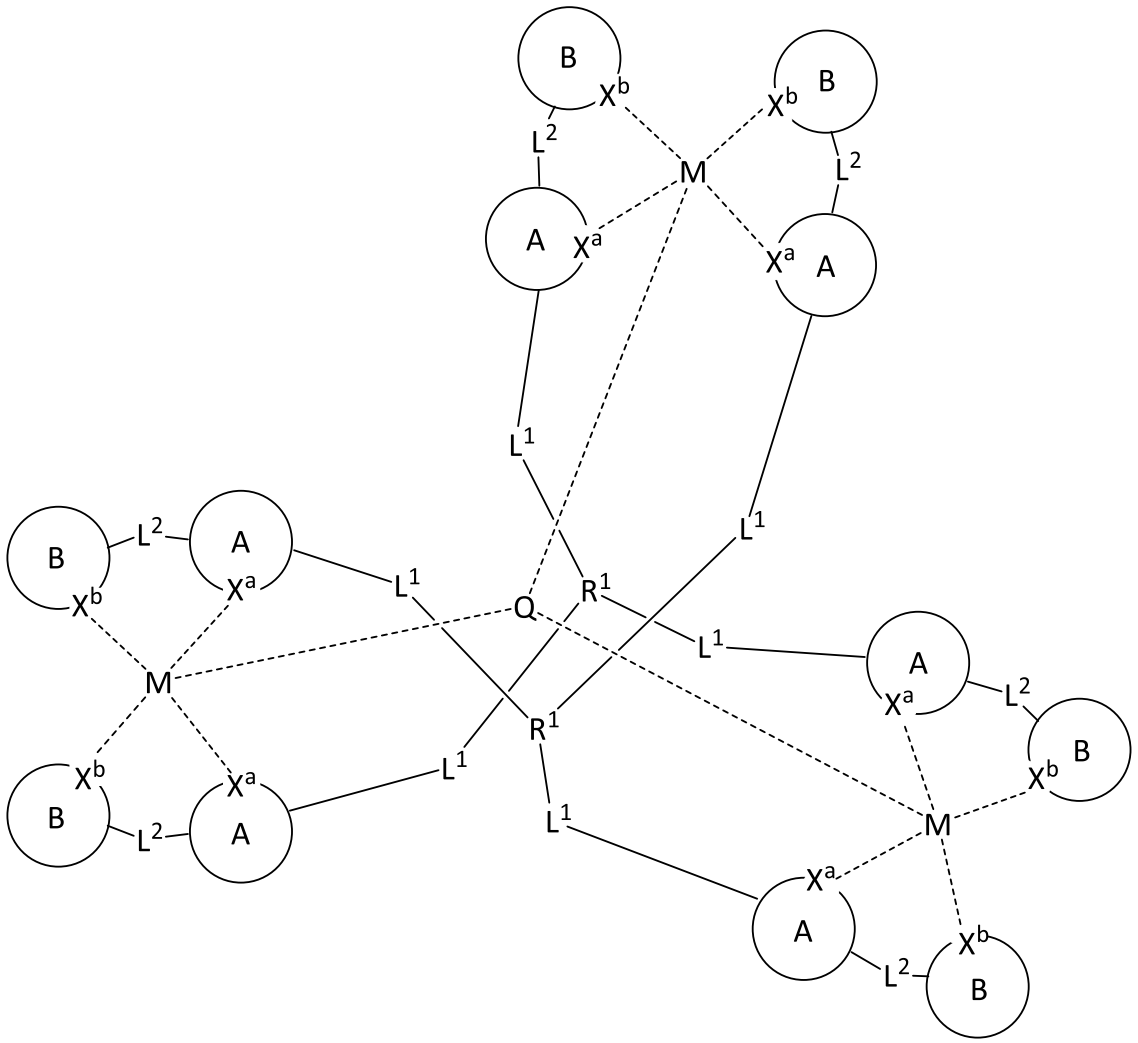
22. The compound, pharmaceutically acceptable salt, hydrate or solvate for use according to claim 20 or 21, wherein the compound of Formula II has a structure according to any one of the following:





or a pharmaceutically-acceptable salt, hydrate and/or solvate thereof.

23. A compound having a structure according to Formula III shown below, or a pharmaceutically acceptable salt, hydrate or solvate thereof, for use as a medicament:

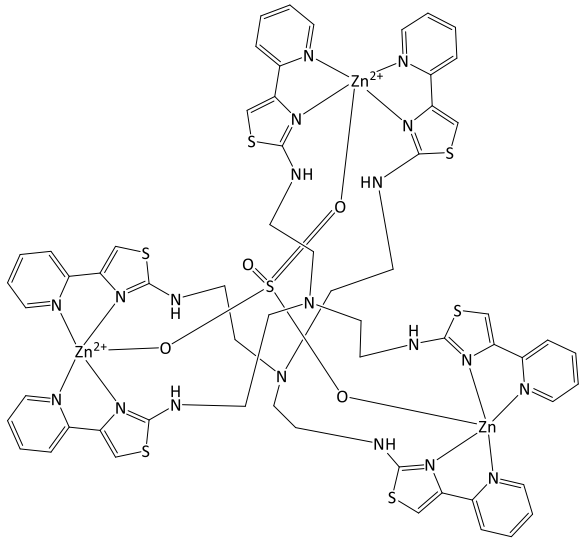


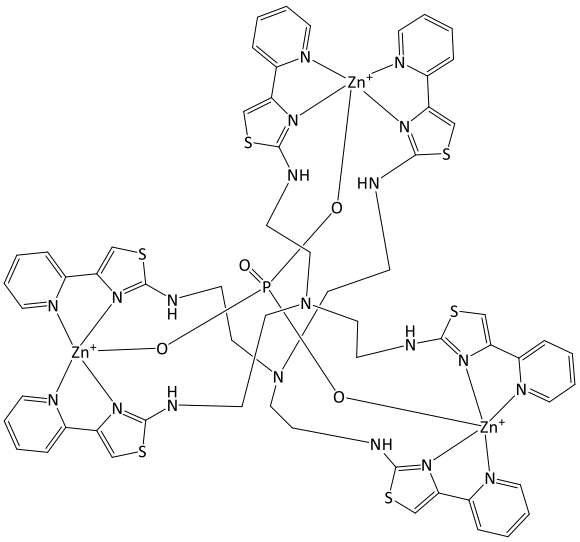
Formula III

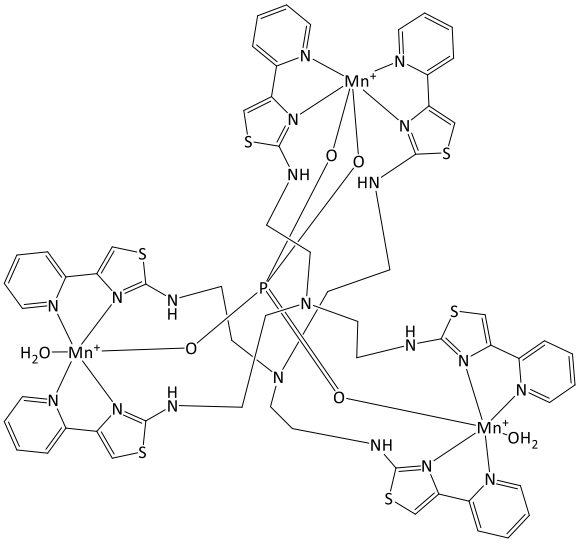
wherein

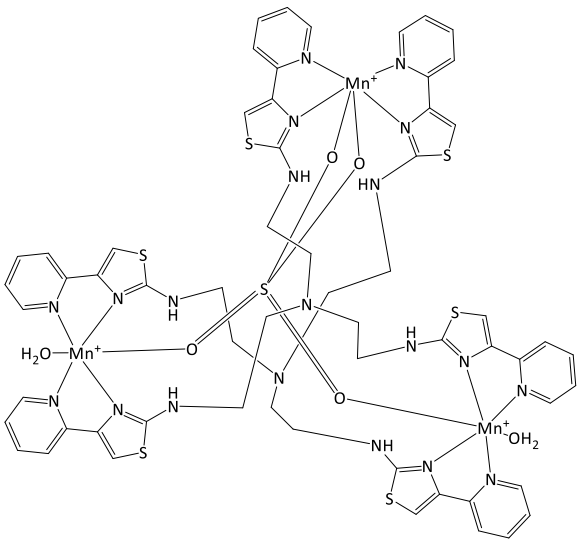
M, Q, R^1, L^1, A, X^a, L^2, B, X^b and any associated subgroups are as defined in any one of claims 1-19.

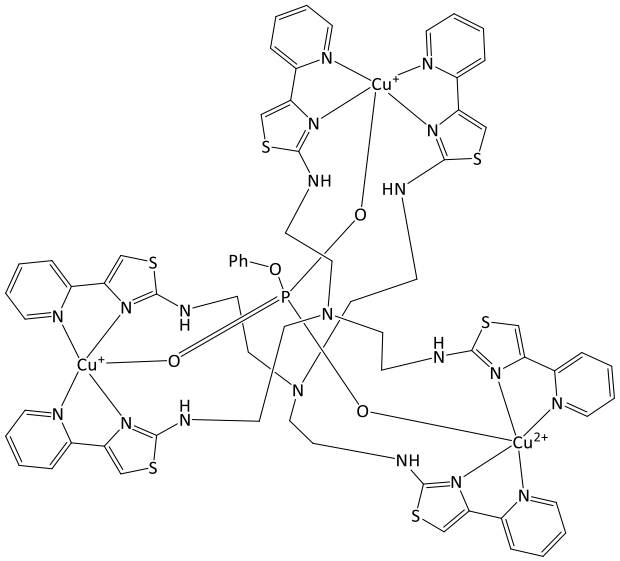
24. The compound, pharmaceutically acceptable salt, hydrate or solvate for use according to claim 23, wherein the compound of Formula III has a structure according to any one of the following:











or a pharmaceutically-acceptable salt, hydrate and/or solvate thereof.

25. The compound, pharmaceutically acceptable salt, hydrate or solvate for use according to any preceding claim, wherein the medicament is for the treatment of a proliferative disorder (e.g. cancer).

26. Use of the compound, pharmaceutically acceptable salt, hydrate or solvate according to claims 1-24, in the manufacture of a medicament for treatment of a proliferative disorder (e.g. cancer).