CLAIMS

1) A MTA synergistic PRMT5 inhibitor for use in the treatment of cancer, wherein the cancer is characterised as being wild type *MTAP* gene silenced.

2) Use of a MTA synergistic PRMT5 inhibitor in the manufacture of a medicament, wherein the medicament is for use in the treatment of a cancer that is wild type *MTAP* gene silenced.

3) A pharmaceutical composition comprising a MTA synergistic PRMT5 inhibitor for use in the treatment of cancer, wherein the cancer is characterised as being wild type *MTAP* gene silenced.

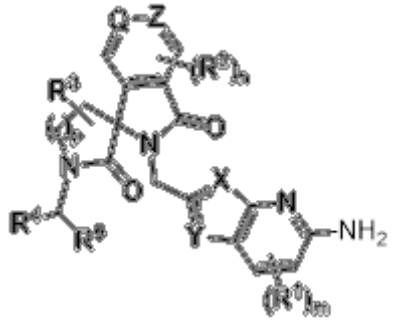
4) A kit comprising a MTA synergistic inhibitor and instructions for its use in the treatment of a *MTAP* gene silenced cancer.

5) A inhibitor for use, use, composition for use or kit according to any one of claims 1 to 4, wherein the wild type *MTAP* gene silenced cancer is selected from bladder cancer, breast cancer, Diffuse Large B-cell Lymphoma (DLBCL), Hodgkin Lymphoma, kidney cancer, leukaemia, lung cancer, Non-Hodgkin Lymphoma, ovarian cancer, pancreatic, sarcoma and skin cancer.

6) A inhibitor for use, use, composition for use or kit according to claim 5, wherein the wild type *MTAP* gene silenced cancer is Hodgkin Lymphoma.

7) A inhibitor for use, use, composition for use or kit according to claim 6, wherein the Hodgkin Lymphoma is a classical Hodgkin Lymphoma, such as nodular sclerosing (NSHL), mixed cellularity (MCHL), lymphocyte-rich (LRHL) and lymphocyte depleted (LDHL) or nodular lymphocyte-predominant Hodgkin Lymphoma.

8) A inhibitor for use, use, composition for use or kit according to any one of claims 1 to 7, wherein the MTA synergistic PRMT5 inhibitor is a compound of Formula (IV), or a pharmaceutically acceptable salt thereof:



(IV)

wherein:

the ring containing X and Y is a pyrrole and X is NH and Y is CH or X is CH and Y is NH;

Z is selected from CH, CF, CCl or, if Q is not N, N;

Q is selected from CH, CF, CCl or, if Z is not N, N;

m is 0, 1 or 2;

n is 0, 1 or 2;

p is 1 or 2;

R^1 is in each occurrence independently selected from F, Cl, CN, Me, CF_3, C_1-C_3 alkyl, cyclopropyl, C_1-C_3 fluoroalkyl, OMe or C_1-C_3 alkoxy;

R^2 is in each occurrence independently selected from F, Cl, Me, MeO and CF_3;

R^3 is H, Me, C_1-C_3 alkyl or C_1-C_3 fluoroalkyl;

R^4 is H, Me or C_1-C_3 alkyl;

R^5 is H, Me, C_1-C_3 alkyl, C_1-C_3 fluoroalkyl, CH_2OMe, CH_2OCHF_2, CH_2OCF_3, $CH_2O(C_1$-C_3 alkyl), $CH_2O(C_1$-C_3 fluoroalkyl), $C(CH_2CH_2)R^6$, CCR^7, CH_2R^8, R^9 or CH_2R^{10};

R^6 is H, Me, CH_2F, CHF_2, CF_3, CH_2OH or CH_2OMe;

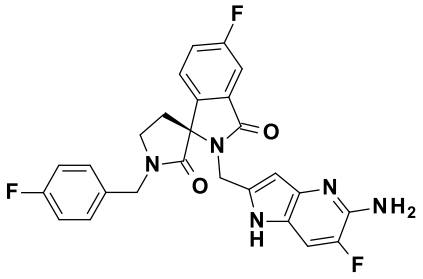
R^7 is H, Me, cyclopropyl, C_1-C_3 alkyl, C_1-C_3 fluoroalkyl, C_3-C_6 cycloalkyl or a 5-membered heteroaryl group optionally substituted with Me, C_1-C_3 alkyl, F or Cl;

R^8 is a 5-membered heteroaryl optionally substituted with Me, C_1-C_3 alkyl, F or Cl;

R^9 is an optionally substituted phenyl, 5- or 6-membered heteroaryl, or bicyclic heteroaryl group; and

R^{10} is an optionally substituted phenyl, 5- or 6-membered heteroaryl, or bicyclic heteroaryl group.

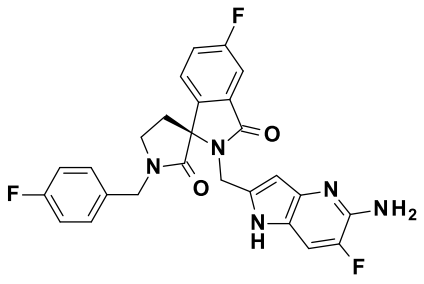
9) A inhibitor for use, use, composition for use or kit according to claim 8, wherein the MTA synergistic PRMT5 inhibitor is (*S*)-2-((5-Amino-6-fluoro-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl)methyl)-5-fluoro-1'-(4-fluorobenzyl)spiro[isoindoline-1,3'-pyrrolidine]-2',3-dione:



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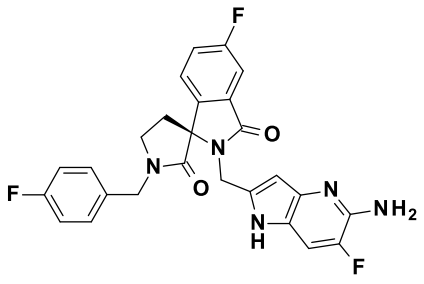
or a pharmaceutically acceptable salt thereof.

10) A inhibitor for use, use, composition for use or kit according to claim 9, wherein the MTA synergistic PRMT5 inhibitor is (*S*)-2-((5-Amino-6-fluoro-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl)methyl)-5-fluoro-1'-(4-fluorobenzyl)spiro[isoindoline-1,3'-pyrrolidine]-2',3-dione:



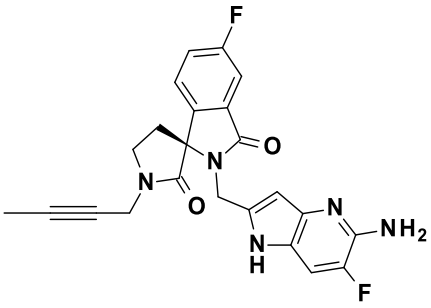
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11) A inhibitor for use, use composition for use or kit according to claim 9, wherein the MTA synergistic PRMT5 inhibitor is a pharmaceutically acceptable salt of (*S*)-2-((5-Amino-6-fluoro-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl)methyl)-5-fluoro-1'-(4-fluorobenzyl)spiro[isoindoline-1,3'-pyrrolidine]-2',3-dione:



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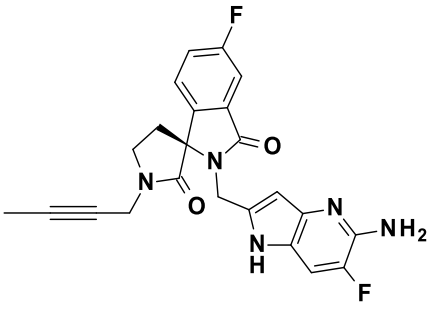
12) A inhibitor for use, use, composition for use or kit according to claim 8, wherein the MTA synergistic PRMT5 inhibitor is (*S*)-2-((5-Amino-6-fluoro-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl)methyl)-1'-(but-2-yn-1-yl)-5-fluorospiro[isoindoline-1,3'-pyrrolidine]-2',3-dione:



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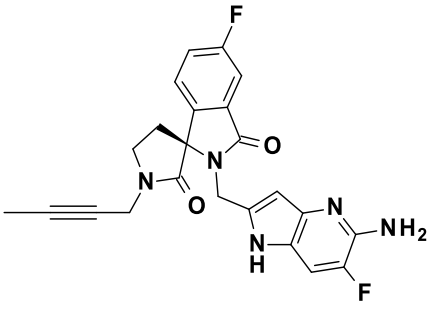
or a pharmaceutically acceptable salt thereof.

13) A inhibitor for use, use, composition for use or kit according to claim 12, wherein the MTA synergistic PRMT5 inhibitor is (*S*)-2-((5-Amino-6-fluoro-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl)methyl)-1'-(but-2-yn-1-yl)-5-fluorospiro[isoindoline-1,3'-pyrrolidine]-2',3-dione:



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14) A inhibitor for use, use, composition for use or kit according to claim 12, wherein the MTA synergistic PRMT5 inhibitor is a pharmaceutically acceptable salt of (*S*)-2-((5-Amino-6-fluoro-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl)methyl)-1'-(but-2-yn-1-yl)-5-fluorospiro[isoindoline-1,3'-pyrrolidine]-2',3-dione:



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