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(54) Title: COMBINATION THERAPIES COMPRISING A METTL3 INHIBITOR AND A FURTHER ANTICANCER AGENT

(57) Abstract: The present invention relates to novel combination therapies for the treatment of proliferative disorders, such as, for example, cancer. The combination therapies comprises the administration of a METTL3 inhibitor in combination with (i) an immune oncology agent or therapy; (ii) a BCL2 inhibitor, or a pharmaceutically acceptable salt thereof; (iii) an anthracycline topoisomerase 2 inhibitor, or a pharmaceutically acceptable salt thereof; (iv) cytarabine, or a pharmaceutically acceptable salt thereof; (v) a hypomethylating agent, or a pharmaceutically acceptable salt thereof; or (vi) a FLT3 inhibitor, or a pharmaceutically acceptable salt thereof.

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COMBINATION THERAPIES COMPRISING A METTL3 INHIBITOR AND A FURTHER ANTICANCER AGENT

FIELD OF THE INVENTION

[001] The present invention relates to novel combination therapies for the treatment of cancer.

BACKGROUND OF THE INVENTION

[002] Cancer is caused by uncontrolled and unregulated cellular proliferation. Precisely what causes a cell to become malignant and proliferate in an uncontrolled and unregulated manner has been the focus of intense research over recent decades. This research has led to the identification of a number of molecular targets and key metabolic pathways that are known to be associated with malignancy.

[003] Despite numerous advances in the treatment of cancer, there remains a need for new therapies that provide improved therapeutic outcomes.

[004] One particular target that is attracting interest is METTL3. N^6-methyladenosine (m^6A) is an abundant internal RNA modification that is catalysed predominantly by the METTL3–METTL14 methyltransferase complex. The m^6A methyltransferase METTL3 has been linked to the initiation and maintenance of acute myeloid leukaemia (AML). Yankova *et al.* (Nature: volume 593, pages597–601 (2021)) describe the identification and characterisation of STM2457, a highly potent and selective first-in-class catalytic inhibitor of METTL3. Treatment with STM2457 resulted in a reduction in AML growth and an increase in differentiation and apoptosis. These cellular effects are accompanied by selective reduction of m^6A levels on known leukaemogenic mRNAs and a decrease in their expression consistent with a translational defect. The pharmacological inhibition of METTL3 *in vivo* led to impaired engraftment and prolonged survival in various mouse models of AML, specifically targeting key stem cell subpopulations of AML. METTL3 is therefore a potential therapeutic strategy against AML, and the targeting of RNA-modifying enzymes represents a promising avenue for anticancer therapy more generally.

[005] International Patent Publication No. WO2020/050898 describes further small molecule METTL3 inhibitors that are suitable for the treatment of cancer.

[006] METTL3 inhibitors clearly show promise for the treatment of AML and other cancers. However, there is always a need to identify new therapeutic strategies that can be used to more imporve therapeutic outcomes.

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

SUMMARY OF THE INVENTION

1. Combinations of METTL3 inhibitors with immuno-oncology agents (e.g. Immune Checkpoint Inhibitors)

[008] Data presented in the example section herein shows that the administration of the METTL3 inhibitor compound STM3480 in combination with an immune checkpoint inhibitor (anti-PD1 and anti-PD-L1) resulted in a significant increase in the observed anti-tumour immune response (when compared to vehicle controls and the treatment with either the METTL3 inhibitor or the immune checkpoint inhibitor alone). Data is presented for tumour killing co-culture cell assays (see Example 1) as well as *in vivo* studies using the A20 B-cell lymphoma model, EMT6 breast cancer model and CT26 colorectal cancer model (see Example 2). Collectively, these data suggest that the administration of a METTL3 inhibitor together with an immune checkpoint inhibitor significantly enhances the anti-tumour immune response. METTL3 inhibition may therefore play a role in sensitising the cancer cells to immune checkpoint inhibitor therapy.

[009] Thus, the present invention relates, in one aspect, to a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, for use as an immune-sensitiser.

[0010] The present invention also relates to the use of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use as an immune-sensitiser.

[0011] The present invention also relates to a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, wherein the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, is administered in combination with an immune oncology agent or therapy (e.g. immune checkpoint inhibitors (e.g. a PD1, PD-L1 inhibitor, LAG3, CTLA-4, TIGIT, TIM3, or VISTA inhibitor), STING agonists, TLR agonists, anti-CD137 antibodies, CD28 antibodies, OX40 stimulators, CD40 antibodies, ICOS agonists, GITR agonists, A2AR antagonists, Bispecific T cell engagers (BiTE), oncolytic viruses, cancer vaccines, and/or CAR-T cell therapy).

[0012] The present invention also relates to the use of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in

the treatment of cancer, wherein the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, is administered in combination with an immune oncology agent or therapy (e.g. immune checkpoint inhibitors (e.g. a PD1, PD-L1 inhibitor, LAG3, CTLA-4, TIGIT, TIM3, or VISTA inhibitor), STING agonists, TLR agonists, anti-CD137 antibodies, CD28 antibodies, OX40 stimulators, CD40 antibodies, ICOS agonists, GITR agonists, A2AR antagonists, Bispecific T cell engagers (BiTE), oncolytic viruses, cancer vaccines, and/or CAR-T cell therapy).

[0013] The present invention also relates to a method of treating cancer, the method comprising administering a therapeutically effective amount of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, to a patient in combination with an immune oncology agent or therapy (e.g. immune checkpoint inhibitors (e.g. a PD1, PD-L1 inhibitor, LAG3, CTLA-4, TIGIT, TIM3, or VISTA inhibitor), STING agonists, TLR agonists, anti-CD137 antibodies, CD28 antibodies, OX40 stimulators, CD40 antibodies, ICOS agonists, GITR agonists, A2AR antagonists, Bispecific T cell engagers (BiTE), oncolytic viruses, cancer vaccines, and/or CAR-T cell therapy).

[0014] Suitably, the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, is administered simultaneously, sequentially or separately with the immune oncology agent or therapy (e.g. immune checkpoint inhibitors (e.g. a PD1, PD-L1 inhibitor, LAG3, CTLA-4, TIGIT, TIM3, or VISTA inhibitor), STING agonists, TLR agonists, anti-CD137 antibodies, CD28 antibodies, OX40 stimulators, CD40 antibodies, ICOS agonists, GITR agonists, A2AR antagonists, Bispecific T cell engagers (BiTE), oncolytic viruses, cancer vaccines, and/or CAR-T cell therapy.

[0015] In one aspect the present invention relates to a combination comprising a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, and an immune checkpoint inhibitor, or a pharmaceutically acceptable salt thereof.

[0016] In another aspect the present invention relates to a pharmaceutical product comprising a combination as defined herein.

[0017] In another aspect, the present invention relates to a pharmaceutical composition comprising a combination as defined herein, and one or more pharmaceutically acceptable excipients.

[0018] In another aspect, the present invention relates to a combination as defined herein, or a pharmaceutical product as defined herein, or a pharmaceutical composition as defined herein for use in therapy.

[0019] In another aspect, the present invention relates to a combination as defined herein, or a pharmaceutical product as defined herein, or a pharmaceutical composition as defined herein for use in the treatment of cancer.

[0020] In another aspect, the present invention relates to a use of a combination as defined herein in the manufacture of a medicament for the treatment of cancer.

[0021] In another aspect, the present invention relates to a method of treating of cancer in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a combination as defined herein.

[0022] In another aspect, the present invention relates to a method of potentiating the immune response to a tumour, the method comprising administering to a patient in need of such treatment a therapeutically effective amount of a combination as defined herein.

[0023] In another aspect, the present invention relates to a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, wherein the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, is for simultaneous, separate or sequential administration with an immune checkpoint inhibitor, or a pharmaceutically acceptabel salt thereof.

[0024] In another aspect, the present invention relates to an immune checkpoint inhibitor, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, wherein the immune checkpoint inhibitor is for simultaneous, separate or sequential administration with a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof.

[0025] In another aspect, the present invention relates to a use of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer, wherein the medicament is for simultaneous, separate or sequential administration with an immune checkpoint inhibitor, or a pharmaceutically acceptable salt thereof.

[0026] In another aspect, the present invention relates to a use of an immune checkpoint inhibitor, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer, wherein the medicament is for simultaneous, separate or sequential administration with a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof.

[0027] In another aspect, the present invention relates to a method of treating cancer comprising adminstering to a subject in need thereof a therapeutically effective amount of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, and an immune checkpoint inhibitor, or a pharmaceutically acceptable salt thereof, wherein the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, and the immune checkpoint inhibitor, or a pharmaceutically acceptable salt thereof are administered sequentially, separately or simultaneously with one another.

[0028] In another aspect, the present invention relates to a method of treating cancer or potentiating the effect of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, the method comprising administering to a patient in need of such treatment a therapeutically effective amount of the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, separately, sequentially or simultaneously with an immune checkpoint inhibitor, or a pharmaceutically acceptable salt thereof.

[0029] In another aspect, the present invention relates to a method of potentiating the immune response to a tumour, the method comprising administering to a patient in need of such treatment a therapeutically effective amount of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, and an immune checkpoint inhibitor, or a pharmaceutically acceptable salt thereof, wherein the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, and the immune checkpoint inhibitor, or a pharmaceutically acceptable salt thereof are administered sequentially, separately or simultaneously with one another.

[0030] Suitably, the cancer is a solid tumour.

2. Combinations of METTL3 inhibitors with BCL2 inhibitors (e.g. Venetoclax)

[0031] Data presented in the example section shows that the METTL3 inhibitor compounds STM3480, STM3006 and STM3675, when administered in combination with a BCL2 inhibitor (venetoclax), produced a synergistic increase in the observed anticancer effect. Data is presented for Kasumi1 and MOLM13 AML cell lines (see Example 3). Collectively, these data suggest that METTL3 inhibition synergistically enhances the antitumour effect of BCL2 inhibitor (e.g. venetoclax) therapy. The combination of a METTL3 inhibitor with a BCL2 inhibitor (e.g. venetoclax) therefore offers a promising therapy for diseases or conditions in which BCL2 inhibitor therapy is beneficial (e.g. the treatment of cancers such as acute myeloid leukaemia (AML), chronic lymphocytic leukaemia (CLL), small lymphocytic lymphoma (SLL) and myelodysplastic syndromes (MDS)).

[0032] Thus, the present invention also relates to a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of diseases or conditions in which BCL2 inhibitor therapy is beneficial (e.g. the treatment of cancer), wherein the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, is administered in combination with a BCL2 inhibitor (e.g. venetoclax).

[0033] The present invention also relates to the use of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of diseases or conditions in which BCL2 inhibitor therapy is beneficial (e.g. the treatment of cancer), wherein the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, is administered in combination with a BCL2 inhibitor (e.g. venetoclax).

[0034] The present invention also relates to a method of treating diseases or conditions in which BCL2 inhibitor therapy is beneficial (e.g. the treatment of cancer), the method comprising administering a therapeutically effective amount of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, to a patient in combination with a BCL2 inhibitor (e.g. venetoclax).

[0035] Suitably, the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, is administered simultaneously, sequentially or separately with the BCL2 inhibitor (e.g. venetoclax) therapy.

[0036] In one aspect the present invention relates to a combination comprising a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, and a BCL2 inhibitor (e.g. venetoclax), or a pharmaceutically acceptable salt thereof.

[0037] In another aspect the present invention relates to a pharmaceutical product comprising a combination as defined above.

[0038] In another aspect, the present invention relates to a pharmaceutical composition comprising a combination as defined above, and one or more pharmaceutically acceptable excipients.

[0039] In another aspect, the present invention relates to a combination as defined above, or a pharmaceutical product as defined above, or a pharmaceutical composition as defined above for use in therapy.

[0040] In another aspect, the present invention relates to a combination as defined herein, or a pharmaceutical product as defined above, or a pharmaceutical composition as defined

above for use in the treatment of diseases or conditions in which BCL2 inhibitor therapy is beneficial (e.g. the treatment of cancer).

[0041] In another aspect, the present invention relates to the use of a combination as defined above in the manufacture of a medicament for the treatment of diseases or conditions in which BCL2 inhibitor therapy is beneficial (e.g. the treatment of cancer).

[0042] In another aspect, the present invention relates to a method of treating of diseases or conditions in which BCL2 inhibitor therapy is beneficial (e.g. the treatment of cancer) in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a combination as defined above.

[0043] In another aspect, the present invention relates to a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, wherein the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, is for simultaneous, separate or sequential administration with a BCL2 inhibitor (e.g. venetoclax), or a pharmaceutically acceptable salt thereof.

[0044] In another aspect, the present invention relates to a BCL2 inhibitor (e.g. venetoclax), or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, wherein the BCL2 inhibitor (e.g. venetoclax), or a pharmaceutically acceptable salt thereof, is for simultaneous, separate or sequential administration with a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof.

[0045] In another aspect, the present invention relates to a use of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer, wherein the medicament is for simultaneous, separate or sequential administration with a BCL2 inhibitor (e.g. venetoclax), or a pharmaceutically acceptable salt thereof.

[0046] In another aspect, the present invention relates to a use of a BCL2 inhibitor (e.g. venetoclax), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer, wherein the medicament is for simultaneous, separate or sequential administration with a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof.

[0047] In another aspect, the present invention relates to a method of treating cancer comprising adminstering to a subject in need thereof a therapeutically effective amount of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, and a BCL2

inhibitor (e.g. venetoclax), or a pharmaceutically acceptable salt thereof, wherein the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, and the BCL2 inhibitor (e.g. venetoclax), or a pharmaceutically acceptable salt thereof, are administered sequentially, separately or simultaneously with one another.

[0048] In another aspect, the present invention relates to a method of treating cancer, or potentiating the effect of a BCL2 inhibitor (e.g. venetoclax), or a pharmaceutically acceptable salt thereof, the method comprising administering to a patient in need of such treatment a therapeutically effective amount the BCL2 inhibitor (e.g. venetoclax), or a pharmaceutically acceptable salt thereof, separately, sequentially or simultaneously with a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof.

[0049] In another aspect, the present invention relates to a method of treating cancer or potentiating the effect of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, the method comprising administering to a patient in need of such treatment a therapeutically effective amount of the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, separately, sequentially or simultaneously with a BCL2 inhibitor (e.g. venetoclax), or a pharmaceutically acceptable salt thereof.

[0050] Suitably, the cancer is selected from acute myeloid leukaemia (AML), chronic lymphocytic leukaemia (CLL), small lymphocytic lymphoma (SLL) and myelodysplastic syndromes (MDS).

3. Combinations of METTL3 inhibitors with anthracycline topoisomerase 2 inhibitors (e.g. daunorubicin), cytarabine, hypomethylating agents (e.g. 5-azacitidine or decitabine) or FLT3 inhibitors (e.g. quizartinib)

[0051] Data presented in the example section herein shows that the METTL3 inhibitor compounds STM3480 and STM3006, when administered in combination with various standard of care drugs for the treatment of AML, such as daunorubicin, cytarabine, 5-azacitidine and quizartinib, produced an enhanced therapeutic effect in Kasumi1 or MOLM-14 AML cell lines (see Example 4). Collectively, these data suggest that the administration of a METTL3 inhibitor enhances the antitumour effects of AML standard of care agents, including anthracycline topoisomerase 2 inhibitors (e.g. daunorubicin), cytarabine, hypomethylating agents (e.g. 5-azacitidine or decitabine), and/or FLT3 inhibitors (e.g. quizartinib).

[0052] The combination of a METTL3 inhibitor with either an anthracycline topoisomerase 2 inhibitor (e.g. daunorubicin), cytarabine, a hypomethylating agent (e.g. 5-azacitidine or decitabine), and/or a FLT3 inhibitors (e.g. quizartinib) therefore offers a promising therapeutic

strategies for the treatment of cancer (e.g. acute myeloid leukaemia (AML), chronic lymphocytic leukaemia (CLL), small lymphocytic lymphoma (SLL) and myelodysplastic syndromes (MDS)).

[0053] Thus, the present invention also relates to a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, wherein the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, is administered in combination with one or more additional agents selected from:

(i) an anthracycline topoisomerase 2 inhibitos (e.g. daunorubicin);

(ii) cytarabine;

(iii) a hypomethylating agent (e.g. 5-azacitidine or decitabine); or

(iv) a FLT3 inhibitor (e.g. quizartinib);

or a pharmaceutically-acceptable salt thereof.

[0054] The present invention also relates to the use of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of cancer, wherein the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, is administered in combination with one or more additional agents selected from:

(i) an anthracycline topoisomerase 2 inhibitor (e.g. daunorubicin);

(ii) cytarabine;

(iii) a hypomethylating agent (e.g. 5-azacitidine or decitabine); or

(iv) a FLT3 inhibitor (e.g. quizartinib);

or a pharmaceutically-acceptable salt thereof.

[0055] The present invention also relates to a method of treating cancer, the method comprising administering a therapeutically effective amount of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, to a patient in combination with one or more additional agents selected from:

(i) an anthracycline topoisomerase 2 inhibitor (e.g. daunorubicin);

(ii) cytarabine;

(iii) a hypomethylating agent (e.g. 5-azacitidine or decitabine); or

(iv) a FLT3 inhibitor (e.g. quizartinib);

or a pharmaceutically-acceptable salt thereof.

[0056] Suitably, the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, is administered simultaneously, sequentially or separately with:

(i) an anthracycline topoisomerase 2 inhibitor (e.g. daunorubicin);

(ii) cytarabine;

(iii) a hypomethylating agent (e.g. 5-azacitidine or decitabine); or

(iv) a FLT3 inhibitor (e.g. quizartinib);

or a pharmaceutically-acceptable salt thereof.

[0057] In one aspect the present invention relates to a combination comprising a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, and one or more additional agents selected from:

(i) an anthracycline topoisomerase 2 inhibitos (e.g. daunorubicin);

(ii) cytarabine;

(iii) a hypomethylating agent (e.g. 5-azacitidine or decitabine); or

(iv) a FLT3 inhibitor (e.g. quizartinib);

or a pharmaceutically-acceptable salt thereof.

[0058] In another aspect the present invention relates to a pharmaceutical product comprising a combination as defined above.

[0059] In another aspect, the present invention relates to a pharmaceutical composition comprising a combination as defined above, and one or more pharmaceutically acceptable excipients.

[0060] In another aspect, the present invention relates to a combination as defined above, or a pharmaceutical product as defined above, or a pharmaceutical composition as defined above for use in therapy.

[0061] In another aspect, the present invention relates to a combination as defined above, or a pharmaceutical product as defined above, or a pharmaceutical composition as defined above for use in the treatment of cancer.

[0062] In another aspect, the present invention relates to the use of a combination as defined above in the manufacture of a medicament for the treatment of cancer.

[0063] In another aspect, the present invention relates to a method of treating of cancer in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a combination as defined above.

[0064] In another aspect, the present invention relates to a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, wherein the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, is for simultaneous, separate or sequential administration with one or more additional agents selected from:

(i) an anthracycline topoisomerase 2 inhibitor (e.g. daunorubicin);

(ii) cytarabine;

(iii) a hypomethylating agent (e.g. 5-azacitidine or decitabine); or

(iv) a FLT3 inhibitor (e.g. quizartinib);

or a pharmaceutically-acceptable salt thereof.

[0065] In another aspect, the present invention relates to an agent selected from:

(i) an anthracycline topoisomerase 2 inhibitor (e.g. daunorubicin);

(ii) cytarabine;

(iii) a hypomethylating agent (e.g. 5-azacitidine or decitabine); or

(iv) a FLT3 inhibitor (e.g. quizartinib);

or a pharmaceutically-acceptable salt thereof, for use in the treatment of cancer, wherein the agent, or a pharmaceutically acceptable salt thereof, is for simultaneous, separate or sequential administration with a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof.

[0066] In another aspect, the present invention relates to a use of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer, wherein the medicament is for simultaneous, separate or sequential administration with one or more additional agents selected from:

(i) an anthracycline topoisomerase 2 inhibitor (e.g. daunorubicin);

(ii) cytarabine;

(iii) a hypomethylating agent (e.g. 5-azacitidine or decitabine); or

(iv) a FLT3 inhibitor (e.g. quizartinib);

or a pharmaceutically-acceptable salt thereof.

[0067] In another aspect, the present invention relates to a use of an agent selected from:

(i) an anthracycline topoisomerase 2 inhibitor (e.g. daunorubicin);

(ii) cytarabine;

(iii) a hypomethylating agent (e.g. 5-azacitidine or decitabine); or

(iv) a FLT3 inhibitor (e.g. quizartinib);

or a pharmaceutically-acceptable salt thereof, in the manufacture of a medicament for treating cancer, wherein the medicament is for simultaneous, separate or sequential administration with a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof.

[0068] In another aspect, the present invention relates to a method of treating cancer comprising adminstering to a subject in need thereof a therapeutically effective amount of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, and an agent selected from:

(i) an anthracycline topoisomerase 2 inhibitor (e.g. daunorubicin);

(ii) cytarabine;

(iii) a hypomethylating agent (e.g. 5-azacitidine or decitabine); or

(iv) a FLT3 inhibitor (e.g. quizartinib);

or a pharmaceutically-acceptable salt thereof,

wherein the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, and the agent, or a pharmaceutically acceptable salt thereof, are administered sequentially, separately or simultaneously with one another.

[0069] In another aspect, the present invention relates to a method of treating cancer, or potentiating the effect of an agent selected from:

(i) an anthracycline topoisomerase 2 inhibitor (e.g. daunorubicin);

(ii) cytarabine;

(iii) a hypomethylating agent (e.g. 5-azacitidine or decitabine); or

(iv) a FLT3 inhibitor (e.g. quizartinib);

or a pharmaceutically-acceptable salt thereof, the method comprising administering to a patient in need of such treatment a therapeutically effective amount the agent, or a pharmaceutically acceptable salt thereof, separately, sequentially or simultaneously with a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof.

[0070] In another aspect, the present invention relates to a method of treating cancer, or potentiating the effect of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, the method comprising administering to a patient in need of such treatment a therapeutically effective amount of the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, separately, sequentially or simultaneously with an agent selected from:

(i) an anthracycline topoisomerase 2 inhibitor (e.g. daunorubicin);

(ii) cytarabine;

(iii) a hypomethylating agent (e.g. 5-azacitidine or decitabine); or

(iv) a FLT3 inhibitor (e.g. quizartinib);

or a pharmaceutically-acceptable salt thereof.

[0071] Suitably, the cancer is selected from acute myeloid leukaemia (AML), chronic lymphocytic leukaemia (CLL), small lymphocytic lymphoma (SLL) and myelodysplastic syndromes (MDS), especially AML.

[0072] Preferred, suitable, and optional features of any one particular aspect of the present invention described herein are also preferred, suitable, and optional features of any other aspect.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0073] Unless otherwise stated, the following terms used in the specification and claims have the following meanings set out below.

[0074] 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 predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition, (2) inhibiting the state, disorder or condition, i.e., arresting, reducing or delaying the development of the disease or a relapse thereof (in case of maintenance treatment) or at least one clinical or subclinical symptom thereof, or (3) relieving or attenuating the disease, i.e., causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms.

[0075] A "therapeutically effective amount" means the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

[0076] An "inhibitor" may be a polypeptide, nucleic acid, carbohydrate, lipid, small molecular weight compound, an oligonucleotide, an oligopeptide, siRNA, antisense, a recombinant protein, an antibody, a peptibody, or conjugates or fusion proteins thereof. For a review of siRNA see Milhavet O, Gary DS, Mattson MP. (Pharmacol Rev. 2003 Dec;55(4):629-48. For a review of antisense see Opalinska JB, Gewirtz AM. Sci STKE. 2003 Oct 28; 2003 (206): p47. A small molecular weight compound refers to a compound with a molecular weight of

less than 2000 Daltons, less than 1000 Daltons, less than 700 Daltons or less than 500 Daltons.

[0077] References to "a pharmaceutically acceptable salt" of an inhibitor defined herein is refers to any salt form suitable for pharmaceutical use. Examples of pharmaceutically acceptable salts include an acid-addition salt of an inhibitor of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulfuric, phosphoric, trifluoracetic, formic, citric methane sulfonate or maleic acid. In addition, a suitable pharmaceutically acceptable salt of an inhibitor of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a pharmaceutically acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

[0078] References herein to a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, and an immune checkpoint inhibitor, or a pharmaceutically acceptable salt thereof, include, where appropriate, any isomeric, tautomeric, polymorphic, amorphous and solvate (e.g. hydrate) forms of the inhibitors. An inhibitor may also be administered in the form of a prodrug which is broken down in the human or animal body to release the active inhibitor. Examples of pro-drugs include *in vivo* cleavable ester derivatives of the inhibitors that may be formed at a carboxy group or a hydroxy group in an inhibitor compound and *in-vivo* cleavable amide derivatives that may be formed at a carboxy group or an amino group in an inhibitor compound. Various forms of pro-drug have been described, for example in the following documents :-

a) Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);

b) Design of Pro-drugs, edited by H. Bundgaard, (Elsevier, 1985);

c) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Pro-drugs", by H. Bundgaard p. 113-191 (1991);

d) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

e) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988);

f) N. Kakeya, *et al.*, Chem. Pharm. Bull., 32, 692 (1984);

g) T. Higuchi and V. Stella, "Pro-Drugs as Novel Delivery Systems", A.C.S. Symposium Series, Volume 14; and

h) E. Roche (editor), "Bioreversible Carriers in Drug Design", Pergamon Press, 1987.

[0079] References herein to a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, being administered "in combination with" another agent, or a pharmaceutically acceptable salt thereof, or *vice versa*, unless otherwise stated otherwise, include the inhibitors being administered sequentially, separately or simultaneously with one another.

[0080] As used herein "simultaneous administration" refers to therapy in which the both agents (e.g. a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, and immune checkpoint inhibitor) are administered at the same time, suitably as a mono-therapy.

[0081] As used herein "sequential administration" means that one agent is administered after the other, however, the time period between the administration of each agent is such that both agents are capable of acting therapeutically concurrently. Thus, administration "sequentially" may permit one agent to be administered within seconds, minutes, or a matter of hours after the other provided the circulatory half-life of the first administered agent is such that they are both concurrently present in therapeutically effective amounts. The time delay between the administration of the agents may vary depending on the exact nature of the agents, the interaction there between, and their respective half-lives.

[0082] As used herein, "separate administration" means that one agent is administered after the other, however, the time period between administration is such that the first administered agent is no longer present a therapeutically effective amount when the second agent is administered. Accordingly, the two agents exert their therapeutic effects separately. Nevertheless, the overall therapeutic effect observed when the two agents separately act therapeutically may be greater than either agent used alone.

[0083] As used herein the, "subject(s)" and/or "patient(s)", suitably refer to mammals (e.g. humans and non-human mammals such as livestock (cows, sheep, goats) or companion animals (cats, dogs, horses, rabbits). Suitably, the subject(s) and/or patient(s) are human(s).

[0084] As used herein, a "pharmaceutical product" refers to a product comprising a pharmaceutical. For instance, examples of a pharmaceutical product include a medical device, a pharmaceutical composition and a kit of parts suitably comprising one or more devices, containers and/or pharmaceuticals.

COMBINATION THERAPIES OF THE PRESENT INVENTION

METTL3 Inhibitors

[0085] The present invention resides in the recognition that METTL3 inhibitors are viable agents for use in combination with

(i) immuno-oncology agents (e.g. immune checkpoint inhibitors);

(ii) BCL2 inhibitors (e.g. venetoclax);

(iii) anthracycline topoisomerase 2 inhibitors (e.g. daunorubicin);

(iv) cytarabine;

(v) hypomethylating agents (e.g. 5-azacitidine or decitabine); and/or

(vi) FLT3 inhibitors (e.g. quizartinib).

[0086] Any suitable METTL3 inhibitor may be used in the combination therapies defined herein.

[0087] Examples of suitable METTL3 inhibitors include:

(i) compounds defined in International Patent Publication No. WO2020/050898, which have the generic formula I set out below;

(ii) the specific compounds of fomula I set out in list 1 below;

(iii) compounds of the formulae (II), (VI) or (VII) defined below;

(iv) the specific compounds of formula II set out in List 2 below; or

(v) the sepcific compounds STM3006, STM3480 and STM3675 defined further below.

(i) Compounds defined in International Patent Publication No. WO2020/050898

[0088] The entire contents of International Patent Publication No. WO2020/050898 are incorporated herein by reference.

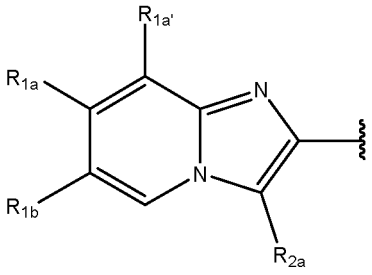
[0089] The compounds defined therein have the following formula (I):

$$X - Y - Z$$

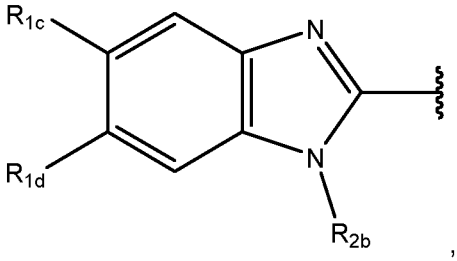
(I)

wherein:

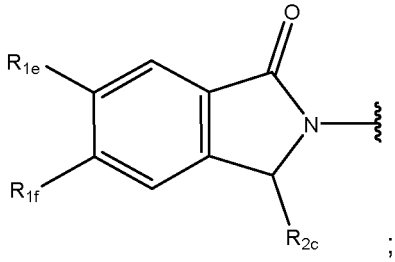
X is selected from:



,



, and



;

wherein:

R_{1a}, R_{1b}, R_{1c}, R_{1d}, R_{1e} and R_{1f} are independently selected from hydrogen, cyano, halo or a group of the formula:

$$-L_{1a}-L_{1b}-Q_1$$

wherein

L_{1a} is absent or selected from C_{1-3}alkylene and C_{3-5}cycloalkylene, wherein C_{1-3}alkylene and C_{3-5}cycloalkylene are optionally substituted by one or more substituents selected from aryl, aryl-(1-2C)alkyl, heteroaryl, aryl-(1-2C)alkyl, C_{1-3}alkyl, cyano, C_{1-3}alkoxy, halo, hydroxy, C_{1-3}haloalkoxy, -O-C_{3-4}cycloalkyl, NH_2 or oxo; wherein any -O-C_{3-6}cycloalkyl aryl, aryl-(1-2C)alkyl, heteroaryl, aryl-(1-2C)alkyl or C_{1-3}alkyl is optionally further substituted by one or more substituents selected from cyano, hydroxy, C_{1-3}alkoxy, halo, C_{1-3}haloalkoxy, -O-C_{3-4}cycloalkyl, or NH_2; wherein -O-C_{3-6}cycloalkyl is optionally further substituted with halo, cyano or hydroxy; ; or C_{1-3}alkylene is optionally spiro-fused to a 3- to 5-membered cycloalkyl or heterocyclic

ring, or a spirocyclic ring system, each of which is optionally substituted by one or more substituents selected from C_{1-2}alkyl, C_{1-2}haloalkyl, cyano, hydroxy, C_{1-2}alkoxy, halo or C_{1-2}haloalkoxy;

L_{1b} is absent or selected from O, S, SO, SO_2, $N(R_r)$, C(O), C(O)O, OC(O), $C(O)N(R_r)$, $N(R_r)C(O)$, $N(R_r)C(O)N(R_s)$, $S(O)_2N(R_r)$, or $N(R_r)SO_2$, wherein R_r and R_s are each independently selected from hydrogen or C_{1-3}alkyl, wherein C_{1-3}alkyl is optionally further substituted by cyano, hydroxy, C_{1-2}alkoxy, halo, C_{1-2}haloalkoxy, NH_2, C_{3-6}-cycloalkyl or a 3 to 6 membered heterocyclyl, wherein the C_{3-6}cycloalkyl or a 3 to 6 membered heterocyclyl in turn are optionally further substituted by halo, hydroxy, C_{1-2}alkoxy or C_{1-2}haloalkoxy; and

Q_1 is hydrogen, cyano, C_{1-6}alkyl, C_{3-8}cycloalkyl (including a spirocyclic carbocyclic and a bridged C_{3-8}cycloalkyl), C_{2-3}alkenyl, C_{2-3}alkynyl, aryl, heterocyclyl (including a mono- or bicyclic-heterocyclic ring system, a spirocyclic heterocyclic ring system, or a bridged heterocyclic ring system) or heteroaryl; and wherein Q_1 is optionally substituted by one or more substituents selected from C_{1-4}alkyl, halo, trifluoromethyl, trifluoromethoxy, amino, oxo, cyano, hydroxy, carboxy, carbamoyl, sulphamoyl, NR_tR_u, OR_t, $C(O)R_t$, $C(O)OR_t$, $OC(O)R_t$, $C(O)N(R_t)R_u$, $N(R_t)C(O)R_u$, $-S(O)_{0-2}R_tR_u$, $S(O)_yR_t$ (where y is 0, 1 or 2), $SO_2N(R_t)R_u$, $N(R_t)SO_2R_u$ or $(CH_2)_zNR_tR_u$ (where z is 1, 2 or 3), wherein C_{1-4}alkyl is in turn optionally substituted by one more substituents selected from cyano, hydroxy, C_{1-2}alkoxy, halo, C_{1-2}haloalkoxy, -O-C_3cycloalkyl, wherein -O-C_3cycloalkyl is optionally substituted with halo, cyano or hydroxy; and wherein R_t and R_u are each independently selected from hydrogen or C_{1-4}alkyl; or

Q_1 is optionally substituted by one or more groups of the formula:

$$-L_{1c}-L_{1d}-Z_1$$

wherein

L_{1c} is absent or C_{1-3}alkylene optionally substituted by C_{1-2}alkyl or oxo;

L_{1d} is absent or selected from C(O), O, C(O)O, OC(O), $C(O)N(R_v)$, $N(R_v)C(O)$, $N(R_v)C(O)N(R_w)$, $S(O)_2N(R_v)$, or $N(R_v)SO_2$, wherein R_v and R_w are each independently selected from hydrogen or C_{1-2}alkyl; and

Z_1 is C_{3-8}cycloalkyl (including a spirocyclic carbocyclic and a bridged C_{3-8}cycloalkyl), heterocyclyl (including a mono- or bicyclic-heterocyclic ring system, a spirocyclic heterocyclic ring system, or a bridged heterocyclic ring system), aryl or heteroaryl, ; wherein Z_1 is optionally substituted by one or more substituents selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, heterocyclyl, halo, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{1-4}alkoxy,

cyano, hydroxyl, $NR_{t1}R_{u1}$, OR_{t1}, $C(O)R_{t1}$, $C(O)OR_{t1}$, $OC(O)R_{t1}$, $C(O)N(R_{t1})R_{u1}$, $N(R_{t1})C(O)R_{u1}$, $-S(O)_{0-2}R_{t1}R_{u1}$, $S(O)_yR_{t1}$ (where y is 0, 1 or 2), $SO_2N(R_{t1})R_{u1}$, $N(R_{t1})SO_2R_{u1}$ or $(CH_2)_zNR_{t1}R_{u1}$ (where z is 1, 2 or 3), wherein R_{t1} and R_{u1} are each independently selected from hydrogen or C_{1-4}alkyl; and when Z_1 is C_{3-8}cycloalkyl or heterocyclyl, Z_1 is optionally spiro-fused to a C_{3-6}cycloalkyl or heterocyclyl ring;

$R_{1a'}$ is selected from hydrogen, halo and methyl;

R_{2a}, R_{2b} and R_{2c} are selected from hydrogen, halo or a group of the formula:

$$-L_{2a}-L_{2b}-Q_2$$

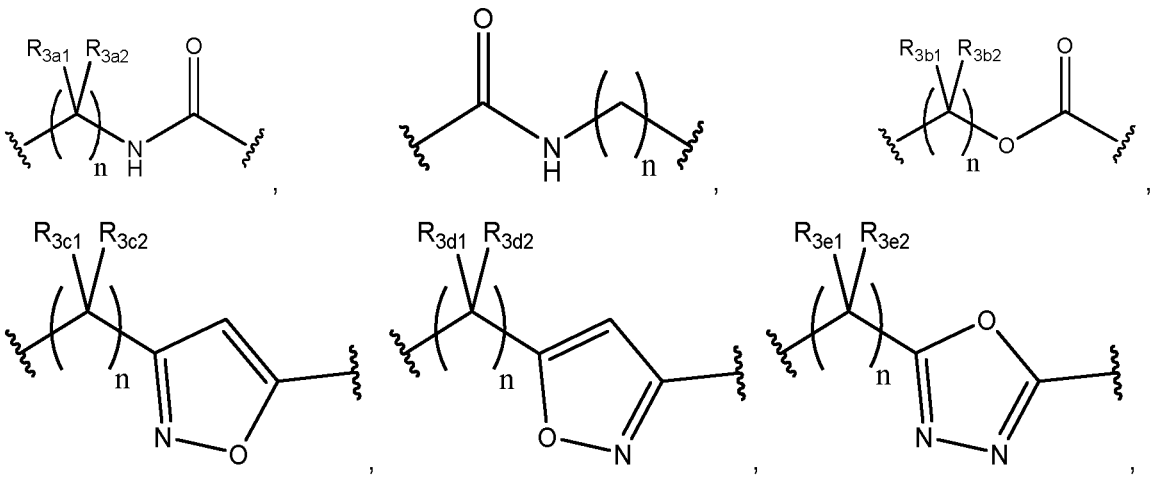
wherein

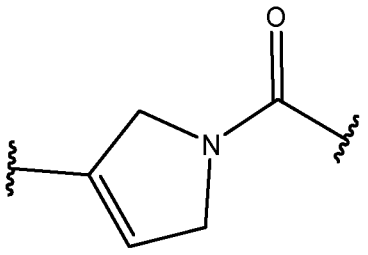
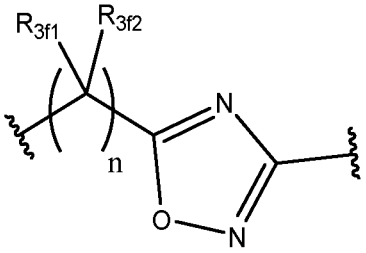
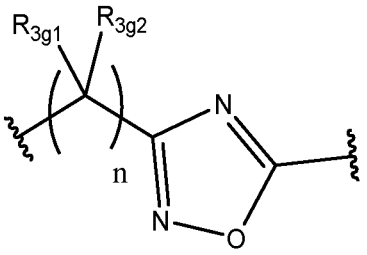
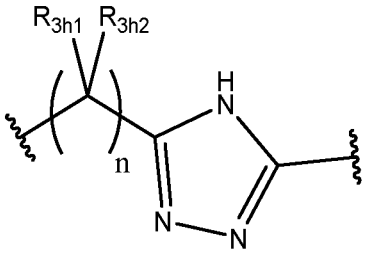
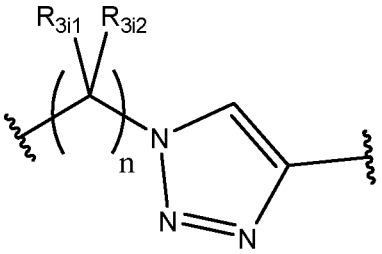
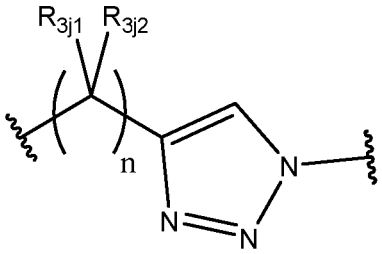
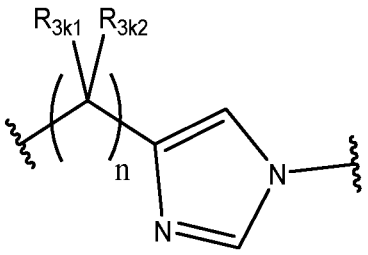
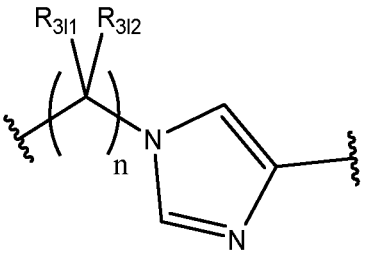
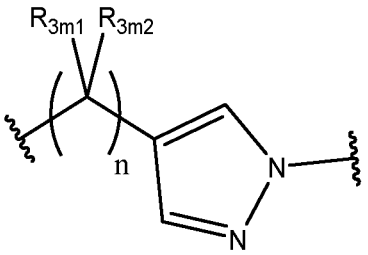
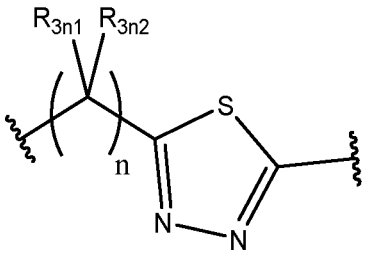
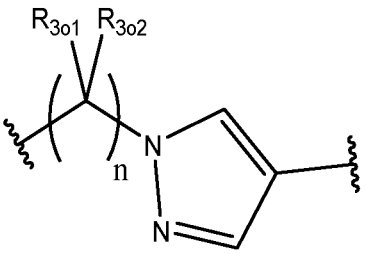
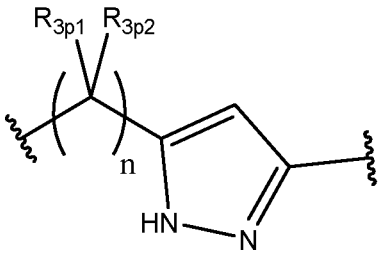
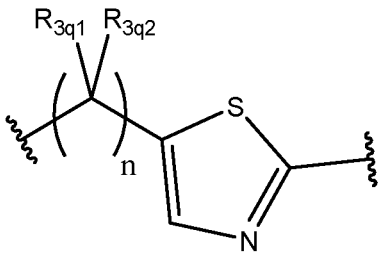
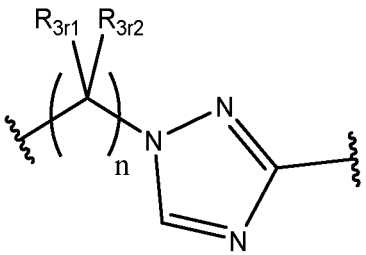
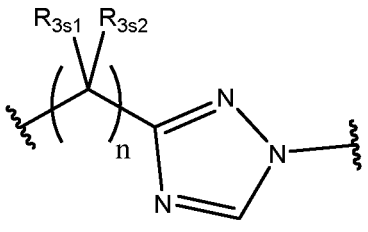
L_{2a} is absent or C_{1-3}alkylene optionally substituted by C_{1-2} alkyl or oxo;

L_{2b} is absent or selected from O, S, SO, SO_2, $N(R_n)$, C(O), C(O)O, OC(O), $C(O)N(R_n)$, $N(R_n)C(O)$, $N(R_n)C(O)N(R_o)$, $S(O)_2N(R_n)$, or $N(R_n)SO_2$, wherein R_n and R_o are each independently selected from hydrogen or C_{1-2}alkyl; and

Q_2 is hydrogen, cyano, C_{1-6}alkyl, C_{3-6}cycloalkyl, aryl, heterocyclyl or heteroaryl, each of which is optionally substituted by one or more substituents selected from halo, trifluoromethyl, trifluoromethoxy, amino, cyano, hydroxy, amino, carboxy, carbamoyl, sulphamoyl, C_{1-4}alkyl, NR_pR_q, OR_p, $C(O)R_p$, $C(O)OR_p$, $OC(O)R_p$, $C(O)N(R_p)R_q$, $N(R_r)C(O)R_p$, $S(O)_yR_p$ (where y is 0, 1 or 2), $SO_2N(R_p)R_q$, $N(R_r)SO_2R_p$ or $(CH_2)_zNR_pR_q$ (where z is 1, 2 or 3), wherein R_p and R_q are each independently selected from hydrogen or C_{1-4}alkyl;

Y is selected from:




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and

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wherein:

R_{3a1}, R_{3b1}, R_{3c1}, R_{3d1}, R_{3e1}, R_{3f1}, R_{3g1}, R_{3h1}, R_{3i1}, R_{3j1}, R_{3k1}, R_{3l1}, R_{3m1}, R_{3n1}, R_{3o1}, R_{3p1},R_{3q1}, R_{3r1} and R_{3s1} are independently selected from hydrogen (including

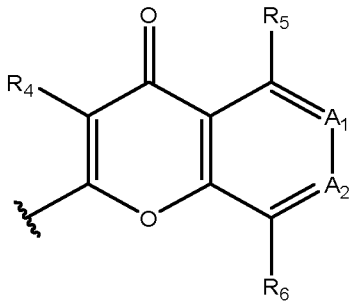
deuterium), C_{1-6}alkyl, C_{3-4} cycloalkyl, hydroxy, and halo; and wherein C_{1-6}alkyl, or C_{3-4} cycloalkyl is optionally substituted with one or more substituents selected from halo, amino, cyano, and hydroxy;

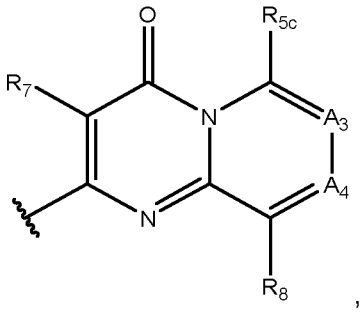
R_{3a2}, R_{3b2}, R_{3c2}, R_{3d2}, R_{3e2}, R_{3f2}, R_{3g2}, R_{3h2}, R_{3i2}, R_{3j2}, R_{3k2}, R_{3l2}, R_{3m2}, R_{3n2}, R_{3o2}, R_{3p2}, R_{3q2}, R_{3r2} and R_{3s2} are hydrogen or halo;

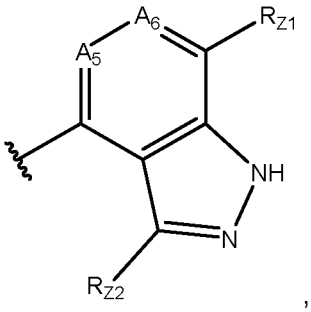
with the proviso that R_{3a1}, R_{3b1}, R_{3i1}, R_{3l1}, R_{3o1}, R_{3r1}, R_{3a2}, R_{3b2}, R_{3i2}, R_{3l2}, R_{3o2} and R_{3s1} cannot be halo when n=1 or when n=2 and the carbon atom to which they are attached is linked to an oxygen or nitrogen atom;

or R_{3a1} and R_{3a2}, R_{3b1} and R_{3b2}, R_{3c1} and R_{3c2}, R_{3d1} and R_{3d2}, R_{3e1} and R_{3e2}, R_{3f1} and R_{3f2}, R_{3g1} and R_{3g2}, R_{3h1} and R_{3h2}, R_{3i1} and R_{3i2}, R_{3j1} and R_{3j2}, R_{3k1} and R_{3k2}, R_{3l1} and R_{3l2}, R_{3m1} and R_{3m2}, R_{3n1} and R_{3n2}, R_{3o1} and R_{3o2}, R_{3p1} and R_{3p2}, R_{3q1} and R_{3q2}, or R_{3r1} and R_{3r2} or R_{3s1} and R_{3s2} may be linked such that, together with the carbon atom to which they are attached, they form a spiro-fused C_{3-4}cycloalkyl which is optionally substituted with one or more substituents selected from halo, methyl, amino, cyano, and hydroxy;

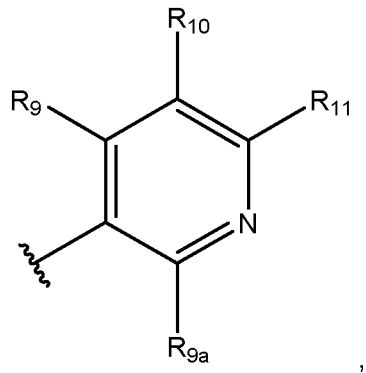
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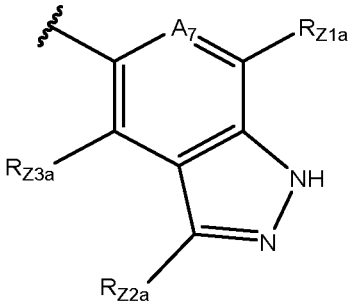


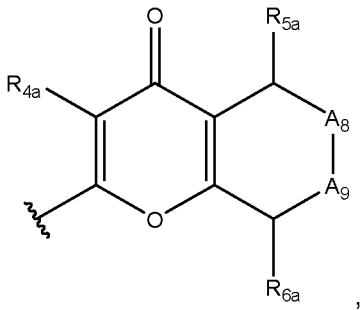
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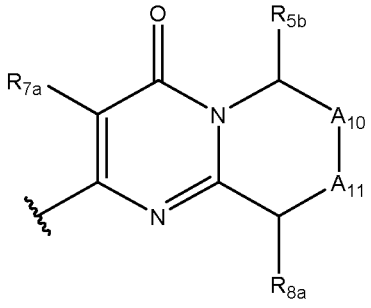
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wherein:

R_4, R_7, R_{4a} and R_{7a} are independently selected from hydrogen, halo, cyano and methyl;

R_5, R_{5a}, R_{5b} and R_{5c} are independently selected from hydrogen, halo, cyano and methyl;

R_6, R_8, R_{6a} and R_{8a} are independently selected from hydrogen, halo, cyano and methyl;

R_9, R_{9a}, R_{10} and R_{11} are independently selected from hydrogen, NH_2, halo, cyano, and C_{1-6} alkyl; or

R_9 and R_{10} may be linked together to form a fused 5- or 6-membered saturated or unsaturated ring system or R_{10} and R_{11} may be linked together to form a fused 5- or 6-membered saturated or unsaturated ring system; wherein either of the fused 5- or 6-membered saturated or unsaturated ring system may be optionally substituted by one or more substituents selected from C_{1-2}alkyl, cyano, C_{1-2}haloalkyl, hydroxy, C_{1-2}alkoxy, halo, C_{1-2}haloalkoxy, $NR_{1ia}R_{1ja}$ or $-S(O)_{0-2}R_{1ia}R_{1ja}$, wherein R_{1ia} and R_{1ja} are H or C_{1-2}alky;

R_{Z1} and R_{Z1a} are selected from hydrogen, C_{1-4}alkyl, cyano, halo, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{1-4}alkoxy, C_{3-6}cycloalkyl and $-O-C_{3-6}$cycloalkyl, wherein C_{3-6}cycloalkyl and $-O-C_{3-6}$cycloalkyl are optionally substituted by one or more of halo, methyl or methoxy;

R_{Z2} and R_{Z2a} are selected from hydrogen, C_{1-4}alkyl, cyano, halo, NH_2 and C_{1-4}alkoxy;

R_{Z3a} is selected from hydrogen, C_{1-4}alkyl, cyano, halo, NH_2 and C_{1-4}alkoxy

A_1 is selected from CR_{12} and N;

A_2 is selected from CR_{13} and N;

A_3 is selected from CR_{14} and N;

A_4 is selected from CR_{15} and N;

A_5 is selected from CR_{16} and N;

A_6 is selected from CR_{17} and N;

A_7 is selected from CR_{18} and N;

A_8 is selected from $CR_{19}R_{20}$ and NR_{21};

A_9 is selected from $CR_{22}R_{23}$ and NR_{24};

A_{10} is selected from $CR_{25}R_{26}$ and NR_{27};

A_{11} is selected from $CR_{28}R_{29}$ and NR_{30};

R_{12} and R_{14} are independently selected from hydrogen, halo, cyano and C_{1-4} alkyl;

R_{13} is selected from hydrogen, halo, cyano, methoxy and methyl;

R_{15} is selected from hydrogen, halo, cyano methoxy and methyl;

R_{16} is selected from hydrogen, halo, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{3-4}cycloalkyl, a 3- to 4-membered heterocyclyl and C_{3-4}cycloalkoxy;

R_{17} is selected from hydrogen, hydroxy, halo, cyano, C_{1-5} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, a 5- or 6-membered or heteroaryl, C_{3-6}cycloalkyl, -O-C_{3-6}cycloalkyl, heterocyclyl, -O-heterocyclyl (carbon-linked), -$(OCH_2CH_2)_m$-NR_qR_r, -$(OCH_2CH_2)_m$-OCH_3 wherein m is an integer from 1 to 6, NR_qR_r, -C(O)-NR_qR_r, -C(O)OR_q;

wherein R_q and R_r are each independently hydrogen, C_{1-5} alkyl, C_{3-6}cycloalkyl, a 3- to 6- membered carbon-linked heterocyclyl, wherein C_{1-5} alkyl, C_{3-6}cycloalkyl, a 3- to 6-membered carbon-linked heterocyclyl may be optionally substituted by one or more substituents selected from C_{1-2}alkyl, cyano, C_{1-2}haloalkyl, hydroxy, C_{1-2}alkoxy, halo, C_{1-2}haloalkoxy, $NR_{1ea}R_{1fa}$ or -$S(O)_{0-2}R_{1ea}R_{1fa}$, wherein R_{1ea} and R_{1fa} are H or C_{1-2}alkyl;

or R_q and R_r are linked together such that, together with the nitrogen atom to which they are attached, they form a 3- to 6-membered heterocyclic ring, which may be

optionally substituted by one or more substituents selected from C_{1-2}alkyl, cyano, C_{1-2}haloalkyl, hydroxy, C_{1-2}alkoxy, halo, C_{1-2}haloalkoxy;

wherein any C_{1-5}alkyl, C_{1-4} alkoxy, C_{2-4}alkenyl, C_{2-4}alkynyl, phenyl, 5- or 6-membered or heteroaryl, C_{3-6}cycloalkyl, -O-C_{3-6}cycloalkyl, heterocyclyl or -O-heterocyclyl (carbon-linked)is optionally further substituted by one or more substituents selected from C_{1-2}alkyl, cyano, C_{1-2}haloalkyl, hydroxy, C_{1-2}alkoxy, halo, C_{1-2}haloalkoxy, $NR_{1ea}R_{1fa}$ or $-S(O)_{0-2}R_{1ea}R_{1fa}$, wherein R_{1ea} and R_{1fa} are H or C_{1-2}alkyl;

R_{18} is selected from hydrogen, halo, cyano, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, a 5- or 6-membered heteroaryl, C_{1-4} alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{3-4}cycloalkyl, a 3- to 4-membered heterocyclyl and C_{3-4}cycloalkoxy;

R_{19}, R_{20}, R_{25} and R_{26} are selected from hydrogen, halo, cyano and C_{1-4} alkyl;

R_{22} and R_{23} are selected from hydrogen, halo, cyano and methyl;

R_{28} and R_{29} are selected from hydrogen, methoxy and methyl;

R_{21}, R_{24}, R_{27} and R_{30} are hydrogen; and

n is 0, 1 or 2;

with the proviso that the compound is not:

2-((1H-benzo[d]imidazol-2-yl)methyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;

2-((6-chloro-1-phenyl-1H-benzo[d]imidazol-2-yl)methyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole;

N-({6-methylimidazo[1,2-a]pyridin-2-yl}methyl)-1H-indazole-5-carboxamide.

(ii) Specific compounds of fomula I – List 1

[0090] Particular compounds of formula I disclosed in International Patent Publication No. WO2020/050898 include any of the following in List 1 below, or a pharmaceutically acceptable salt thereof:

List 1

N-({6-methylimidazo[1,2-a]pyridin-2-yl}methyl)-1H-indazole-4-carboxamide;

N-({7-bromoimidazo[1,2-a]pyridin-2-yl}methyl)-1H-indazole-4-carboxamide;

N-({6-bromoimidazo[1,2-a]pyridin-2-yl}methyl)-1H-indazole-4-carboxamide;

N-({6-chloroimidazo[1,2-a]pyridin-2-yl}methyl)-1H-indazole-4-carboxamide;

N-({7-fluoroimidazo[1,2-a]pyridin-2-yl}methyl)-1H-indazole-4-carboxamide;

N-({6-fluoroimidazo[1,2-a]pyridin-2-yl}methyl)-1H-indazole-4-carboxamide;

N-({7-methoxyimidazo[1,2-a]pyridin-2-yl}methyl)-1H-indazole-4-carboxamide;

N-({6-methylimidazo[1,2-a]pyridin-2-yl}methyl)-6-(1H-pyrazol-5-yl)-1H-indazole-4-carboxamide;

N-({7-methylimidazo[1,2-a]pyridin-2-yl}methyl)-1H-indazole-4-carboxamide;

6-bromo-N-({6-methylimidazo[1,2-a]pyridin-2-yl}methyl)-1H-indazole-4-carboxamide;

6-bromo-N-({7-methylimidazo[1,2-a]pyridin-2-yl}methyl)-1H-indazole-4-carboxamide;

N-({6-methylimidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-chromene-2-carboxamide;

N-({imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-chromene-2-carboxamide;

6-ethynyl-N-({6-methylimidazo[1,2-a]pyridin-2-yl}methyl)-1H-indazole-4-carboxamide;

N-({6-methylimidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-({7-methylimidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-chromene-2-carboxamide;

N-({7-methylimidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-({6-cyanoimidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

8-methoxy-N-({6-methylimidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-({6-methylimidazo[1,2-a]pyridin-2-yl}methyl)-1H-indazole-5-carboxamide;

7-chloro-N-({6-methylimidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-({6-fluoroimidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-({6-bromoimidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-({6-methoxyimidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-({7-methoxyimidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-({imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-({8-methylimidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-({6-methylimidazo[1,2-a]pyridin-2-yl}methyl)-1H-pyrazolo[4,3-c]pyridine-4-carboxamide;

N-({7-bromoimidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-(2-hydroxy-1-{6-methylimidazo[1,2-a]pyridin-2-yl}ethyl)-1H-indazole-4-carboxamide;

4-(3-{imidazo[1,2-a]pyridin-2-yl}-2,5-dihydro-1H-pyrrole-1-carbonyl)-1H-indazole;

N-[(6-{[(pyridin-3-yl)methyl]amino}imidazo[1,2-a]pyridin-2-yl)methyl]-1H-indazole-4-carboxamide;

N-[(6-{[(1-methyl-1H-imidazol-4-yl)methyl]amino}imidazo[1,2a]pyridin-2-yl)methyl]-1H-indazole-4-carboxamide;

N-{[6-(3-methoxyphenyl)imidazo[1,2-a]pyridin-2-yl]methyl}-1H-indazole-4-carboxamide;

N-{[6-(1H-pyrazol-5-yl)imidazo[1,2-a]pyridin-2-yl]methyl}-1H-indazole-4-carboxamide;

N-[[6-(3-chlorophenyl)imidazo[1,2-a]pyridin-2-yl]methyl]-1H-indazole-4-carboxamide;

N-({6-[(pyridin-3-yl)amino]imidazo[1,2-a]pyridin-2-yl}methyl)-1H-indazole-4-carboxamide;

N-({6-[(piperazin-1-yl)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-1H-indazole-4-carboxamide;

N-{[6-(aminomethyl)imidazo[1,2-a]pyridin-2-yl]methyl}-1H-indazole-4-carboxamide;

N-{[6-(acetamidomethyl)imidazo[1,2-a]pyridin-2-yl]methyl}-1H-indazole-4-carboxamide;

{6-methylimidazo[1,2-a]pyridin-2-yl}methyl 1H-indazole-4-carboxylate;

{6-methylimidazo[1,2-a]pyridin-2-yl}methyl 1H-indazole-4-carboxylate hydrochloride;

N-{[6-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl]methyl}-1H-indazole-4-carboxamide;

N-({6-hydroxyimidazo[1,2-a]pyridin-2-yl}methyl)-1H-indazole-4-carboxamide;

N-({6-[(methylamino)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-1H-indazole-4-carboxamide;

N-({6-[(methylamino)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-1H-indazole-4-carboxamide dihydrochloride;

N-[(6-{[(2-hydroxyethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-1H-indazole-4-carboxamide;

N-[(6-{[(2,2,2-trifluoroethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-1H-indazole-4-carboxamide;

N-{[6-(1-hydroxyethyl)imidazo[1,2-a]pyridin-2-yl]methyl}-1H-indazole-4-carboxamide;

N-({6-[hydroxy(phenyl)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-1H-indazole-4-carboxamide;

N-({6-formylimidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-{[6-(aminomethyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

4-oxo-N-[(6-{[(2,2,2-trifluoroethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-[(6-{[(2-hydroxyethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

4-oxo-N-[(6-{[(2-phenylethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-({6-[(benzylamino)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

4-oxo-N-[(6-{[(3-phenylpropyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-({6-[hydroxy(phenyl)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-{[6-(1-hydroxyethyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-({6-ethenylimidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-({6-cyclopropylimidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-({7-ethenylimidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-{[6-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

2-(1H-indazol-4-yl)-5-[(6-methylimidazo[1,2-a]pyridin-2-yl)methyl]-1,3,4-oxadiazole;

N-{[6-(2-aminoethyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-({6-methylimidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H,6H,7H,8H,9H-pyrido[1,2-a]pyrimidine-2-carboxamide;

4-oxo-N-{[6-(trifluoromethyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

tert-butyl N-(2-{2-[({4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl}formamido)methyl]imidazo[1,2-a]pyridin-6-yl}ethyl)carbamate;

N-benzyl-2-[({4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl}formamido)methyl]imidazo[1,2-a]pyridine-6-carboxamide;

N-[(6-{[(cyclohexylmethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-chromene-2-carboxamide;

7-chloro-N-[(6-{[(cyclohexylmethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-chromene-2-carboxamide;

6-chloro-N-[(6-{[(cyclohexylmethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-chromene-2-carboxamide;

N-[(6-{[(cyclohexylmethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H,6H,7H,8H,9H-pyrido[1,2-a]pyrimidine-2-carboxamide;

6-amino-N-[(6-{[(cyclohexylmethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]pyridine-3-carboxamide;

N-({6-[(benzyloxy)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-({6-[(benzylamino)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-1H-indazole-4-carboxamide;

N-[(6-{[(cyclohexylmethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-7-fluoro-4-oxo-4H-chromene-2-carboxamide;

N-[(6-{[(cyclohexylmethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-7-methyl-4-oxo-4H-chromene-2-carboxamide;

N-[(6-{[(cyclohexylmethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-1H-indazole-4-carboxamide;

8-chloro-N-[(6-{[(cyclohexylmethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-chromene-2-carboxamide;

6-bromo-N-[(6-{[(cyclohexylmethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-1H-indazole-4-carboxamide;

N-[(6-{[(cyclohexylmethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]quinoline-3-carboxamide;

N-[(6-{1-[(cyclohexylmethyl)amino]ethyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

6-chloro-N-[(6-{[(cyclohexylmethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-1H-indazole-4-carboxamide;

4-[5-({6-methylimidazo[1,2-a]pyridin-2-yl}methyl)-1,3,4-thiadiazol-2-yl]-1H-indazole;
4-[1-({6-methylimidazo[1,2-a]pyridin-2-yl}methyl)-1H-1,2,3-triazol-4-yl]-1H-indazole;
N-[(6-{[(3-chlorophenyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[(6-{[(1-cyclohexyl-2-hydroxyethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-{[6-({[(pyridin-3-yl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-{[6-({[(4-methoxyphenyl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[(6-{[(cyclohexylmethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-{[6-({[(4-chlorophenyl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[(6-{[benzyl(methyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-{[6-({[(1R)-1-phenylethyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-{[6-({[(1S)-1-phenylethyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-{[6-({[(2-fluorophenyl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-[(6-{[(2-phenylpropan-2-yl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-{[6-({[(3-fluorophenyl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-{[6-({[(4-fluorophenyl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-[(6-{[(4,4,4-trifluorobutyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-{[6-({[(oxan-4-yl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-{[6-({[(3,3-difluorocyclobutyl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[(6-{[(cyclopropylmethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-[(6-{[(3,3,3-trifluoropropyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-({6-[(cyclohexylamino)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-({6-[({[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]methyl}amino)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-{[6-({[(oxan-2-yl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-[(6-{[(3-phenyloxetan-3-yl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-{[6-({[(oxan-3-yl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-{[6-({[(1-fluorocyclohexyl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-{[6-({[(3-cyclopropylphenyl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[(6-{[(3,3-dimethylbutyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-{[6-({[2-(trifluoromethoxy)ethyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-{[6-({[(oxolan-2-yl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[(6-{[(2-methanesulfonylethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-({6-[(3-phenylpyrrolidin-1-yl)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-[(6-{[(1-cyclohexylcyclopropyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-{[6-({[(1,3-thiazol-5-yl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
tert-butyl 3-{[({2-[({4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl}formamido)methyl]imidazo[1,2-a]pyridin-6-yl}methyl)amino]methyl}piperidine-1-carboxylate;
N-{[6-({[(4,4-difluorocyclohexyl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
tert-butyl 2-{[({2-[({4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl}formamido)methyl]imidazo[1,2-a]pyridin-6-yl}methyl)amino]methyl}piperidine-1-carboxylate;
N-[(6-{[(2-cyclopropylethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-({6-[(piperidin-1-yl)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-({6-[({[1-(2,2,2-trifluoroethyl)-1H-pyrazol-3-yl]methyl}amino)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-{[6-({[(1-methylcyclohexyl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-{[6-({[2-(pyridin-3-yl)ethyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-{[6-({[(1,4-dioxan-2-yl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-({6-[(cyclopropylamino)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[(6-{[(3,3-difluorocyclobutyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-{[6-({[(oxetan-3-yl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-{[6-({[(1R,2R)-2-(trifluoromethyl)cyclopropyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[(6-{[(2,2-dimethylpropyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[(6-{[(cyclohexylmethyl)(methyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[(6-{[(4,4-difluorocyclohexyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-({6-[({bicyclo[1.1.1]pentan-1-yl}amino)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-({6-[({[(2S)-oxolan-2-yl]methyl}amino)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-({6-[({[(2R)-oxolan-2-yl]methyl}amino)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[(6-{[(2,2-difluoroethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-{[6-({[(oxolan-3-yl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-{[6-({[(1-methylcyclopropyl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-[(6-{[(oxolan-3-yl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
methyl 3-methyl-2-[({2-[({4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl}formamido)methyl]imidazo[1,2-a]pyridin-6-yl}methyl)amino]butanoate;
N-[(6-{[(oxan-3-yl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-{[6-({[(2S)-3,3,3-trifluoro-2-hydroxypropyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-({6-[(cyclobutylamino)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-({6-[(tert-butylamino)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[(6-{[(2-fluoroethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-({6-[(4,4-difluoropiperidin-1-yl)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-({6-[(4-phenylpiperazin-1-yl)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-({6-[(1,2,3,4-tetrahydroisoquinolin-2-yl)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-({6-[(diethylamino)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-({6-[(pyrrolidin-1-yl)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

4-oxo-N-[(6-{[3-(pyridin-2-yl)azetidin-1-yl]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[(6-{[(dicyclopropylmethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[(6-{[(cyclopropylmethyl)(methyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-({6-[(4-methylpiperidin-1-yl)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-[(6-{[4-(trifluoromethyl)piperidin-1-yl]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-({6-[(3-methylpiperidin-1-yl)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-[(6-{[({spiro[2.2]pentan-1-yl}methyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-({6-[(3,3-dimethylpiperidin-1-yl)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-[(6-{[3-(trifluoromethyl)piperidin-1-yl]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-{[6-({[(5,5-dimethyloxolan-2-yl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-({6-[(4-fluoropiperidin-1-yl)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[(6-{[(3-methoxypropyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[(6-{[(1-methylcyclohexyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-{[6-({[(4,4-dimethyloxolan-2-yl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[(6-{[(1-methylcyclopentyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-({6-[(propylamino)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-{[6-({[(3,3-dimethyloxolan-2-yl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[(6-{[(2-methylpropyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-{[6-({[2-(tert-butoxy)ethyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[(6-{[(4-chlorophenyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-{[6-({[2-(oxan-2-yl)ethyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-({6-[(4-benzylpiperidin-1-yl)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-({6-[(4-phenoxypiperidin-1-yl)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-{[6-({[(2,2-difluorocyclopropyl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-{[6-({[(2,2-dimethylcyclopropyl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-{[6-({[(2-methyloxolan-2-yl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-({6-[(4-tert-butylpiperidin-1-yl)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[(6-{[(4-tert-butylcyclohexyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[(6-{[(2-cyclopentylethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[(6-{[4-(2,2-dimethylpropanoyl)piperazin-1-yl]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-({6-[(4-acetylpiperazin-1-yl)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-{[6-({7-azabicyclo[2.2.1]heptan-7-yl}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-({6-[(4,4-dimethylpiperidin-1-yl)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-({6-[(2,2-dimethylpiperidin-1-yl)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-[(6-{[(2,3,3-trimethylbutan-2-yl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[(6-{[(5-fluoropyridin-2-yl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-({6-[({[1,1'-bi(cyclopropane)]-1-yl}amino)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-{[6-({[(1-fluorocyclopentyl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-({6-[(2,6-dimethylmorpholin-4-yl)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
methyl 1-({2-[({4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl}formamido)methyl]imidazo[1,2-a]pyridin-6-yl}methyl)piperidine-3-carboxylate;
N-[(6-{[(2-fluoro-2-methylpropyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[(6-{[(1-cyclohexylethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[(6-{[(2-cyclopropylethyl)(methyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[(6-{[(2,2-dimethylpropyl)(methyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-{[6-({[(1-fluorocyclobutyl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-({6-[(4-fluoro-4-methylpiperidin-1-yl)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-({6-[(3,3-difluoropiperidin-1-yl)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-{[6-({[(1-hydroxycyclohexyl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[(6-{[(cyclopentylmethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-{[6-({[(3,3-difluorocyclopentyl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[(6-{[(cyclobutylmethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-{[6-({[2-(3,3-difluorocyclobutyl)ethyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-{[6-({[(2-fluorocyclobutyl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-{[6-({[(2S)-3,3-dimethylbutan-2-yl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-{[6-({6-azaspiro[2.5]octan-6-yl}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-({6-[({[(1r,3r)-3-fluorocyclobutyl]methyl}amino)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-({6-[(2-phenylethyl)amino]imidazo[1,2-a]pyridin-2-yl}methyl)-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-({6-[2-(benzylamino)ethyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-({6-[2-(cyclohexylamino)ethyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-({6-[(phenylformamido)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-({6-[(cyclohexylformamido)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

4-oxo-N-{[6-({[(piperidin-3-yl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

4-oxo-N-{[6-({[(piperidin-2-yl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[(6-{[(azetidin-3-yl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-({6-[(cyclohexylamino)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-chromene-2-carboxamide;
N-[(6-{[(2-cyclopropylethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-chromene-2-carboxamide;
4-oxo-N-({6-[(piperidin-1-yl)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4H-chromene-2-carboxamide;
N-{[6-({[(4-chlorophenyl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-chromene-2-carboxamide;
N-({6-[(benzylamino)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-chromene-2-carboxamide;
N-{[6-({[(1-methylcyclohexyl)methyl]amino}methyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-chromene-2-carboxamide;
N-[(6-{[(2,2-dimethylpropyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-chromene-2-carboxamide;
4-oxo-N-[(7-{[(2-phenylethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-[(7-{[(cyclohexylmethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[(7-{[(cyclopropylmethyl)amino]methyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[(6-{1-[(cyclohexylmethyl)amino]cyclopropyl}imidazo[1,2-a]pyridin-2-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-{[6-(2-amino-3-phenylpropyl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
(cyclohexylmethyl)[(2-{[4-(1H-indazol-4-yl)-1H-1,2,3-triazol-1-yl]methyl}imidazo[1,2-a]pyridin-6-yl)methyl]amine;
N-(cyclohexylmethyl)-2-{[4-(1H-indazol-4-yl)-1H-1,2,3-triazol-1-yl]methyl}imidazo[1,2-a]pyridine-6-carboxamide;
(2,2-dimethylpropyl)[(2-{[4-(1H-indazol-4-yl)-1H-1,2,3-triazol-1-yl]methyl}imidazo[1,2-a]pyridin-6-yl)methyl]amine;
4-[1-({6-[(4,4-dimethylpiperidin-1-yl)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-1H-1,2,3-triazol-4-yl]-1H-indazole;
[(2-{[4-(6-bromo-1H-indazol-4-yl)-1H-1,2,3-triazol-1-yl]methyl}imidazo[1,2-a]pyridin-6-yl)methyl][(3,3-difluorocyclobutyl)methyl]amine;
[(2-{[4-(6-bromo-1H-indazol-4-yl)-1H-1,2,3-triazol-1-yl]methyl}imidazo[1,2-a]pyridin-6-yl)methyl](2,2-dimethylpropyl)amine;
[(2-{[4-(6-bromo-1H-indazol-4-yl)-1H-1,2,3-triazol-1-yl]methyl}imidazo[1,2-a]pyridin-6-yl)methyl](cyclohexylmethyl)amine;
6-bromo-4-[1-({6-[(4,4-dimethylpiperidin-1-yl)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-1H-1,2,3-triazol-4-yl]-1H-indazole;
(2-{[4-(6-bromo-1H-indazol-4-yl)-1H-1,2,3-triazol-1-yl]methyl}imidazo[1,2-a]pyridin-6-yl)methanol;
(2,2-dimethylpropyl)[(2-{[4-(1H-indazol-5-yl)-1H-1,2,3-triazol-1-yl]methyl}imidazo[1,2-a]pyridin-6-yl)methyl]amine;
((cyclohexylmethyl)[1-(2-{[4-(1H-indazol-4-yl)-1H-1,2,3-triazol-1-yl]methyl}imidazo[1,2-a]pyridin-6-yl)ethyl]amine;
(2,2-dimethylpropyl)({2-[(4-{1H-pyrazolo[3,4-c]pyridin-4-yl}-1H-1,2,3-triazol-1-yl)methyl]imidazo[1,2-a]pyridin-6-yl}methyl)amine;
{2-[(4-{1H-pyrazolo[3,4-c]pyridin-4-yl}-1H-1,2,3-triazol-1-yl)methyl]imidazo[1,2-a]pyridin-6-yl}methanol;
N-({6-[(3R,5S)-5-tert-butylmorpholin-3-yl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-({6-[(3S,5R)-5-tert-butylmorpholin-3-yl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-({6-[(3S,5R)-5-cyclohexylmorpholin-3-yl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-({6-[(3S,5R)-5-cyclohexylmorpholin-3-yl]imidazo[1,2-a]pyridin-2-yl}methyl)-1H-indazole-4-carboxamide;
N-({6-[(3S,5R)-5-cyclohexylmorpholin-3-yl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-chromene-2-carboxamide;
N-({6-[4-(2,2-dimethylpropyl)morpholin-3-yl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-({6-[(3S,5R)-5-methylmorpholin-3-yl]imidazo[1,2-a]pyridin-2-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide; and
N-{[6-(9-methoxy-2,3,4,5-tetrahydro-1,4-benzoxazepin-3-yl)imidazo[1,2-a]pyridin-2-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-[1-[[6-[(cyclobutylmethylamino)methyl]imidazo[1,2-a]pyridin-2-yl]methyl]triazol-4-yl]-1H-indazol-6-ol;
4-[1-[[6-[[(1-hydroxycyclobutyl)methylamino]methyl]imidazo[1,2-a]pyridin-2-yl]methyl]triazol-4-yl]-1H-indazol-6-ol;
1-[[[2-[[4-(5-methoxy-1H-indazol-4-yl)triazol-1-yl]methyl]imidazo[1,2-a]pyridin-6-yl]methylamino]methyl]cyclobutanol;
1-[[[2-[[4-(6-methoxy-1H-indazol-4-yl)triazol-1-yl]methyl]imidazo[1,2-a]pyridin-6-yl]methylamino]methyl]cyclobutanol;
N-(cyclobutylmethyl)-1-[2-[[4-(6-methoxy-1H-indazol-4-yl)triazol-1-yl]methyl]imidazo[1,2-a]pyridin-6-yl]methanamine;
N-(cyclobutylmethyl)-1-[2-[[4-(5-methoxy-1H-indazol-4-yl)triazol-1-yl]methyl]imidazo[1,2-a]pyridin-6-yl]methanamine;
4-[1-[(6-methylimidazo[1,2-a]pyridin-2-yl)methyl]triazol-4-yl]-1H-indazol-3-amine
N-[[6-[[(1-methoxycyclobutyl)methylamino]methyl]imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[[6-(1,4-oxazepan-3-yl)imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[[6-[[(2-cyano-2-methyl-propyl)amino]methyl]imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[[6-[[(3-fluoro-1-bicyclo[1.1.1]pentanyl)methylamino]methyl]imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-[[6-[(spiro[3.3]heptan-2-ylmethylamino)methyl]imidazo[1,2-a]pyridin-2-yl]methyl]pyrido[1,2-a]pyrimidine-2-carboxamide;

4-oxo-N-[[6-[(spiro[2.3]hexan-5-ylmethylamino)methyl]imidazo[1,2-a]pyridin-2-yl]methyl]pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[[6-[(1-bicyclo[1.1.1]pentanylmethylamino)methyl]imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-[[6-[(spiro[2.3]hexan-2-ylamino)methyl]imidazo[1,2-a]pyridin-2-yl]methyl]pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[[6-[[(2-methoxy-2-methyl-propyl)amino]methyl]imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[[6-[[(1-methylcyclobutyl)methylamino]methyl]imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[[6-(butylaminomethyl)imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[[6-[[(1-hydroxycyclopentyl)methylamino]methyl]imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[[6-[(2-methylbutylamino)methyl]imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[[6-[(2-cyclobutylethylamino)methyl]imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[[6-[[(2-hydroxy-2-methyl-propyl)amino]methyl]imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[[6-[[(1-hydroxycyclobutyl)methylamino]methyl]imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[[6-[(2-hydroxybutylamino)methyl]imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[[6-[[(3-methylcyclobutyl)methylamino]methyl]imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[[6-[[(3,3-dimethylcyclobutyl)methylamino]methyl]imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[[6-[(2,2-dimethylbutylamino)methyl]imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[[6-[[[(2S)-2-methylbutyl]amino]methyl]imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;
1-[[[2-[[4-(6-bromo-1H-indazol-4-yl)triazol-1-yl]methyl]imidazo[1,2-a]pyridin-6-yl]methylamino]methyl]cyclohexanol;
1-[[[2-[[4-(6-bromo-1H-indazol-4-yl)triazol-1-yl]methyl]imidazo[1,2-a]pyridin-6-yl]methylamino]methyl]cyclobutanol;

1-[2-[[4-(6-bromo-1H-indazol-4-yl)triazol-1-yl]methyl]imidazo[1,2-a]pyridin-6-yl]-N-(cyclobutylmethyl)methanamine;
4-[1-[[6-[(cyclobutylmethylamino)methyl]imidazo[1,2-a]pyridin-2-yl]methyl]triazol-4-yl]-1H-indazole-6-carboxylic acid;
4-[1-[[6-[(cyclobutylmethylamino)methyl]imidazo[1,2-a]pyridin-2-yl]methyl]triazol-4-yl]-1H-indazole-6-carboxamide;
4-[1-[[6-[(cyclobutylmethylamino)methyl]imidazo[1,2-a]pyridin-2-yl]methyl]triazol-4-yl]-N,N-dimethyl-1H-indazole-6-carboxamide;
[4-[1-[[6-[(cyclobutylmethylamino)methyl]imidazo[1,2-a]pyridin-2-yl]methyl]triazol-4-yl]-1H-indazol-6-yl]-morpholino-methanone;
4-[1-[[6-[(cyclobutylmethylamino)methyl]imidazo[1,2-a]pyridin-2-yl]methyl]triazol-4-yl]-N-(2-hydroxyethyl)-1H-indazole-6-carboxamide;
1-[2-[[4-(6-chloro-1H-indazol-4-yl)triazol-1-yl]methyl]imidazo[1,2-a]pyridin-6-yl]-N-(cyclobutylmethyl)methanamine;
1-[[[2-[[4-(6-chloro-1H-indazol-4-yl)triazol-1-yl]methyl]imidazo[1,2-a]pyridin-6-yl]methylamino]methyl]cyclobutanol;
N-[[2-[[4-(6-chloro-1H-indazol-4-yl)triazol-1-yl]methyl]imidazo[1,2-a]pyridin-6-yl]methyl]-2,2-dimethyl-propan-1-amine;
N-(cyclobutylmethyl)-1-[2-[[4-(7-fluoro-1H-indazol-4-yl)triazol-1-yl]methyl]imidazo[1,2-a]pyridin-6-yl]methanamine;
1-[[[2-[[4-(7-fluoro-1H-indazol-4-yl)triazol-1-yl]methyl]imidazo[1,2-a]pyridin-6-yl]methylamino]methyl]cyclohexanol;
N-(cyclohexylmethyl)-1-[2-[[4-(7-fluoro-1H-indazol-4-yl)triazol-1-yl]methyl]imidazo[1,2-a]pyridin-6-yl]methanamine;
1-[[[2-[[4-(7-fluoro-1H-indazol-4-yl)triazol-1-yl]methyl]imidazo[1,2-a]pyridin-6-yl]methylamino]methyl]cyclobutanol;
1-[[[2-[[4-(7-fluoro-1H-indazol-4-yl)triazol-1-yl]methyl]imidazo[1,2-a]pyridin-6-yl]methylamino]methyl]cyclopentanamine;
N-[[6-[(4,4-dimethyl-1-piperidyl)methyl]imidazo[1,2-a]pyridin-2-yl]methyl]-5-fluoro-4-oxo-chromene-2-carboxamide;
N-(cyclobutylmethyl)-1-[2-[[4-(6-morpholino-1H-indazol-4-yl)triazol-1-yl]methyl]imidazo[1,2-a]pyridin-6-yl]methanamine;
6-[2-(2-aminoethoxy)ethoxy]-N-[[6-[(4,4-dimethyl-1-piperidyl)methyl]imidazo[1,2-a]pyridin-2-yl]methyl]-1H-indazole-4-carboxamide;
N-[[6-[1-(cyclobutylmethylamino)-2-phenyl-ethyl]imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-[[6-[1-[bis(cyclobutylmethyl)amino]-2-phenyl-ethyl]imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;
1-[2-[[4-(7-chloro-1H-indazol-4-yl)triazol-1-yl]methyl]imidazo[1,2-a]pyridin-6-yl]-N-(cyclobutylmethyl)methanamine;
1-[[[2-[[4-(7-chloro-1H-indazol-4-yl)triazol-1-yl]methyl]imidazo[1,2-a]pyridin-6-yl]methylamino]methyl]cyclobutanol;
[2-[[4-(6-fluoro-1H-indazol-4-yl)triazol-1-yl]methyl]imidazo[1,2-a]pyridin-6-yl]methanol
N-(cyclobutylmethyl)-1-[2-[[4-(6-fluoro-1H-indazol-4-yl)triazol-1-yl]methyl]imidazo[1,2-a]pyridin-6-yl]methanamine;
1-[[[2-[[4-(6-fluoro-1H-indazol-4-yl)triazol-1-yl]methyl]imidazo[1,2-a]pyridin-6-yl]methylamino]methyl]cyclobutanol;
N-(cyclohexylmethyl)-1-[2-[[4-(6-fluoro-1H-indazol-4-yl)triazol-1-yl]methyl]imidazo[1,2-a]pyridin-6-yl]methanamine;
N-[[2-[[4-(6-cyclopropyl-1H-indazol-4-yl)triazol-1-yl]methyl]imidazo[1,2-a]pyridin-6-yl]methyl]-2,2-dimethyl-propan-1-amine;
N-[[6-[(cyclobutylmethylamino)methyl]imidazo[1,2-a]pyridin-2-yl]methyl]-1H-indazole-4-carboxamide;
N-(cyclobutylmethyl)-1-[2-[[4-(1H-pyrazolo[4,3-c]pyridin-4-yl)triazol-1-yl]methyl]imidazo[1,2-a]pyridin-6-yl]methanamine;
N-(cyclohexylmethyl)-1-[2-[[4-(1H-pyrazolo[4,3-c]pyridin-4-yl)triazol-1-yl]methyl]imidazo[1,2-a]pyridin-6-yl]methanamine;
1-[[[2-[[4-(1H-pyrazolo[4,3-c]pyridin-4-yl)triazol-1-yl]methyl]imidazo[1,2-a]pyridin-6-yl]methylamino]methyl]cyclobutanol;
N-(cyclobutylmethyl)-1-[2-[[4-(1H-indazol-4-yl)triazol-1-yl]methyl]imidazo[1,2-a]pyridin-6-yl]methanamine;
1-[[[2-[[4-(1H-indazol-4-yl)triazol-1-yl]methyl]imidazo[1,2-a]pyridin-6-yl]methylamino]methyl]cyclohexanol;
2-[[4-(1H-indazol-4-yl)imidazol-1-yl]methyl]-6-methyl-imidazo[1,2-a]pyridine;
N-[[6-[2-cyano-1-(cyclobutylmethylamino)ethyl]imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[[6-(6-methylmorpholin-3-yl)imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[[6-(7-bromo-9-methoxy-2,3,4,5-tetrahydro-1,4-benzoxazepin-3-yl)imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-[(6-piperazin-2-ylimidazo[1,2-a]pyridin-2-yl)methyl]pyrido[1,2-a]pyrimidine-2-carboxamide;

N-[[6-(6-cyclohexyl-4-oxo-2-piperidyl)imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;
1-[2-(1H-indazol-4-yl)thiazol-5-yl]-1-(6-methylimidazo[1,2-a]pyridin-2-yl)ethanol;
2-[[1-(1H-indazol-4-yl)triazol-4-yl]methyl]imidazo[1,2-a]pyridine;
N-[(3,3-difluorocyclobutyl)methyl]-1-[2-[[1-(1H-indazol-4-yl)triazol-4-yl]methyl]imidazo[1,2-a]pyridin-6-yl]methanamine;
4-[1-[[6-[(cyclobutylmethylamino)methyl]imidazo[1,2-a]pyridin-2-yl]methyl]triazol-4-yl]-1H-indazole-6-carbonitrile;
N-(cyclobutylmethyl)-1-[2-[[4-(1H-indazol-4-yl)imidazol-1-yl]methyl]imidazo[1,2-a]pyridin-6-yl]methanamine;
N-[[6-[[acetyl(cyclobutylmethyl)amino]methyl]imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-(cyclobutylmethyl)-1-[2-[[3-(1H-indazol-4-yl)-1,2,4-triazol-1-yl]methyl]imidazo[1,2-a]pyridin-6-yl]methanamine;
2-[1-[[6-[(cyclobutylmethylamino)methyl]imidazo[1,2-a]pyridin-2-yl]methyl]triazol-4-yl]pyrido[1,2-a]pyrimidin-4-one;
N-[[6-[(2-bicyclo[2.2.1]hept-5-enylmethylamino)methyl]imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[[6-[[[(1R,2R,4S)-norbornan-2-yl]methylamino]methyl]imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[[6-[[[(1R,2S,4S)-norbornan-2-yl]methylamino]methyl]imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[[6-(2-oxa-5-azabicyclo[2.2.1]heptan-5-ylmethyl)imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[[6-(2-azabicyclo[2.2.1]heptan-2-ylmethyl)imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[[6-(2-azabicyclo[2.2.2]octan-2-ylmethyl)imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;
N-[[6-[[(2,2-difluorospiro[3.3]heptan-6-yl)amino]methyl]imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-[[6-[[[rac-(1S,2S,4S)-7-oxabicyclo[2.2.1]hept-5-en-2-yl]methylamino]methyl]imidazo[1,2-a]pyridin-2-yl]methyl]pyrido[1,2-a]pyrimidine-2-carboxamide;
4-oxo-N-[[6-[[[rac-(1S,2R,4S)-7-oxabicyclo[2.2.1]hept-5-en-2-yl]methylamino]methyl]imidazo[1,2-a]pyridin-2-yl]methyl]pyrido[1,2-a]pyrimidine-2-carboxamide; and

N-[(1-methoxycyclobutyl)methyl]-1-[2-[[4-(6-methoxy-1H-indazol-4-yl)triazol-1-yl]methyl]imidazo[1,2-a]pyridin-6-yl]methanamine.

(iii) Compounds of formulae (II), (VI) or (VII)

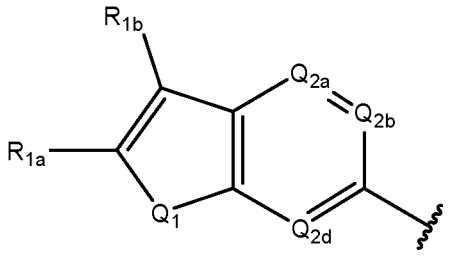
[0091] A further group of METTL3 inhibitors is defined by the formula II shown below:

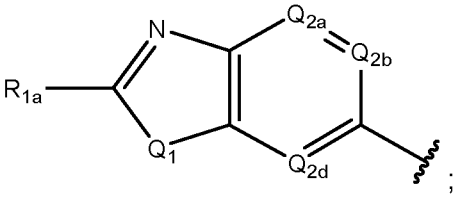
$$X - Y - Z$$

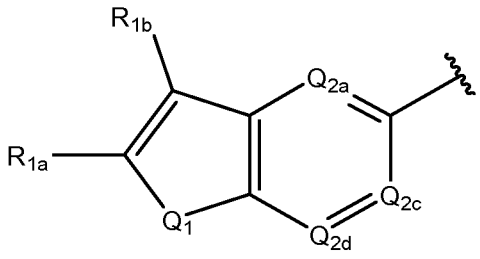
(II)

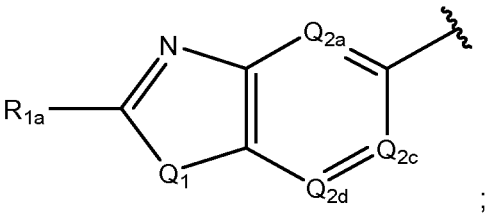
wherein:

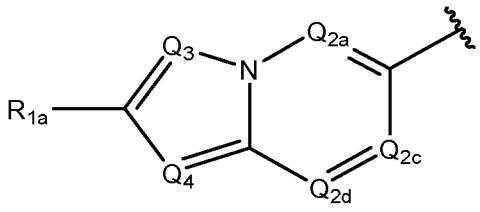
X is selected from:

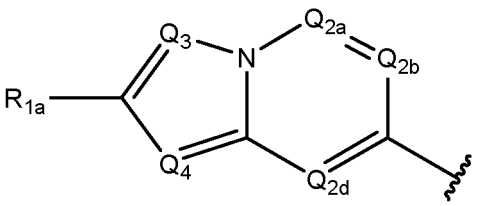

;


;


;


;


; and



wherein

Q_1 is selected from NH, N-C_{1-4}alkyl, O or S;

Q_{2a} is selected from N or CR_{2a};

Q_{2b} is selected from N or CR_{2b};

Q_{2c} is selected from N or CR_{2c};

Q_{2d} is selected from N or CR_{2d};

Q_3 is selected from N or CR_{1b};

Q_4 is selected from N or CR_{1x};

subject to the proviso that no more than 3 of Q_1, Q_{2a}, Q_{2b}, Q_{2c}, Q_{2d}, Q_3 and Q_4 are nitrogen;

R_{1a} is selected from:

(i) C_{1-4}alkyl or C_{1-4}alkoxy, each of which being optionally substituted by halo, cyano, hydroxy, C_{3-6}cycloalkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, aryl or heteroaryl; or

(ii) a group of the formula:

$$-(CR_{1c}R_{1d})_p-NR_{1e}R_{1f};$$

wherein

p is an integer selected from 0, 1, 2 or 3

R_{1c} and R_{1d} are independently selected from:

(i) hydrogen (including deuterium),

(ii) C_{1-6}alkyl which is optionally substituted by one more substituents selected from cyano, oxo, hydroxy, C_{1-4}alkoxy, halo, C_{1-4}haloalkoxy, C_{3-6}cycloalkyl, -O-C_{3-6}cycloalkyl, $NR_{1ca}R_{1da}$ or -$S(O)_{0-2}R_{1ca}R_{1da}$, wherein R_{1ca} and R_{1da} are H or C_{1-2}alkyl; and wherein C_{3-6}cycloalkyl and -O-C_{3-6}cycloalkyl are optionally further substituted with halo, cyano or hydroxy;

(iii) C_{3-4}cycloalkyl or 3 to 5 membered heterocyclyl, each of which is optionally substituted by C_{1-4}alkyl, C_{1-4}haloalkyl, cyano, hydroxy, C_{1-2}alkoxy, halo, C_{1-2}haloalkoxy, $NR_{1ca}R_{1da}$ or -$S(O)_{0-2}R_{1ca}R_{1da}$, wherein R_{1ca} and R_{1da} are H or C_{1-2}alkyl; and;

(iv) or R_{1c} and R_{1d} are linked together such that, together with the carbon atom to which they are attached, they form a 3- to 6-membered cycloalkyl or heterocyclic ring, or a spirocyclic ring system, each of which is optionally substituted by one or more substituents selected from C_{1-2}alkyl, C_{1-2}haloalkyl, cyano, hydroxy, C_{1-2}alkoxy, halo, C_{1-2}haloalkoxy, $NR_{1ca}R_{1da}$ or -$S(O)_{0-2}R_{1ca}R_{1da}$, wherein R_{1ca} and R_{1da} are H or C_{1-2}alkyl;

R_{1e} and R_{1f} are each independently selected from:

(i) hydrogen (including deuterium);

(ii) C_{1-6}alkyl which is optionally substituted by one more substituents selected from cyano, oxo, hydroxy, C_{1-2}alkoxy, halo, C_{1-2}haloalkoxy, $NR_{1ea}R_{1fa}$ or -$S(O)_{0-2}R_{1ea}R_{1fa}$, wherein R_{1ea} and R_{1fa} are H or C_{1-2}alkyl;

(iii) a group with the formula:

$-(CR_{1g}R_{1h})_q-T_1$

wherein:

q is 0, 1, 2, 3, 4, 5 or 6;

R_{1g} and R_{1h} are independently selected from:

a) hydrogen;

b) C_{1-6}alkyl which is optionally substituted by one more substituents selected from cyano, hydroxy, C_{1-4}alkoxy, halo, C_{1-4}haloalkoxy, -O-C_{3-6}cycloalkyl, $NR_{1ga}R_{1ha}$ or $-S(O)_{0-2}R_{1ga}R_{1ha}$, wherein R_{1ga} and R_{1ha} are H or C_{1-2}alkyl; and wherein -O-C_{3-6}cycloalkyl is optionally substituted with halo, cyano or hydroxy;

c) an aryl-C_{1-6}alkyl, heteroarylC_{1-6}alkyl, C_{3-6}-cycloalkyl or C_{3-6}cycloalkylC_{1-6}alkyl group, each of which is optionally substituted by one or more substituents selected from C_{1-2}alkyl, cyano, C_{1-2}haloalkyl, hydroxy, C_{1-2}alkoxy, halo, C_{1-2}-haloalkoxy, $NR_{1ga}R_{1ha}$ or $-S(O)_{0-2}R_{1ga}R_{1ha}$, wherein R_{1ga} and R_{1ha} are H or C_{1-2}alkyl; or

d) or R_{1g} and R_{1h} are optionally linked together such that, together with the carbon atom to which they are attached, they form a 3- to 6-membered cycloalkyl or heterocyclic ring which is optionally substituted by one or more substituents selected from C_{1-2}alkyl, cyano, C_{1-2}haloalkyl, hydroxy, C_{1-2}alkoxy, halo, C_{1-2}haloalkoxy, $NR_{1ga}R_{1ha}$ or $-S(O)_{0-2}R_{1ga}R_{1ha}$, wherein R_{1ga} and R_{1ha} are H or C_{1-2}alkyl;

and T_1 is selected from hydrogen, cyano, hydroxy, $NR_{1t}R_{2t}$ or $-S(O)_{0-2}R_{1t}R_{2t}$ (wherein R_{1t} and R_{2t} are H or C_{1-4}alkyl), C_{3-8}cycloalkyl, C_{2-3}alkenyl, C_{2-3}alkynyl, aryl, heterocyclyl, heteroaryl, a spirocyclic carbocyclic or heterocyclic ring system, a bridged C_{3-8}cycloalkyl, a bridged bicyclic C_{5-12}cycloalkyl, or a bridged heterocyclic ring system, each of which is optionally substituted by one or more substituents selected from C_{1-2}alkyl, C_{1-2}-

haloalkyl, cyano, hydroxy, C_{1-2}alkoxy, halo, C_{1-2}-haloalkoxy, $NR_{3t}R_{4t}$ or $-S(O)_{0-2}R_{3t}R_{4t}$, wherein R_{3t} and R_{4t} are H or C_{1-2}alkyl;

(iv) or R_{1e} and R_{1f} are linked such that, together with the nitrogen atom to which they are attached, they form a mono- or bicyclic-heterocyclic ring, which is optionally substituted by one or more substituents selected from C_{1-4}alkyl, C_{1-4}haloalkyl, cyano, hydroxy, C_{1-4}alkoxy, halo, C_{1-4}haloalkoxy, $NR_{1i}R_{1j}$ or $-S(O)_{0-2}R_{1i}R_{1j}$, wherein R_{1i} and R_{1j} are H or C_{1-4}alkyl, and/or the mono- or bicyclic heterocyclic ring formed by R_{1e} and R_{1f} is optionally spiro-fused to a C_{3-6}cycloalkyl or a heterocyclic ring, which in turn is optionally substituted by one or more substituents selected from C_{1-4}alkyl, C_{1-4}haloalkyl, cyano, hydroxy, C_{1-4}alkoxy, halo, C_{1-4}haloalkoxy, $NR_{1i}R_{1j}$ or $-S(O)_{0-2}R_{1i}R_{1j}$, wherein R_{1i} and R_{1j} are H or C_{1-4}alkyl;

R_{1b} is selected from hydrogen, cyano, halo or C_{1-3} alkyl;

R_{1x} is selected from hydrogen, cyano, halo or C_{1-3} alkyl;

R_{2a}, R_{2b}, R_{2c} and R_{2d} are independently selected from hydrogen, cyano, halo or a group of the formula:

$$-L_{2a}-L_{2b}-Q_2$$

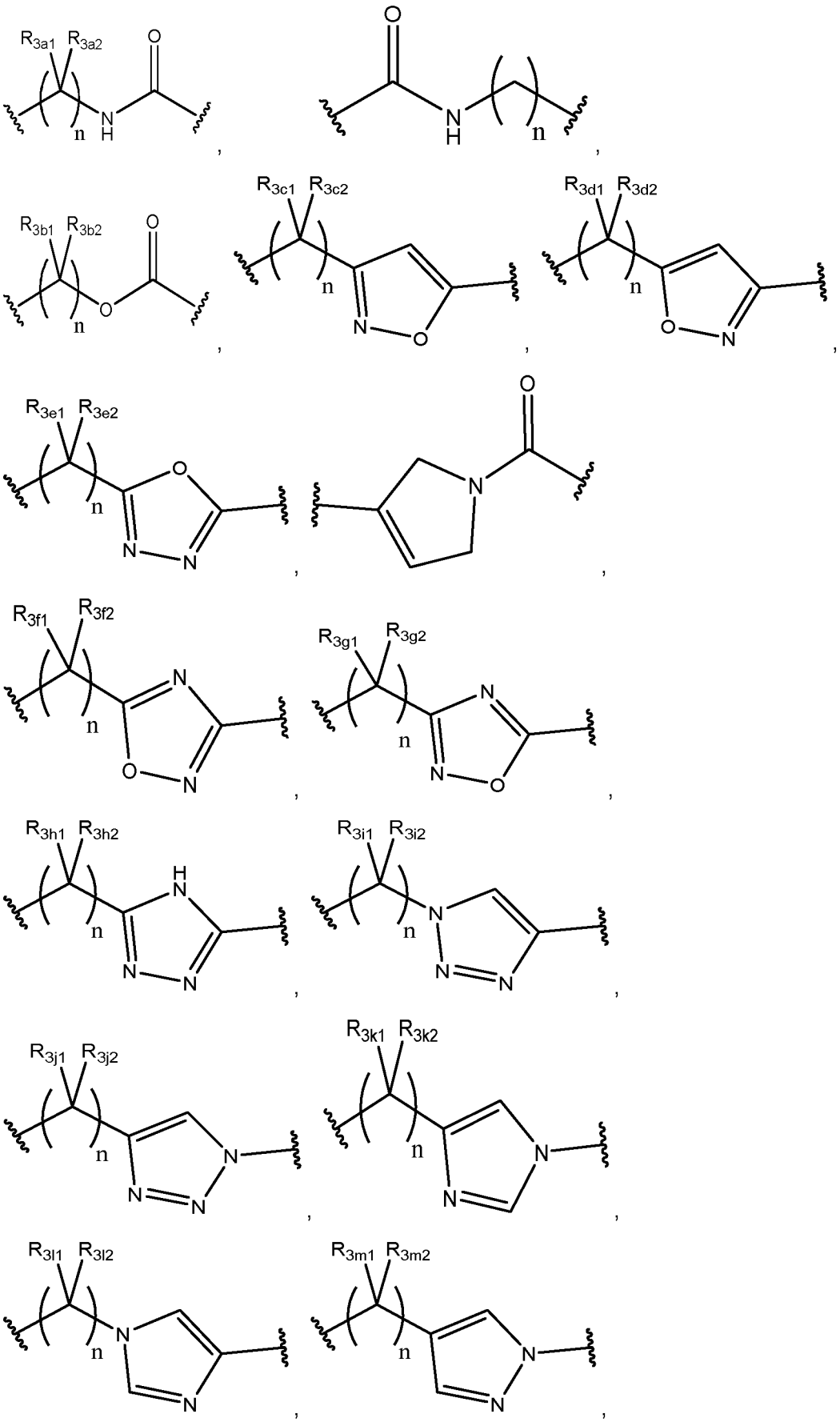
wherein

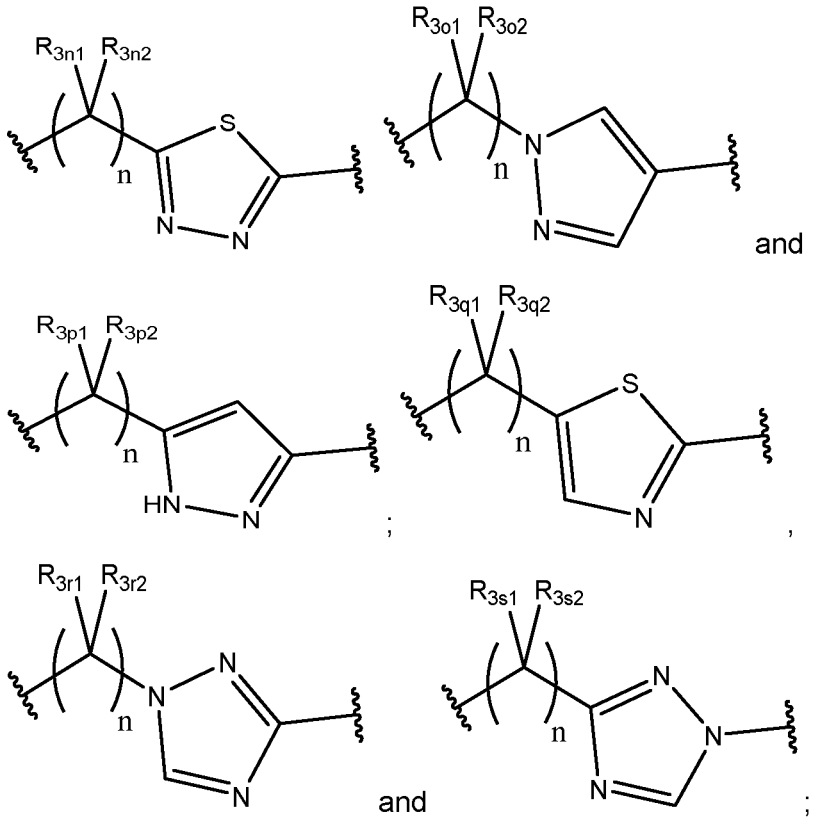
L_{2a} is absent or C_{1-3}alkylene optionally substituted by C_{1-2} alkyl or oxo;

L_{2b} is absent or selected from O, S, SO, SO_2, $N(R_n)$, C(O), C(O)O, OC(O), $C(O)N(R_n)$, $N(R_n)C(O)$, $N(R_n)C(O)N(R_o)$, $S(O)_2N(R_n)$, or $N(R_n)SO_2$, wherein R_n and R_o are each independently selected from hydrogen or C_{1-2}alkyl; and

Q_2 is hydrogen, cyano, C_{1-6}alkyl, C_{3-6}cycloalkyl, aryl, heterocyclyl or heteroaryl, each of which is optionally substituted by one or more substituents selected from halo, trifluoromethyl, trifluoromethoxy, amino, cyano, hydroxy, amino, carboxy, carbamoyl, sulphamoyl, C_{1-4}alkyl, NR_pR_q, OR_p, $C(O)R_p$, $C(O)OR_p$, $OC(O)R_p$, $C(O)N(R_p)R_q$, $N(R_r)C(O)R_p$, $S(O)_yR_p$ (where y is 0, 1 or 2), $SO_2N(R_p)R_q$, $N(R_r)SO_2R_p$ or $(CH_2)_zNR_pR_q$ (where z is 1, 2 or 3), wherein R_p and R_q are each independently selected from hydrogen or C_{1-4}alkyl;

Y is selected from:





wherein:

R_{3a1}, R_{3b1}, R_{3c1}, R_{3d1}, R_{3e1}, R_{3f1}, R_{3g1}, R_{3h1}, R_{3i1}, R_{3j1}, R_{3k1}, R_{3l1}, R_{3m1}, R_{3n1}, R_{3o1}, R_{3p1},R_{3q1}, R_{3r1} and R_{3s1} are independently selected from hydrogen (including deuterium), $C_{1\text{-}6}$alkyl, $C_{3\text{-}4}$ cycloalkyl, hydroxy, and halo; and wherein $C_{1\text{-}6}$alkyl, or $C_{3\text{-}4}$ cycloalkyl is optionally substituted with one or more substituents selected from halo, amino, cyano, and hydroxy;

R_{3a2}, R_{3b2}, R_{3c2}, R_{3d2}, R_{3e2}, R_{3f2}, R_{3g2}, R_{3h2}, R_{3i2}, R_{3j2}, R_{3k2}, R_{3l2}, R_{3m2}, R_{3n2}, R_{3o2}, R_{3p2}-,R_{3q2}, R_{3r2} and R_{3s2} are hydrogen or halo;

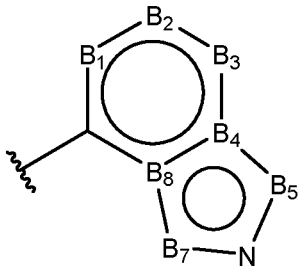
with the proviso that R_{3a1}, R_{3b1}, R_{3i1}, R_{3l1}, R_{3o1}, R_{3r1}, R_{3a2}, R_{3b2}, R_{3i2}, R_{3l2}, R_{3o2} and R_{3s1} cannot be halo when n=1 or when n=2 and the carbon atom to which they are attached is linked to an oxygen or nitrogen atom;

or R_{3a1} and R_{3a2}, R_{3b1} and R_{3b2}, R_{3c1} and R_{3c2}, R_{3d1} and R_{3d2}, R_{3e1} and R_{3e2}, R_{3f1} and R_{3f2}, R_{3g1} and R_{3g2}, R_{3h1} and R_{3h2}, R_{3i1} and R_{3i2}, R_{3j1} and R_{3j2}, R_{3k1} and R_{3k2}, R_{3l1} and R_{3l2}, R_{3m1} and R_{3m2}, R_{3n1} and R_{3n2}, R_{3o1} and R_{3o2}, R_{3p1} and R_{3p2}, R_{3q1} and R_{3q2}, or R_{3r1} and R_{3r2} or R_{3s1} and R_{3s2} may be linked such that, together with the carbon atom to which they are attached, they form a spiro-fused $C_{3\text{-}4}$cycloalkyl which is optionally substituted with one or more substituents selected from halo, methyl, amino, cyano, and hydroxy;

n is 0, 1 or 2

Z is selected from one of the following structures:

i)



wherein:

B_1 is A_5, wherein A_5 is selected from CR_{16} and N, wherein R_{16} is selected from hydrogen, halo, cyano, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, a 5- or 6-membered heteroaryl, C_{1-4} alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{3-4}cycloalkyl, a 3- to 4-membered heterocyclyl and C_{3-4}cycloalkoxy;

B_2 is A_6, wherein A_6 is selected from N or CR_{17}, wherein R_{17}, R_{H2}, R_{H4} and R_{H5} are selected from hydrogen, hydroxy, halo, cyano, C_{1-5} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, a 5- or 6-membered or heteroaryl, C_{3-6}cycloalkyl, -O-C_{3-6}cycloalkyl, heterocyclyl, -O-heterocyclyl (carbon-linked), -$(OCH_2CH_2)_m$-NR_qR_r, -$(OCH_2CH_2)_m$-OCH_3 wherein m is an integer from 1 to 6, NR_qR_r, -C(O)-NR_qR_r, -C(O)OR_q,

wherein R_q and R_r are each independently hydrogen, C_{1-5} alkyl, C_{3-6}cycloalkyl, a 3- to 6- membered carbon-linked heterocyclyl, or R_q and R_r are linked together such that, together with the nitrogen atom to which they are attached, they form a 3- to 6-membered heterocyclic ring;
wherein any C_{1-5}alkyl, C_{1-4} alkoxy, C_{2-4}alkenyl, C_{2-4}alkynyl, phenyl, 5- or 6-membered or heteroaryl, C_{3-6}cycloalkyl, -O-C_{3-6}cycloalkyl, heterocyclyl or -O-heterocyclyl (carbon-linked)is optionally further substituted by one or more substituents selected from C_{1-2}alkyl, cyano, C_{1-2}haloalkyl, hydroxy, C_{1-2}alkoxy, halo, C_{1-2}haloalkoxy, $NR_{1ea}R_{1fa}$ or -$S(O)_{0-2}R_{1ea}R_{1fa}$, wherein R_{1ea} and R_{1fa} are H or C_{1-2}alkyl;

B_3 is N or CR_{Z1}, wherein R_{Z1} is selected from hydrogen, C_{1-4}alkyl, cyano, halo, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{1-4}alkoxy, C_{3-6}cycloalkyl and -O-C_{3-6}cycloalkyl, wherein C_{3-6}cycloalkyl and -O-C_{3-6}cycloalkyl are optionally substituted by one or more of halo, methyl or methoxy;
B_4 is selected from C or N;

B_5 is selected from CR_{zi1b} or NR_{B5N}, wherein:

R_{Zi1b} is selected from hydrogen, C_{1-4}alkyl, cyano, halo, NH_2 and C_{1-4}alkoxy; and

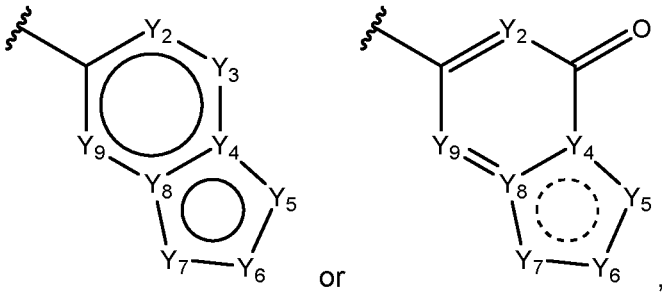
R_{B5N} is selected from hydrogen or C_{1-4}alkyl;

B_7 is N, NR_{Z2N} or CR_{Z2}, wherein R_{Z2} is selected from hydrogen, C_{1-4}alkyl, cyano, halo, NH_2 and C_{1-4}alkoxy; and R_{Z2N} is selected from hydrogen or C_{1-4}alkyl;

B_8 is selected from C or N;

with the proviso that no more than four of B_1 to B_8 are N.

ii)



Y_2 is A_7, wherein A_7 is selected from CR_{18} and N; wherein R_{18} is selected from hydrogen, halo, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{3-4}cycloalkyl, a 3- to 4-membered heterocyclyl and C_{3-4}cycloalkoxy;

Y_3 is N or CR_{z1a} wherein R_{Z1a}, is selected from hydrogen, hydroxy, C_{1-4}alkyl, cyano, halo, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{1-4}alkoxy, C_{3-6}cycloalkyl and -O-C_{3-6}cycloalkyl, wherein C_{3-6}cycloalkyl and -O-C_{3-6}cycloalkyl are optionally substituted by one or more of halo, methyl or methoxy;

Y_4 is C or N

Y_5 is C-R_{Y5} or NR_{Y5N}, wherein:

R_{Y5} is selected from hydrogen, C_{1-4}alkyl, cyano, halo, NH_2 and C_{1-4}alkoxy;

R_{Y5N} is selected from hydrogen or C_{1-4}alkyl;

Y_6 is C-R_{Zi2e} or N, wherein R_{Zi2e} is selected from hydrogen, C_{1-4}alkyl, cyano, halo, NH_2 and C_{1-4}alkoxy

Y_7 is O, S, CR_{Z2a} or N, wherein R_{Z2a} is selected from hydrogen, C_{1-4}alkyl, cyano, halo, NH_2 and C_{1-4}alkoxy;

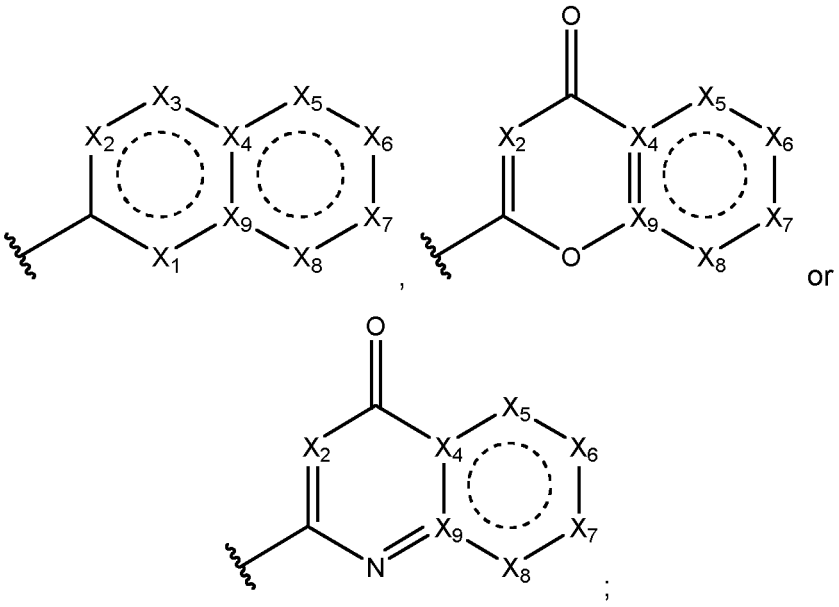
Y_8 Is C or N;

Y_9 is CR_{Z3a} or N; wherein

R_{Z3a} is selected from hydrogen, C_{1-4}alkyl, cyano, halo, NH_2 and C_{1-4}alkoxy;

with the proviso that no more than four of Y_1 to Y_8 are N.

(iii)



X_1 is N or C-R_{Z9}, wherein R_{Z9} is selected from hydrogen, halo, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkoxy, C_{1-4} haloalkoxy;

X_2 is selected from N or CR_4 wherein:

R_4 is selected from hydrogen, halo, cyano, C1-4 alkyl, C1-4 haloalkyl, C1-4alkoxy, C1-4 haloalkoxy (e.g. hydrogen, halo, cyano and methyl);

X_3 is N;

X_4 is N or C;

X_5 is selected from N, CR_5 and $CRx_{5a}R_{X5b}$ wherein:

R_5 is selected from hydrogen, halo, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkoxy, C_{1-4} haloalkoxy (e.g. hydrogen, halo, cyano and methyl);

Rx_{5a} and R_{X5b} are independently selected from hydrogen, halo, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkoxy, C_{1-4} haloalkoxy (e.g. hydrogen, halo, cyano and methyl);

either:

X_6 is A_1 and X_7 is A_2; or

X_6 is A_8 and X_7 is A_9 or A_{11}, wherein:

A_1 is selected from CR_{12} and N; wherein

R_{12} is selected from selected from hydrogen, halo, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkoxy and C_{1-4} haloalkoxy (e.g. hydrogen, halo, cyano and C_{1-4} alkyl);

A_2 is selected from CR_{13} and N, wherein

R_{13} selected from hydrogen, halo, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkoxy, C_{1-4} haloalkoxy (e.g. hydrogen, halo, cyano, methoxy and methyl);

A_8 is selected from $CR_{19}R_{20}$ and NR_{21}; wherein

R_{19} and R_{20} are independently selected from hydrogen, halo, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkoxy, C_{1-4} haloalkoxy (e.g. hydrogen, halo, cyano and C_{1-4} alkyl);

R_{21} is hydrogen or C_{1-4}alkyl.

A_9 is selected from $CR_{22}R_{23}$ and NR_{24};

wherein R_{22} and R_{23} are independently selected from selected from hydrogen, halo, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkoxy, C_{1-4} haloalkoxy (e.g. hydrogen, halo, cyano and methyl);

R_{24} is selected from hydrogen or C_{1-4}alkyl

A_{11} is selected from $CR_{28}R_{29}$ and NR_{30};

R_{28} and R_{29} are selected from hydrogen, halo, methoxy and methyl;

R_{30} is selected from hydrogen or C_{1-4}alkyl.

X_8 is selected from CR_6, N or $CR_{X6a}R_{X6b}$;

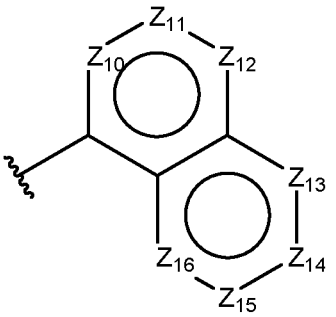
wherein R_6 is selected from hydrogen, halo, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkoxy and C_{1-4} haloalkoxy;

R_{X6a} and R_{X6b} are each independently selected from hydrogen, halo, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkoxy and C_{1-4} haloalkoxy;

X_9 is N or C;

with the proviso that no more than four of X_2 to X_9 are N.

(iv)



Z_{10} is N or C-R_{Z10}, wherein R_{Z10} is selected from hydrogen, halo, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkoxy, C_{1-4} haloalkoxy;;

Z_{11} is N or C-R_{Z11}, wherein R_{Z11} is selected from hydrogen, halo, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkoxy, C_{1-4} haloalkoxy;;

Z_{12} is N or C-R_{Z12}, wherein R_{Z12} is selected from hydrogen, halo, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkoxy, C_{1-4} haloalkoxy;

Z_{13} is N or C-R_{Z13}, wherein R_{Z13} is selected from hydrogen, halo, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkoxy, C_{1-4} haloalkoxy;

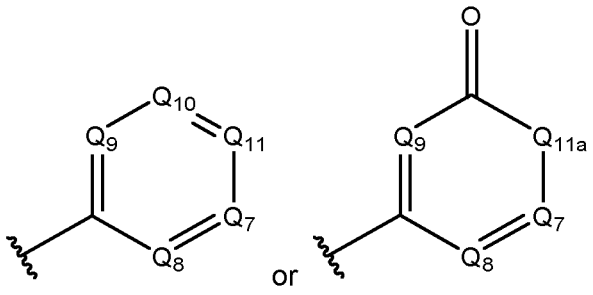
Z_{14} is N or C-R_{Z14}, wherein R_{Z14} is selected from hydrogen, halo, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkoxy, C_{1-4} haloalkoxy;

Z_{15} is N or C-R_{Z15}, wherein R_{Z15} is selected from hydrogen, halo, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkoxy, C_{1-4} haloalkoxy;

Z_{16} is N or C-R_{Z16}, wherein R_{Z16} is selected from hydrogen, halo, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkoxy, C_{1-4} haloalkoxy;

with the proviso that no more than three of Z_{10} to Z_{16} are N;

(v)



Q_7 is CR_7 or N;

Q_8 is CR_8 or N;

Q_9 is CR_9 or N;

Q_{10} is CR_{10} or N;

Q_{11} is CR_{11} or N;

Q_{11a} is NR_{11N} or $CR_{11a}R_{11b}$;

wherein R_7, R_8, R_9, R_{10}, R_{11}, R_{11a} and R_{11b} are each independently selected from hydrogen, NH_2, halo, cyano, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{1-6} alkyl, $-CH_2OCH_3$, $-CH_2SO_2CH_3$, $-SO_2CH_3$, $-NHC(O)CH_3$ and $-C(O)NR_{v1}R_{v2}$, wherein R_{v1} and R_{v2} are independently selected from hydrogen and methyl and; and R_{11N} is selected from hydrogen, NH_2, halo, cyano, and C_{1-6} alkyl;

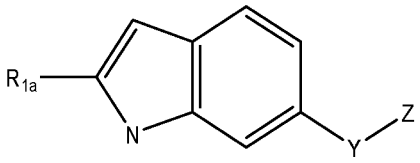
or

R_9 and R_{10} may be linked together such that, together to the atoms to which they are attached, they form a fused 5- or 6-membered saturated or unsaturated ring system, or R_{10} and R_{11} may be linked together such that, together to the atoms to which they are attached, they form a fused 5- or 6-membered saturated or unsaturated ring system, wherein either of the fused 5- or 6-membered saturated or unsaturated ring

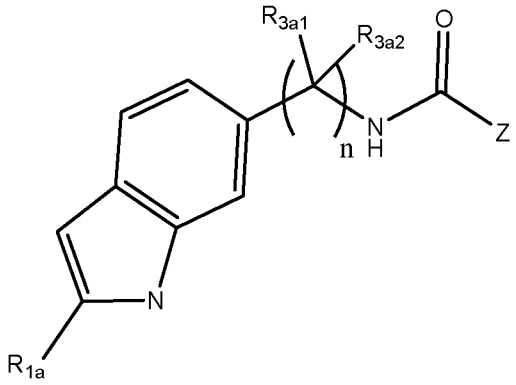
system may be optionally substituted by one or more substituents selected from C_{1-2}alkyl, cyano, C_{1-2}haloalkyl, hydroxy, C_{1-2}alkoxy, halo, C_{1-2}haloalkoxy, $NR_{1ia}R_{1ja}$ or -$S(O)_{0-2}R_{1ia}R_{1ja}$, wherein R_{1ia} and R_{1ja} are H or C_{1-2}alky;

with the proviso that no more than three of Q_7 to Q_{11} are N.

[0095] In a particular group of compounds of formula II above, the compounds are of the formula:



VI



VII

wherein R_{1a}, Y, Z, n, R_{3a1} and R_{3a2} each have any one of the meanings defined above; or a pharmaceutically acceptable salt thereof.

[0096] Suitably, n is 1 and R_{3a1} and R_{3a2} are hydrogen.

[0097] Suitably, R_{1a} is a group of the formula:

$$-(CR_{1c}R_{1d})_p-NR_{1e}R_{1f};$$

wherein

p is 1;

R_{1c} and R_{1d} are independently selected from hydrogen (including deuterium) or C_{1-2}alkyl;

R_{1e} is selected from hydrogen (including deuterium) or C_{1-2}alkyl; and

R_{1f} is a group with the formula:

$$-(CR_{1g}R_{1h})_q-T_1$$

wherein:

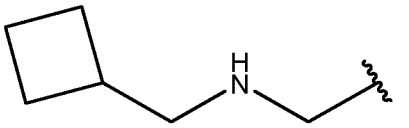
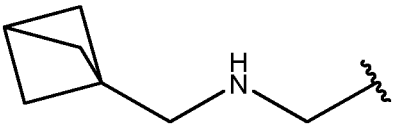
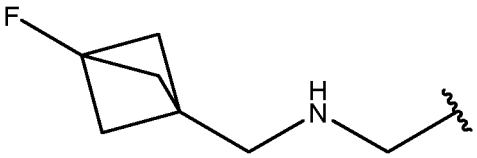
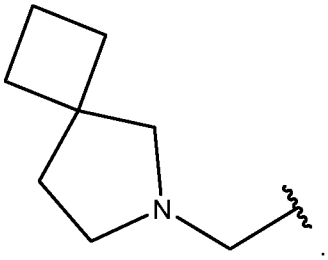
q is 1;

R_{1g} and R_{1h} are independently selected from hydrogen (including deuterium) or C_{1-2}alkyl;

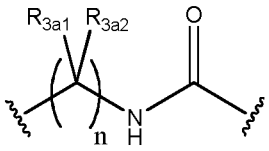
and T_1 is selected from C_{3-4}cycloalkyl, heterocyclyl, a spirocyclic carbocyclic or heterocyclic ring system, a bridged C_{3-8}cycloalkyl, a bridged bicyclic C_{5-12}cycloalkyl, or a bridged heterocyclic ring system, each of which is optionally substituted by one or more substituents selected from C_{1-2}alkyl, C_{1-2}haloalkyl, cyano, hydroxy, C_{1-2}alkoxy, halo, C_{1-2}haloalkoxy or C_{3-6}cycloalkyl,

wherein any alkyl or alkoxy is optionally further substituted by one or more substituents selected from cyano, hydroxy or halo.

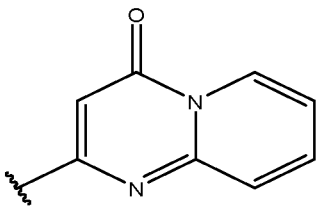
[0098] Most suitably, R_{1a} is selected from:


,


and

.

[0099] Suitably Y is:


wherein n is 1 and R_{3a1} and R_{3a2} are hydrogen.

[00100] Suitably, Z is:



(iv) specific compounds of formula II - List 2

[00101] Particular compounds of formula II above include any of the following, or a pharmaceutically acceptable salt thereof:

List 2

N-({2-[(4,4-dimethylpiperidin-1-yl)methyl]-1H-indol-6-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[(2-{[(cyclobutylmethyl)amino]methyl}-1H-indol-6-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-[[(3,3-difluorocyclobutyl)methylamino]methyl]-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-[[(1-hydroxycyclobutyl)methylamino]methyl]-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-[[(1-fluorocyclobutyl)methylamino]methyl]-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-[[(1-methylcyclopropyl)methylamino]methyl]-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide.

N-[[2-(2-azabicyclo[2.1.1]hexan-2-ylmethyl)-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-(3-azabicyclo[3.1.1]heptanean-3-ylmethyl)-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-[[2-(hydroxymethyl)pyrrolidin-1-yl]methyl]-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-(morpholinomethyl)-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-[(1-adamantylamino)methyl]-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

4-oxo-N-[[2-(1-piperidylmethyl)-1H-indol-6-yl]methyl]pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-[(4-fluoro-1-piperidyl)methyl]-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

4-oxo-N-[[2-[[[rac-(1S,2S,4S)-7-oxabicyclo[2.2.1]heptane-5-en-2-yl]methylamino]methyl]-1H-indol-6-yl]methyl]pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-[[(1-hydroxycyclopentyl)methylamino]methyl]-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

4-oxo-N-[[2-[[[rac-(1S,2R,4S)-7-oxabicyclo[2.2.1]heptane-5-en-2-yl]methylamino]methyl]-1H-indol-6-yl]methyl]pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-[(1-bicyclo[1.1.1]pentanylamino)methyl]-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-[(cyclobutylamino)methyl]-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-({2-[({bicyclo[2.2.1]heptanean-2-yl}amino)methyl]-1H-indol-6-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-[(cyclopropylamino)methyl]-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-(2-azabicyclo[2.2.2]octan-2-ylmethyl)-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-[[(2,2-difluorocyclopropyl)methylamino]methyl]-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[(2-{[({3-fluorobicyclo[1.1.1]pentan-1-yl}methyl)amino]methyl}-1H-indol-6-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-[(cyclohexylmethylamino)methyl]-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-[[(1-hydroxycyclohexyl)methylamino]methyl]-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-[(cyclopentylamino)methyl]-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-[(cyclopentylmethylamino)methyl]-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-[[(1-methoxycyclobutyl)methylamino]methyl]-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-[(isobutylamino)methyl]-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-[(cyclohexylamino)methyl]-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-[(cyclopropylmethylamino)methyl]-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

4-oxo-N-[[2-[(prop-2-ynylamino)methyl]-1H-indol-6-yl]methyl]pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-[(oxetan-2-ylmethylamino)methyl]-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-[(2,2-dimethylpropylamino)methyl]-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-[(1-bicyclo[1.1.1]pentanylmethylamino)methyl]-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-{[2-({[(1S,2S)-2-hydroxycyclopentyl]amino}methyl)-1H-indol-6-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-{[2-({[(1R,2R)-2-hydroxycyclopentyl]amino}methyl)-1H-indol-6-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-{[2-({[(1S,2R)-2-hydroxycyclopentyl]amino}methyl)-1H-indol-6-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-{[2-({[(1R,2S)-2-hydroxycyclopentyl]amino}methyl)-1H-indol-6-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-[(cyclopropylmethylamino)methyl]-5-fluoro-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-[(cyclobutylmethylamino)methyl]-5-fluoro-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

4-oxo-N-[[2-[(2,2,2-trifluoroethylamino)methyl]-1H-indol-6-yl]methyl]pyrido[1,2-a]pyrimidine-2-carboxamide

N-[(2-{[N-(cyclobutylmethyl)acetamido]methyl}-1H-indol-6-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

4-oxo-N-{[2-(piperidin-2-yl)-1H-indol-6-yl]methyl}-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[(2-{[(cyclobutylmethyl)amino]methyl}-3-fluoro-1H-indol-6-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[(2-{[(cyclobutylmethyl)amino]methyl}-1-methyl-1H-indol-6-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-[(Cyclobutylmethylamino)-dideuterio-methyl]-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-[(cyclobutylmethylamino)methyl]-1H-indol-6-yl]methyl]-1H-indazole-4-carboxamide

N-[[2-[(cyclobutylmethylamino)methyl]-1H-pyrrolo[3,2-b]pyridin-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-(1H-indol-6-ylmethyl)-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-(1H-indol-2-ylmethyl)-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-(indolizin-2-ylmethyl)-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[(6-{[4-(1H-indazol-4-yl)-1H-1,2,3-triazol-1-yl]methyl}-1H-indol-2-yl)methyl]cyclopropanamine

(1R,2S)-2-[[6-[[4-(1H-indazol-4-yl)triazol-1-yl]methyl]-1H-indol-2-yl]methylamino]cyclopentanol

N-[[6-[[4-(1H-indazol-4-yl)triazol-1-yl]methyl]-1H-indol-2-yl]methyl]cyclopentanamine

N-(cyclopropylmethyl)-1-[6-[[4-(1H-indazol-4-yl)triazol-1-yl]methyl]-1H-indol-2-yl]methanamine

1-[[[6-[[4-(1H-indazol-4-yl)triazol-1-yl]methyl]-1H-indol-2-yl]methylamino]methyl]cyclobutanol

N-(cyclobutylmethyl)-1-[6-[[4-(1H-indazol-4-yl)triazol-1-yl]methyl]-1H-indol-2-yl]methanamine

N-(cyclobutylmethyl)-1-[6-[[4-(1H-indazol-4-yl)triazol-1-yl]methyl]-1H-pyrrolo[3,2-b]pyridin-2-yl]methanamine

N-(cyclobutylmethyl)-1-[6-[[4-(1H-indazol-4-yl)triazol-1-yl]methyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methanamine

N-(cyclobutylmethyl)-1-[6-[[4-(1H-indazol-4-yl)triazol-1-yl]methyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methanamine

2-[1-[[2-[(cyclobutylmethylamino)methyl]-1H-indol-6-yl]methyl]triazol-4-yl]pyrido[1,2-a]pyrimidin-4-one

N-(cyclobutylmethyl)-1-[6-[[4-(6-methoxyimidazo[1,5-a]pyridin-8-yl)triazol-1-yl]methyl]-1H-indol-2-yl]methanamine

N-(cyclobutylmethyl)-1-[6-[[4-(1H-indazol-4-yl)imidazol-1-yl]methyl]-1H-indol-2-yl]methanamine

N-(cyclobutylmethyl)-1-[6-[[3-(1H-indazol-4-yl)-1,2,4-oxadiazol-5-yl]methyl]-1H-indol-2-yl]methanamine

N-[[2-(2-azaspiro[3.3]heptanean-2-ylmethyl)-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-[(benzylamino)methyl]-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-(3-azabicyclo[3.1.0]hexan-3-ylmethyl)-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-[[cyclobutylmethyl(methyl)amino]methyl]-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[[2-[(cyclobutylmethylamino)methyl]-1H-pyrrolo[2,3-b]pyridin-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[(2-{[(cyclobutylmethyl)amino]methyl}-1H-1,3-benzodiazol-6-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[(2-{[(but-2-yn-1-yl)amino]methyl}-1H-indol-6-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[(2-{[(3-cyclopropylprop-2-yn-1-yl)amino]methyl}-1H-indol-6-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-({2-[({bicyclo[3.1.0]hexan-6-yl}amino)methyl]-1H-indol-6-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[(2-{[({bicyclo[2.1.1]hexan-1-yl}methyl)amino]methyl}-1H-indol-6-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[(2-{[({3-methylbicyclo[1.1.1]pentan-1-yl}methyl)amino]methyl}-1H-indol-6-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-({2-[(3-methylazetidin-1-yl)methyl]-1H-indol-6-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-({2-[(3-fluoroazetidin-1-yl)methyl]-1H-indol-6-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-({2-[(azetidin-1-yl)methyl]-1H-indol-6-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-{[2-({2-azaspiro[3.4]octan-2-yl}methyl)-1H-indol-6-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-({2-[(3-hydroxyazetidin-1-yl)methyl]-1H-indol-6-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-({2-[(3,3-dimethylazetidin-1-yl)methyl]-1H-indol-6-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

4-oxo-N-[(2-{[3-(2,2,2-trifluoroethoxy)azetidin-1-yl]methyl}-1H-indol-6-yl)methyl]-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[(2-{[3-(difluoromethyl)azetidin-1-yl]methyl}-1H-indol-6-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-({2-[(3-methoxyazetidin-1-yl)methyl]-1H-indol-6-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[(2-{[3-(tert-butoxy)azetidin-1-yl]methyl}-1H-indol-6-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

4-oxo-N-[(2-{[3-(trifluoromethyl)azetidin-1-yl]methyl}-1H-indol-6-yl)methyl]-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-({2-[(3-ethoxyazetidin-1-yl)methyl]-1H-indol-6-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-{[2-({2-azaspiro[3.5]nonan-2-yl}methyl)-1H-indol-6-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-({2-[(2-methylazetidin-1-yl)methyl]-1H-indol-6-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-({2-[(3,3-dimethylpyrrolidin-1-yl)methyl]-1H-indol-6-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-{[2-({6-fluoro-2-azaspiro[3.3]heptanean-2-yl}methyl)-1H-indol-6-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-{[2-({6,6-difluoro-2-azaspiro[3.3]heptanean-2-yl}methyl)-1H-indol-6-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-({2-[(3-cyclobutylazetidin-1-yl)methyl]-1H-indol-6-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-({2-[(3-cyclopropylazetidin-1-yl)methyl]-1H-indol-6-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-({2-[(3-tert-butylazetidin-1-yl)methyl]-1H-indol-6-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[(2-{[(1-tert-butylcyclopropyl)amino]methyl}-1H-indol-6-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-{[2-({[(3-methylcyclobutyl)methyl]amino}methyl)-1H-indol-6-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

4-oxo-N-[(2-{[(2,3,3-trimethylbutan-2-yl)amino]methyl}-1H-indol-6-yl)methyl]-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[(2-{[({imidazo[1,2-a]pyridin-2-yl}methyl)amino]methyl}-1H-indol-6-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-({2-[(3,3-diethylazetidin-1-yl)methyl]-1H-indol-6-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

4-oxo-N-[(2-{[(pent-3-yn-1-yl)amino]methyl}-1H-indol-6-yl)methyl]-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-{[2-({6-azaspiro[3.4]octan-6-yl}methyl)-1H-indol-6-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-({2-[(2,2-dimethylpyrrolidin-1-yl)methyl]-1H-indol-6-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-{[2-({octahydrocyclopenta[c]pyrrol-2-yl}methyl)-1H-indol-6-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-{[2-({5-azaspiro[2.4]heptanean-5-yl}methyl)-1H-indol-6-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[(2-{[({3-methoxybicyclo[1.1.1]pentan-1-yl}methyl)amino]methyl}-1H-indol-6-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

4-oxo-N-[(2-{[({spiro[2.2]pentan-1-yl}methyl)amino]methyl}-1H-indol-6-yl)methyl]-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

4-oxo-N-({2-[({spiro[2.3]hexan-1-yl}amino)methyl]-1H-indol-6-yl}methyl)-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[(2-{[({3-cyanobicyclo[1.1.1]pentan-1-yl}methyl)amino]methyl}-1H-indol-6-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-{[2-({1-oxa-6-azaspiro[3.4]octan-6-yl}methyl)-1H-indol-6-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-{[2-({2-azaspiro[4.4]nonan-2-yl}methyl)-1H-indol-6-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[(2-{[(1-methylcyclopentyl)amino]methyl}-1H-indol-6-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-{[2-(hydroxymethyl)-1H-indol-6-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[(2-{[(1-cyclobutylcyclopropyl)amino]methyl}-1H-indol-6-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-{[2-({[(1-methylcyclobutyl)methyl]amino}methyl)-1H-indol-6-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

4-oxo-N-[(2-{[({spiro[2.3]hexan-5-yl}methyl)amino]methyl}-1H-indol-6-yl)methyl]-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-({2-[({[3-(fluoromethyl)bicyclo[1.1.1]pentan-1-yl]methyl}amino)methyl]-1H-indol-6-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[(2-{[(1-{3-fluorobicyclo[1.1.1]pentan-1-yl}ethyl)amino]methyl}-1H-indol-6-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-({2-[(tert-butylamino)methyl]-1H-indol-6-yl}methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

4-(1-{[2-({2-azaspiro[3.3]heptanean-2-yl}methyl)-1H-indol-6-yl]methyl}-1H-1,2,3-triazol-4-yl)-1H-indazole

N-{[2-(2-{2-azaspiro[3.3]heptanean-2-yl}ethyl)-1H-indol-6-yl]methyl}-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

({3-fluorobicyclo[1.1.1]pentan-1-yl}methyl)({6-[(4-{imidazo[1,5-a]pyridin-8-yl}-1H-1,2,3-triazol-1-yl)methyl]-1H-indol-2-yl}methyl)amine

N-[(2-{[({3-fluorobicyclo[1.1.1]pentan-1-yl}methyl)amino]methyl}-1H-indol-6-yl)methyl]-5-oxo-5H-[1,3]thiazolo[3,2-a]pyrimidine-7-carboxamide

N-[(2-{[({bicyclo[1.1.1]pentan-1-yl}methyl)amino]methyl}-1H-pyrrolo[3,2-b]pyridin-6-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[(2-{[({3-fluorobicyclo[1.1.1]pentan-1-yl}methyl)amino]methyl}-1H-pyrrolo[3,2-b]pyridin-6-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[(2-{[(cyclobutylmethyl)amino]methyl}-1H-pyrrolo[3,2-b]pyridin-6-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[(2-{[({3-methylbicyclo[1.1.1]pentan-1-yl}methyl)amino]methyl}-1H-pyrrolo[3,2-c]pyridin-6-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[(2-{[(cyclobutylmethyl)amino]methyl}-1H-pyrrolo[3,2-c]pyridin-6-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[(2-{[({bicyclo[1.1.1]pentan-1-yl}methyl)amino]methyl}-1H-pyrrolo[3,2-c]pyridin-6-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[(2-{[({3-fluorobicyclo[1.1.1]pentan-1-yl}methyl)amino]methyl}-1H-pyrrolo[3,2-c]63yridine-6-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[(2-{[(cyclobutylmethyl)amino]methyl}-1H-indol-6-yl)methyl]-4-oxo-4H,6H,7H,8H,9H-pyrido[1,2-a]pyrimidine-2-carboxamide

(cyclobutylmethyl)({6-[(4-{1H-pyrrolo[2,3-b]pyridin-5-yl}-1H-imidazol-1-yl)methyl]-1H-indol-2-yl}methyl)amine

(cyclobutylmethyl)({6-[(4-{imidazo[1,5-a]pyridin-8-yl}-1H-1,2,3-triazol-1-yl)methyl]-1H-indol-2-yl}methyl)amine

N-[(2-{[(2,2-dimethylpropyl)amino]methyl}-1H-indol-6-yl)methyl]-1H-pyrrolo[2,3-b]pyridine-5-carboxamide

N-[(2-{[(cyclobutylmethyl)amino]methyl}-1H-indol-6-yl)methyl]-1H-pyrrolo[2,3-b]pyridine-5-carboxamide

(cyclobutylmethyl)({6-[(4-{1H-pyrrolo[2,3-b]pyridin-5-yl}-1H-1,2,3-triazol-1-yl)methyl]-1H-indol-2-yl}methyl)amine

N-[[2-(2-azabicyclo[2.2.1]heptanean-2-ylmethyl)-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

N-[(3-fluoro-1-bicyclo[1.1.1]pentanyl)methyl]-1-[6-[(4-imidazo[1,5-a]pyridin-8-yltriazol-1-yl)methyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methanamine

(cyclobutylmethyl)[(6-{[1-(1H-indazol-4-yl)-1H-1,2,3-triazol-4-yl]methyl}-1H-indol-2-yl)methyl]amine

[(3,3-difluorocyclobutyl)methyl][(6-{[1-(1H-indazol-4-yl)-1H-1,2,3-triazol-4-yl]methyl}-1H-indol-2-yl)methyl]amine

(cyclobutylmethyl)[(6-{[1-(isoquinolin-4-yl)-1H-1,2,3-triazol-4-yl]methyl}-1H-indol-2-yl)methyl]amine

(cyclobutylmethyl)({6-[(1-{imidazo[1,5-a]pyridin-8-yl}-1H-1,2,3-triazol-4-yl)methyl]-1H-indol-2-yl}methyl)amine

3-[1-({2-[({(Bicyclo[1.1.1]pent-1-yl)methyl}amino)methyl]-1H-indol-6-yl}methyl)-1H-1,2,3-triazol-4-yl]-5-methoxy-2-pyridinecarbonitrile;

3-[1-({2-[({(3-Fluorobicyclo[1.1.1]pent-1-yl)methyl}amino)methyl]-1H-indol-6-yl}methyl)-1H-1,2,3-triazol-4-yl]-5-methoxy-2-pyridinecarbonitrile;

5-Methoxy-3-[1-({2-[({(3-methylbicyclo[1.1.1]pent-1-yl)methyl}amino)methyl]-1H-indol-6-yl}methyl)-1H-1,2,3-triazol-4-yl]-2-pyridinecarbonitrile;

3-{1-[(2-{[(Cyclobutylmethyl)amino]methyl}-1H-indol-6-yl)methyl]-1H-1,2,3-triazol-4-yl}-5-methoxy-2-pyridinecarbonitrile;

3-{1-[(2-{(6-Aza-6-spiro[3.4]octyl)methyl}-1H-indol-6-yl)methyl]-1H-1,2,3-triazol-4-yl}-5-methoxy-2-pyridinecarbonitrile;

3-[1-({2-[(4,4-Dimethyl-1-piperidyl)methyl]-1H-indol-6-yl}methyl)-1H-1,2,3-triazol-4-yl]-5-methoxy-2-pyridinecarbonitrile;

N-((2-((6-azaspiro[3.4]octan-6-yl)methyl)-1H-pyrrolo[3,2-c]pyridin-6-yl)methyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide

3-(1-((2-(((cyclobutylmethyl)amino)methyl)-1H-indol-6-yl)methyl)-1H-1,2,3-triazol-4-yl)-5-fluoropicolinonitrile

1-cyclobutyl-N-((6-((4-(5-methoxypyridin-3-yl)-1H-1,2,3-triazol-1-yl)methyl)-1H-indol-2-yl)methyl)methanamine;

5-chloro-3-(1-((2-(((cyclobutylmethyl)amino)methyl)-1H-indol-6-yl)methyl)-1H-1,2,3-triazol-4-yl)picolinonitrile;

2-((6-azaspiro[3.4]octan-6-yl)methyl)-6-((4-(imidazo[1,5-a]pyridin-8-yl)-1H-1,2,3-triazol-1-yl)methyl)-1H-pyrrolo[3,2-c]pyridine;

3-[1-({2-[({(Bicyclo[1.1.1]pent-1-yl)methyl}amino)methyl]-1H-indol-6-yl}methyl)-1H-1,2,3-triazol-4-yl]-5-methoxy-2-pyridinecarbonitrile;

3-[1-({2-[({(3-Fluorobicyclo[1.1.1]pent-1-yl)methyl}amino)methyl]-1H-indol-6-yl}methyl)-1H-1,2,3-triazol-4-yl]-5-methoxy-2-pyridinecarbonitrile;

5-Methoxy-3-[1-({2-[({(3-methylbicyclo[1.1.1]pent-1-yl)methyl}amino)methyl]-1H-indol-6-yl}methyl)-1H-1,2,3-triazol-4-yl]-2-pyridinecarbonitrile;

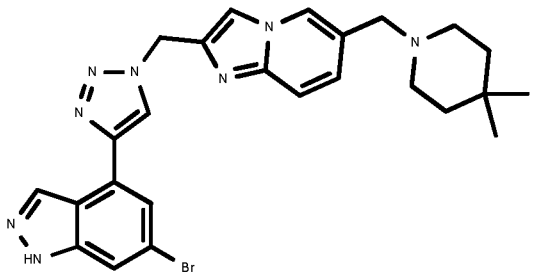
3-{1-[(2-{[(Cyclobutylmethyl)amino]methyl}-1H-indol-6-yl)methyl]-1H-1,2,3-triazol-4-yl}-5-methoxy-2-pyridinecarbonitrile;

3-{1-[(2-{(6-Aza-6-spiro[3.4]octyl)methyl}-1H-indol-6-yl)methyl]-1H-1,2,3-triazol-4-yl}-5-methoxy-2-pyridinecarbonitrile; and

3-[1-({2-[(4,4-Dimethyl-1-piperidyl)methyl]-1H-indol-6-yl}methyl)-1H-1,2,3-triazol-4-yl]-5-methoxy-2-pyridinecarbonitrile.

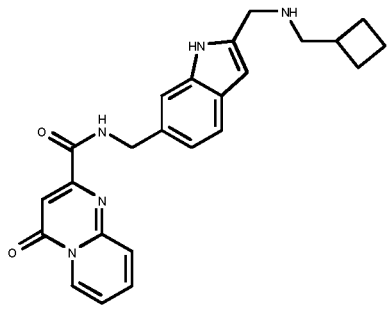
(v) sepcific compounds STM3006, STM3480 and STM3675

[00102] One particular compound of formula I defined above that is disclosed in International Patent Publication No. WO2020/050898 is STM3006, which is 6-bromo-4-[1-({6-[(4,4-dimethylpiperidin-1-yl)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-1H-1,2,3-triazol-4-yl]-1H-indazole, and has the structure shown below

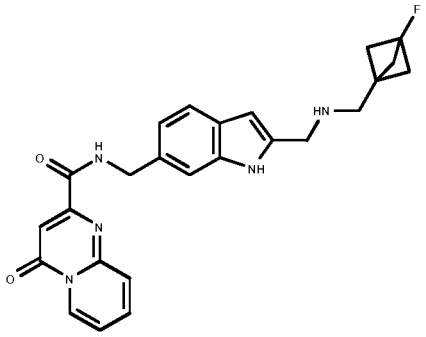


[00103] Two particular compounds of Formulae II, VI and VII defined above are STM3480 and STM3675.

[00104] STM3480 is N-[(2-{[(cyclobutylmethyl)amino]methyl}-1H-indol-6-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide, which has the structure shown below:



[00105] STM3675 is N-[(2-{[({3-fluorobicyclo[1.1.1]pentan-1-yl}methyl)amino]methyl}-1H-indol-6-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide, the structure of which is also depicted below:



[00106] The METTL3 inhibitors used in the combination therapies of the present invention may be any METTL3 inhibitor.

[00107] In a particular embodiment, the METTL3 inhibitor is a compound of formula I, II, VI or VII defined herein, or a pharmaceutically acceptable salt thereof.

[00108] In another embodiment, the METTL3 inhibitor is any one of the specific compounds listed list 1 and/or list 2 above, or a pharmaceutically acceptable salt thereof.

[00109] In another embodiment, the METTL3 inhibitor is any one of the specific compounds STM 3006, STM 3480, or STM3675 identified above, or a pharmaceutically acceptable salt thereof.

[00110] In a particular embodiment, the METTL3 inhibitor is STM3480 identified above, or a pharmaceutically acceptable salt thereof.

1. Combinations of METTL3 inhibitors defined herein with immuno-oncology agents (e.g. Immune Checkpoint Inhibitors)

[00111] One aspect of the present invention resides in the recognition that the METTL3 inhibitor compound, STM3480, is particularly suited to use in combination with immune checkpoint inhibitors (see Examples 1 and 2).

[00112] Immune checkpoint inhibitors are a class of anticancer agents that have shown great promise in some cancer patients. The inhibition of immune checkpoints (e.g. CTLA4, LAG3, PD1 or PD-L1 inhibitors) results in the enhancement of the immune response to a tumour. However, some cancers do not respond sufficiently well to immune checkpoint inhibitor therpay alone, so there is a need for improved treatment strategies.

[00113] The inventors have surprisingly discovered that the METTL3 inhibitor compound STM3480 can significantly potentiate the therapeutic effects of immune checkpoint inhibitors. In an embodiment, the METTL3 inhibitor compound STM3480 synergistically potentiates the therapeutic effects of immune checkpoint inhibitors (and *vice versa*), thereby rendering the tumours more susceptible to the combination therapy (i.e. the therapeutic effect observed is greater than the additive effect of the two agents individually).

[00114] Thus, the combination treatment of the present invention has the potential to provide better therapeutic outcomes in cancer patients, especially cancer patients that do not respond well to therapy with a METTL3 inhibitor or an immune checkpoint inhibitor alone.

[00115] In one aspect, the present invention provides a combination comprising a METTL3 inhibitor as defined herein (e.g. STM3480), or a pharmaceutically acceptable salt thereof, and an immune checkpoint inhibitor, or a pharmaceutically acceptable salt thereof.

[00116] In another aspect, the present invention provides a pharmaceutical product comprising a combination of a METTL3 inhibitor as defined herein (e.g. STM3480), or a pharmaceutically acceptable salt thereof, and an immune checkpoint inhibitor, or a pharmaceutically acceptable salt thereof.

[00117] In one embodiment, the pharmaceutical product may comprise a kit of parts comprising separate formulations of a METTL3 inhibitor as defined herein (e.g. STM3480), or a pharmaceutically acceptable salt thereof, and an immune checkpoint inhibitor, or a pharmaceutically acceptable salt thereof. The separate formulations of a METTL3 inhibitor as defined herein (e.g. STM3480), or a pharmaceutically acceptable salt thereof, and an immune checkpoint inhibitor, or a pharmaceutically acceptable salt thereof, may be administered sequentially, separately and/or simultaneously.

[00118] In another embodiment the pharmaceutical product is a kit of parts which comprises:

a first container comprising a METTL3 inhibitor as defined herein (e.g. STM3480), or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable adjuvant, diluent or carrier; and

a second container comprising an immune checkpoint inhibitor, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable adjuvant, diluent or carrier, and

a container means for containing said first and second containers.

[00119] In one embodiment, the pharmaceutical product may comprise a one or more unit dosage forms (e.g. vials, tablets or capsules in a blister pack). In one embodiment, each unit dose comprises only one agent selected from the a METTL3 inhibitor as defined herein (e.g. STM3480) compound and the immune checkpoint inhibitor. In another embodiment, the unit dosage form comprises both the a METTL3 inhibitor as defined herein (e.g. STM3480) compound and the immune checkpoint inhibitor.

[00120] In one embodiment the pharmaceutical product or kit of parts further comprises means for facilitating compliance with a dosage regimen, for instance instructions detailing how to administer the combination.

[00121] In one embodiment, the pharmaceutical product or kit of parts further comprises instructions indicating that the combination, as defined herein, can be used in the treatment of cancer.

[00122] In one embodiment, the pharmaceutical product is a pharmaceutical composition.

Immune checkpoint inhibitors

[00123] Any immune checkpoint inhibitor may be used in the combination therapy defined herein.

[00124] In one embodiment, the immune checkpoint inhibitor is selected from a PD1, PD-L1 inhibitor, a LAG3 inhibitor and a CTLA-4 inhibitor. In a particular embodiment, the immune checkpoint inhibitor is a PD1 or PD-L1 inhibitor.

[00125] PD-1 is a cell surface receptor protein present on T cells. PD-1 plays an important role in down-regulating the immune system and promoting self-tolerance by suppressing T cell inflammatory activity. The PD-1 protein is an immune checkpoint that

guards against autoimmunity through a dual mechanism of promoting apoptosis (programmed cell death) in antigen specific T cells in lymph nodes, while simultaneously reducing apoptosis in regulatory T cells (anti-inflammatory suppressive T cells).

[00126] PD-1 therefore inhibits the immune system. This prevents autoimmune diseases, but it can also prevent the immune system from killing cancer cells.

[00127] PD1 binds two ligands, PD-L1 and PD-L2. PD-L1 is of particular interest as it is highly expressed in several cancers and hence the role of PD1 in cancer immune evasion is well established. Monoclonal antibodies targeting PD-1 that boost the immune system are being developed for the treatment of cancer. Many tumour cells express PD-L1, an immunosuppressive PD-1 ligand; inhibition of the interaction between PD-1 and PD-L1 can enhance T-cell responses *in vitro* and mediate preclinical antitumour activity. This is known as immune checkpoint blockade.

[00128] Examples of drugs that target PD-1 include pembrolizumab (Keytruda) and nivolumab (Opdivo). These drugs have been shown to be effective in treating several types of cancer, including melanoma of the skin, non-small cell lung cancer, kidney cancer, bladder cancer, head and neck cancers, and Hodgkin lymphoma. They are also being studied for use against many other types of cancer. Examples of drugs in development include BMS-936559 (Bristol Myers Squibb), MGA012 (MacroGenics) and MEDI-0680 (MedImmune).

[00129] Examples of drugs that inhibit PD-L1 include atezolizumab (Tecentriq), avelumab (Bavencio) and durvalumab (Imfinzi). These drugs have also been shown to be helpful in treating different types of cancer, including bladder cancer, non-small cell lung cancer, and Merkel cell skin cancer (Merkel cell carcinoma). They are also being studied for use against other types of cancer.

[00130] Examples of LAG3 inhibitors include BMS-986016/Relatlimab, TSR-033, REGN3767, MGD013 (bispecific DART binding PD-1 and LAG-3), GSK2831781 and LAG525.

[00131] Examples of CTLA-4 inhibitors include MDX-010/Ipilimumab, AGEN1884, and CP-675,206/Tremelimumab.

[00132] In one embodiment, the immune checkpoint inhibitor is selected from BMS-986016/Relatlimab, TSR-033, REGN3767, MGD013 (bispecific DART binding PD-1 and LAG-3), GSK2831781, LAG525, MDX-010/Ipilimumab, AGEN1884, and CP-675,206/Tremelimumab, pembrolizumab, nivolumab, atezolizumab, avelumab and durvalumab, or a pharmaceutically acceptable salt thereof.

[00133] In another embodiment, the immune checkpoint inhibitor is selected from BMS-986016/Relatlimab, MDX-010/Ipilimumab, CP-675,206/Tremelimumab, pembrolizumab, nivolumab, atezolizumab, avelumab, and durvalumab, or a pharmaceutically acceptable salt thereof.

[00134] In another embodiment, the immune checkpoint inhibitor is selected from pembrolizumab, nivolumab, atezolizumab, avelumab and durvalumab, or a pharmaceutically acceptable salt thereof.

[00135] In another embodiment, the immune checkpoint inhibitor is selected from pembrolizumab, nivolumab, atezolizumab, avelumab and durvalumab, or a pharmaceutically acceptable salt thereof.

[00136] In another embodiment, the immune checkpoint inhibitor is selected from pembrolizumab and avelumab, or a pharmaceutically acceptable salt thereof.

Therapeutic Uses

[00137] Thus, the present invention relates, in one aspect, to a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, for use as an immune-sensitiser.

[00138] The present invention also relates to the use of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use as an immune-sensitiser.

[00139] The present invention also relates to a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, wherein the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, is administered in combination with an immune oncology agent or therapy (e.g. immune checkpoint inhibitors (e.g. a PD1, PD-L1 inhibitor, LAG3, CTLA-4, TIGIT, TIM3, or VISTA inhibitor), STING agonists, TLR agonists, anti-CD137 antibodies, CD28 antibodies, OX40 stimulators, CD40 antibodies, ICOS agonists, GITR agonists, A2AR antagonists, Bispecific T cell engagers (BiTE), oncolytic viruses, cancer vaccines, and/or CAR-T cell therapy).

[00140] The present invention also relates to the use of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of cancer, wherein the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, is administered in combination with an immune

oncology agent or therapy (e.g. immune checkpoint inhibitors (e.g. immune checkpoint inhibitors (e.g. a PD1, PD-L1 inhibitor, LAG3, CTLA-4, TIGIT, TIM3, or VISTA inhibitor), STING agonists, TLR agonists, anti-CD137 antibodies, CD28 antibodies, OX40 stimulators, CD40 antibodies, ICOS agonists, GITR agonists, A2AR antagonists, Bispecific T cell engagers (BiTE), oncolytic viruses, cancer vaccines, and/or CAR-T cell therapy).

[00141] The present invention also relates to a method of treating cancer, the method comprising administering a therapeutically effective amount of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, to a patient in combination with an immune oncology agent or therapy (e.g. immune checkpoint inhibitors (e.g. a PD1, PD-L1 inhibitor, LAG3, CTLA-4, TIGIT, TIM3, or VISTA inhibitor), STING agonists, TLR agonists, anti-CD137 antibodies, CD28 antibodies, OX40 stimulators, CD40 antibodies, ICOS agonists, GITR agonists, A2AR antagonists, Bispecific T cell engagers (BiTE), oncolytic viruses, cancer vaccines, and/or CAR-T cell therapy).

[00142] Suitably, the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, is administered simultaneously, sequentially or separately with the immune oncology agent or therapy (e.g. immune checkpoint inhibitors (e.g. a PD1, PD-L1 inhibitor, LAG3, CTLA-4, TIGIT, TIM3, or VISTA inhibitor), STING agonists, TLR agonists, anti-CD137 antibodies, CD28 antibodies, OX40 stimulators, CD40 antibodies, ICOS agonists, GITR agonists, A2AR antagonists, Bispecific T cell engagers (BiTE), oncolytic viruses, cancer vaccines, and/or CAR-T cell therapy).

[00143] Suitably, the immune oncology agent is an immune checkpoint inhibitor (e.g. a PD1, PD-L1 inhibitor, LAG3 or CTLA-4 inhibitor).

[00144] In another aspect, the present invention relates to a combination as defined herein, or a pharmaceutical product as defined herein, or a pharmaceutical composition as defined herein for use in therapy.

[00145] In another aspect, the present invention relates to a combination as defined herein, or a pharmaceutical product as defined herein, or a pharmaceutical composition as defined herein for use in the treatment of cancer.

[00146] In another aspect, the present invention relates to a use of a combination as defined herein in the manufacture of a medicament for the treatment of cancer.

[00147] In another aspect, the present invention relates to a method of treating of cancer in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a combination as defined herein.

[00148] In another aspect, the present invention relates to a method of potentiating the immune response to a tumour, the method comprising administering to a patient in need of such treatment a therapeutically effective amount of a combination as defined herein.

[00149] In another aspect, the present invention relates to a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, wherein the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, is for simultaneous, separate or sequential administration with an immune checkpoint inhibitor, or a pharmaceutically acceptabel salt thereof.

[00150] In another aspect, the present invention relates to an immune checkpoint inhibitor, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, wherein the immune checkpoint inhibitor is for simultaneous, separate or sequential administration with a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof.

[00151] In another aspect, the present invention relates to a use of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer, wherein the medicament is for simultaneous, separate or sequential administration with an immune checkpoint inhibitor, or a pharmaceutically acceptable salt thereof.

[00152] In another aspect, the present invention relates to a use of an immune checkpoint inhibitor, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer, wherein the medicament is for simultaneous, separate or sequential administration with a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof.

[00153] In another aspect, the present invention relates to a method of treating cancer comprising adminstering to a subject in need thereof a therapeutically effective amount of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, and an immune checkpoint inhibitor, or a pharmaceutically acceptable salt thereof, wherein the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, and the immune checkpoint inhibitor, or a pharmaceutically acceptable salt thereof are administered sequentially, separately or simultaneously with one another.

[00154] In another aspect, the present invention relates to a method of treating cancer or potentiating the effect of an immune checkpoint inhibitor, or a pharmaceutically acceptable salt thereof, the method comprising administering to a patient in need of such treatment a therapeutically effective amount the immune checkpoint inhibitor, or a pharmaceutically acceptable salt thereof, separately, sequentially or simultaneously with a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof.

[00155] In another aspect, the present invention relates to a method of treing cancer or potentiating the effect of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, the method comprising administering to a patient in need of such treatment a therapeutically effective amount of the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, separately, sequentially or simultaneously with an immune checkpoint inhibitor, or a pharmaceutically acceptable salt thereof.

[00156] In another aspect, the present invention relates to a method of potentiating the immune response to a tumour, the method comprising administering to a patient in need of such treatment a therapeutically effective amount of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, and an immune checkpoint inhibitor, or a pharmaceutically acceptable salt thereof, wherein the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, and the immune checkpoint inhibitor, or a pharmaceutically acceptable salt thereof are administered sequentially, separately or simultaneously with one another.

[00157] The term "cancer" is used herein to refer to an unwanted, uncontrolled and abnormal malignant cellular proliferation, whether in vitro or in vivo. The term includes benign, pre-malignant and malignant cellular proliferation. Any type of cell may be treated, including but not limited to, lung, colon, breast, ovarian, prostate, liver, pancreas, brain, bladder, kidney, bone, nerves and skin.

[00158] The anti-proliferative effects of the combination therapy of the present invention has particular application in the treatment of human cancers. In particular, the combination therapy of the present invention will be useful for treating any human cancer in which METTL3 and/or immune checkpoint activity is implicated. This includes any cancer that has been unresponsive to therapy comprising either a METTL3 inhibitor or immune checkpoint inhibitor alone.

[00159] In an embodiment of the invention, the anti-tumour effects of the combination therapy of the present invention has particular application in the treatment and/or prevention

of a wide range of cancers including, but not limited to, non-solid tumours such as leukaemia, for example acute myeloid leukaemia, multiple myeloma, haematologic malignancies or lymphoma, and also solid tumours and their metastases such as melanoma, non-small cell lung cancer, glioma, hepatocellular (liver) carcinoma, glioblastoma, carcinoma of the thyroid, bile duct, bone, gastric, brain/CNS, head and neck, hepatic, stomach, prostate, breast, renal, testicular, ovarian, skin, cervical, lung, muscle, neuronal, oesophageal, bladder, lung, uterine, vulval, endometrial, kidney, colorectal, pancreatic, pleural/peritoneal membranes, salivary gland, and epidermoid tumours and haematological malignancies.

[00160] Suitably, the cancer is a solid tumour.

[00161] In one embodiment the cancer is selected from lung, colon, rectal, breast, ovarian, bladder, kidney, prostate, liver, pancreas, brain, bone, blood and skin cancer.

[00162] In one embodiment the cancer is a human cancer. Suitably, the human cancer is selected from lung, colon, breast, ovarian, bladder, kidney, prostate, liver, pancreas, brain, bone, blood and skin cancer. In one embodiment, the human cancer is selected from glioblastoma, lung cancer, breast cancer, renal cell carcinoma and Hodgkin lymphoma.

[00163] The anti-cancer effect may arise through one or more mechanisms, including but not limited to, the promotion of an antitumour immune response, the regulation of cell proliferation, the inhibition of angiogenesis (the formation of new blood vessels), the inhibition of metastasis (the spread of a tumour from its origin), the inhibition of invasion (the spread of tumour cells into neighbouring normal structures or within an organ), or the promotion of apoptosis (programmed cell death).

[00164] As indicated above, the immune checkpoint inhibitor may be any immune checkpoint inhibitor as defined in any of the embodiments herein and the METTL3 inhibitor may be any known METTL3 inhibitor.

[00165] In one embodiment, the immune checkpoint inhibitor is selected from BMS-986016/Relatlimab, TSR-033, REGN3767, MGD013 (bispecific DART binding PD-1 and LAG-3), GSK2831781, LAG525, MDX-010/Ipilimumab, AGEN1884, and CP-675,206/Tremelimumab, pembrolizumab, nivolumab, atezolizumab, avelumab and durvalumab, or a pharmaceutically acceptable salt thereof; and the METTL3 inhibitor is as defined herein.

[00166] In another embodiment, the immune checkpoint inhibitor is selected from BMS-986016/Relatlimab, MDX-010/Ipilimumab, CP-675,206/Tremelimumab, pembrolizumab,

nivolumab, atezolizumab, avelumab, and durvalumab, or a pharmaceutically acceptable salt thereof; and the METTL3 inhibitor is selected from STM3006, STM3480 or STM3675, or a pharmaceutically-acceptable salt thereof, as defined herein.

[00167] In another embodiment, the immune checkpoint inhibitor is selected from pembrolizumab, nivolumab, atezolizumab, avelumab and durvalumab, or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable salt thereof; and the METTL3 inhibitor is selected from STM3006, STM3480 or STM3675, or a pharmaceutically-acceptable salt thereof, as defined herein.

[00168] Suitably, the METTL3 inhibitor is STM3480.

2. Combinations of METTL3 inhibitors with BCL2 inhibitors (e.g. Venetoclax)

[00169] One aspect of the present invention resides in the recognition that the METTL3 inhibitor compounds, STM3480, STM3006 and STM3675, when administered in combination with a BCL2 inhibitor (venetoclax), produced a synergistic increase in potency (see Example 3).

[00170] Thus, the administration of a METTL3 inhibitor synergistically enhances the antitumour effect of BCL2 inhibitor (e.g. venetoclax) therapy and vice versa. The combination of a METTL3 inhibitor with a BCL2 inhibitor (e.g. venetoclax) therefore offers a promising therapy for diseases or conditions in which BCL2 inhibitor therapy is beneficial (e.g. the treatment of cancers including acute myeloid leukaemia (AML), chronic lymphocytic leukaemia (CLL), small lymphocytic lymphoma (SLL) and myelodysplastic syndromes (MDS)).

[00171] The combination treatment of the present invention has the potential to provide better therapeutic outcomes in cancer patients, especially cancer patients that do not respond well to therapy with a METTL3 inhibitor or a BCL2 inhibitor (e.g. venetoclax) alone.

[00172] In one aspect, the present invention provides a combination comprising a METTL3 inhibitor as defined herein (e.g. STM3480, STM3006 and STM3675), or a pharmaceutically acceptable salt thereof, and a BCL2 inhibitor (e.g. venetoclax), or a pharmaceutically acceptable salt thereof.

[00173] In another aspect, the present invention provides a pharmaceutical product comprising a combination of a METTL3 inhibitor as defined herein (e.g. STM3480, STM3006

and STM3675), or a pharmaceutically acceptable salt thereof, and a BCL2 inhibitor (e.g. venetoclax), or a pharmaceutically acceptable salt thereof.

[00174] In one embodiment, the pharmaceutical product may comprise a kit of parts comprising separate formulations of a METTL3 inhibitor as defined herein (e.g. STM3480, STM3006 and STM3675), or a pharmaceutically acceptable salt thereof, and a BCL2 inhibitor (e.g. venetoclax), or a pharmaceutically acceptable salt thereof. The separate formulations of a METTL3 inhibitor as defined herein (e.g. STM3480, STM3006 and STM3675), or a pharmaceutically acceptable salt thereof, and a BCL2 inhibitor (e.g. venetoclax), or a pharmaceutically acceptable salt thereof, may be administered sequentially, separately and/or simultaneously.

[00175] In another embodiment the pharmaceutical product is a kit of parts which comprises:

a first container comprising a METTL3 inhibitor as defined herein (e.g. STM3480, STM3006 and STM3675), or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable adjuvant, diluent or carrier; and

a second container comprising a BCL2 inhibitor (e.g. venetoclax), or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable adjuvant, diluent or carrier, and

a container means for containing said first and second containers.

[00176] In one embodiment, the pharmaceutical product may comprise a one or more unit dosage forms (e.g. vials, tablets or capsules in a blister pack). In one embodiment, each unit dose comprises only one agent selected from the a METTL3 inhibitor as defined herein (e.g. STM3480, STM3006 and STM3675) compound and the BCL2 inhibitor (e.g. venetoclax). In another embodiment, the unit dosage form comprises both the a METTL3 inhibitor as defined herein (e.g. STM3480, STM3006 and STM3675) compound and the BCL2 inhibitor (e.g. venetoclax).

[00177] In one embodiment the pharmaceutical product or kit of parts further comprises means for facilitating compliance with a dosage regimen, for instance instructions detailing how to administer the combination.

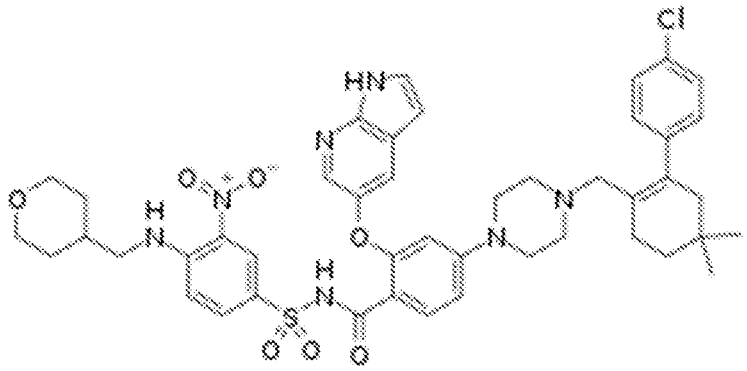
[00178] In one embodiment, the pharmaceutical product or kit of parts further comprises instructions indicating that the combination, as defined herein, can be used in the treatment of cancer.

[00179] In one embodiment, the pharmaceutical product is a pharmaceutical composition.

The BCL2 inhibitor

[00180] Any suitable BCL2 inhibitor approved for therapeutic use may be used in this combination therapy of the present invention

[00181] Suitably, the BCL2 inhibitor is venetoclax, or a pharmaceutically acceptable salt thereof. The chemical name for ventoclax is 4-{4-[(4'-chloro-5,5-dimethyl[3,4,5,6-tetrahydro[1,1'-biphenyl]]-2-yl)methyl]piperazin-1-yl}-N-(3-nitro-4-{[(oxan-4-yl)methyl]amino}benzene-1-sulfonyl)-2-[(1H-pyrrolo[2,3-b]pyridin-5-yl)oxy]benzamide, and its chemical structure is shown below:



Therapeutic Uses

[00182] The present invention also relates to a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of diseases or conditions in which BCL2 inhibitor therapy is beneficial (e.g. the treatment of cancer), wherein the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, is administered in combination with a BCL2 inhibitor (e.g. venetoclax).

[00183] The present invention also relates to the use of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of diseases or conditions in which BCL2 inhibitor therapy is beneficial

(e.g. the treatment of cancer), wherein the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, is administered in combination with a BCL2 inhibitor (e.g. venetoclax).

[00184] The present invention also relates to a method of treating diseases or conditions in which BCL2 inhibitor therapy is beneficial (e.g. the treatment of cancer), the method comprising administering a therapeutically effective amount of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, to a patient in combination with a BCL2 inhibitor (e.g. venetoclax).

[00185] Suitably, the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, is administered simultaneously, sequentially or separately with the BCL2 inhibitor (e.g. venetoclax) therapy.

[00186] In one aspect the present invention relates to a combination comprising a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, and a BCL2 inhibitor (e.g. venetoclax), or a pharmaceutically acceptable salt thereof.

[00187] In another aspect the present invention relates to a pharmaceutical product comprising a combination as defined above.

[00188] In another aspect, the present invention relates to a pharmaceutical composition comprising a combination as defined above, and one or more pharmaceutically acceptable excipients.

[00189] In another aspect, the present invention relates to a combination as defined above, or a pharmaceutical product as defined above, or a pharmaceutical composition as defined above for use in therapy.

[00190] In another aspect, the present invention relates to a combination as defined herein, or a pharmaceutical product as defined above, or a pharmaceutical composition as defined above for use in the treatment of diseases or conditions in which BCL2 inhibitor therapy is beneficial (e.g. the treatment of cancer).

[00191] In another aspect, the present invention relates to the use of a combination as defined above in the manufacture of a medicament for the treatment of diseases or conditions in which BCL2 inhibitor therapy is beneficial (e.g. the treatment of cancer).

[00192] In another aspect, the present invention relates to a method of treating of diseases or conditions in which BCL2 inhibitor therapy is beneficial (e.g. the treatment of

cancer) in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a combination as defined above.

[00193] In another aspect, the present invention relates to a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, wherein the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, is for simultaneous, separate or sequential administration with a BCL2 inhibitor (e.g. venetoclax), or a pharmaceutically acceptable salt thereof.

[00194] In another aspect, the present invention relates to a BCL2 inhibitor (e.g. venetoclax), or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, wherein the BCL2 inhibitor (e.g. venetoclax), or a pharmaceutically acceptable salt thereof, is for simultaneous, separate or sequential administration with a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof.

[00195] In another aspect, the present invention relates to a use of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer, wherein the medicament is for simultaneous, separate or sequential administration with a BCL2 inhibitor (e.g. venetoclax), or a pharmaceutically acceptable salt thereof.

[00196] In another aspect, the present invention relates to a use of a BCL2 inhibitor (e.g. venetoclax), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer, wherein the medicament is for simultaneous, separate or sequential administration with a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof.

[00197] In another aspect, the present invention relates to a method of treating cancer comprising adminstering to a subject in need thereof a therapeutically effective amount of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, and a BCL2 inhibitor (e.g. venetoclax), or a pharmaceutically acceptable salt thereof, wherein the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, and the BCL2 inhibitor (e.g. venetoclax), or a pharmaceutically acceptable salt thereof, are administered sequentially, separately or simultaneously with one another.

[00198] In another aspect, the present invention relates to a method of treating cancer, or potentiating the effect of a BCL2 inhibitor (e.g. venetoclax), or a pharmaceutically acceptable salt thereof, the method comprising administering to a patient in need of such treatment a therapeutically effective amount the BCL2 inhibitor (e.g. venetoclax), or a

pharmaceutically acceptable salt thereof, separately, sequentially or simultaneously with a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof.

[00199] In another aspect, the present invention relates to a method of treating cancer or potentiating the effect of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, the method comprising administering to a patient in need of such treatment a therapeutically effective amount of the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, separately, sequentially or simultaneously with a BCL2 inhibitor (e.g. venetoclax), or a pharmaceutically acceptable salt thereof.

[00200] The anti-proliferative effects of the combination therapy of the present invention has particular application in the treatment of human cancers. In particular, the combination therapy of the present invention will be useful for treating any human cancer in which METTL3 and/or BCL2 activity is implicated. This includes any cancer that has been unresponsive to therapy comprising either a METTL3 inhibitor or BCL2 inhibitor alone.

[00201] Suitably, the cancer is selected from acute myeloid leukaemia (AML), chronic lymphocytic leukaemia (CLL), small lymphocytic lymphoma (SLL) and myelodysplastic syndromes (MDS).

[00202] In an embodiment, this combination therapy of the invention is suitable for the treatment of acute myeloid leukaemia (AML), chronic lymphocytic leukaemia (CLL), small lymphocytic lymphoma (SLL).

[00203] The anti-cancer effect may arise through one or more mechanisms, including but not limited to, the promotion of an antitumour immune response, the regulation of cell proliferation, the inhibition of angiogenesis (the formation of new blood vessels), the inhibition of metastasis (the spread of a tumour from its origin), the inhibition of invasion (the spread of tumour cells into neighbouring normal structures or within an organ), or the promotion of apoptosis (programmed cell death).

[00204] As indicated above, the BCL2 inhibitor may be any BCL2 inhibitor and the METTL3 inhibitor may be any known METTL3 inhibitor.

[00205] In one embodiment, the BCL2 inhibitor is venetoclax, or a pharmaceutically acceptable salt thereof; and the METTL3 inhibitor is as defined herein.

[00206] In one embodiment, the BCL2 inhibitor is venetoclax, or a pharmaceutically acceptable salt thereof; and the METTL3 inhibitor is selected any compound of the formulae I, II, VI or VII defined above, or a pharmaceutically acceptable salt thereof.

[00207] In one embodiment, the BCL2 inhibitor is venetoclax, or a pharmaceutically acceptable salt thereof; and the METTL3 inhibitor is selected from STM3006, STM3480 or STM3675, or a pharmaceutically-acceptable salt thereof.

[00208] In one embodiment, the BCL2 inhibitor is venetoclax, or a pharmaceutically acceptable salt thereof; and the METTL3 inhibitor is STM3480, or a pharmaceutically-acceptable salt thereof.

3. Combinations of METTL3 inhibitors with anthracycline topoisomerase 2 inhibitors (e.g. daunorubicin), cytarabine, hypomethylating agents (e.g. 5-azacitidine), FLT3 inhibitors (e.g. quizartinib) and decitabine

[00209] One aspect of the present invention resides in the recognition that the METTL3 inhibitor compounds, STM3480 and STM3006, when administered in combination with daunorubicin, cytarabine, 5-azacitidine and quizartinib, produced an enhanced therapeutic effect in Kasumi1 or MOLM-14 AML cell lines (see Example 4).

[00210] Collectively, these data suggest that the administration of a METTL3 inhibitor enhances the antitumour effects of these AML standard of care agents. Thus, the combination of a METTL3 inhibitor with either an anthracycline topoisomerase 2 inhibitors (e.g. daunorubicin), cytarabine, hypomethylating agents (e.g. 5-azacitidine or decitabine) and/or FLT3 inhibitors (e.g. quizartinib) offers a promising therapy for the treatment of cancer (and especially acute myeloid leukaemia (AML), chronic lymphocytic leukaemia (CLL), small lymphocytic lymphoma (SLL) and/or Myelodysplastic syndromes (MDS)).

[00211] This combination treatment of the present invention therefore has the potential to provide better therapeutic outcomes in cancer patients, especially cancer patients that do not respond well to therapy with a METTL3 inhibitor or an anthracycline topoisomerase 2 inhibitor (e.g. daunorubicin), cytarabine, a hypomethylating agent (e.g. 5-azacitidine or decitabine) and/or a FLT3 inhibitor (e.g. quizartinib).

[00212] In one aspect, the present invention provides a combination comprising a METTL3 inhibitor as defined herein (e.g. STM3480, STM3006 and STM3675), or a pharmaceutically acceptable salt thereof, and an anthracycline topoisomerase 2 inhibitor (e.g.

daunorubicin), cytarabine, a hypomethylating agent (e.g. 5-azacitidine or decitabine) and/or a FLT3 inhibitor (e.g. quizartinib), or a pharmaceutically acceptable salt thereof.

[00213] In another aspect, the present invention provides a pharmaceutical product comprising a combination of a METTL3 inhibitor as defined herein (e.g. STM3480, STM3006 and STM3675), or a pharmaceutically acceptable salt thereof, and an anthracycline topoisomerase 2 inhibitor (e.g. daunorubicin), cytarabine, a hypomethylating agent (e.g. 5-azacitidine or decitabine) and/or a FLT3 inhibitor (e.g. quizartinib), or a pharmaceutically acceptable salt thereof.

[00214] In one embodiment, the pharmaceutical product may comprise a kit of parts comprising separate formulations of a METTL3 inhibitor as defined herein (e.g. STM3480, STM3006 and STM3675), or a pharmaceutically acceptable salt thereof, and an anthracycline topoisomerase 2 inhibitor (e.g. daunorubicin), cytarabine, a hypomethylating agent (e.g. 5-azacitidine or decitabine) and/or a FLT3 inhibitor (e.g. quizartinib), or a pharmaceutically acceptable salt thereof. The separate formulations of a METTL3 inhibitor as defined herein and an anthracycline topoisomerase 2 inhibitor (e.g. daunorubicin), cytarabine, a hypomethylating agent (e.g. 5-azacitidine or decitabine) and/or a FLT3 inhibitor (e.g. quizartinib), or a pharmaceutically acceptable salt thereof, may be administered sequentially, separately and/or simultaneously.

[00215] In another embodiment the pharmaceutical product is a kit of parts which comprises:

a first container comprising a METTL3 inhibitor as defined herein (e.g. STM3480, STM3006 and STM3675), or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable adjuvant, diluent or carrier; and

a second container comprising an anthracycline topoisomerase 2 inhibitor (e.g. daunorubicin), cytarabine, a hypomethylating agent (e.g. 5-azacitidine or decitabine) and/or a FLT3 inhibitor (e.g. quizartinib), or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable adjuvant, diluent or carrier, and

a container means for containing said first and second containers.

[00216] In one embodiment, the pharmaceutical product may comprise a one or more unit dosage forms (e.g. vials, tablets or capsules in a blister pack). In one embodiment, each unit dose comprises only one agent selected from the a METTL3 inhibitor as defined herein (e.g. STM3480, STM3006 and STM3675) and the anthracycline topoisomerase 2 inhibitor

(e.g. daunorubicin), cytarabine, hypomethylating agent (e.g. 5-azacitidine or decitabine) and/or FLT3 inhibitor (e.g. quizartinib). In another embodiment, the unit dosage form comprises both the a METTL3 inhibitor as defined herein (e.g. STM3480, STM3006 and STM3675) and the anthracycline topoisomerase 2 inhibitor (e.g. daunorubicin), cytarabine hypomethylating agent (e.g. 5-azacitidine or decitabine) and/or FLT3 inhibitor (e.g. quizartinib).

[00217] In one embodiment the pharmaceutical product or kit of parts further comprises means for facilitating compliance with a dosage regimen, for instance instructions detailing how to administer the combination.

[00218] In one embodiment, the pharmaceutical product or kit of parts further comprises instructions indicating that the combination, as defined herein, can be used in the treatment of cancer.

[00219] In one embodiment, the pharmaceutical product is a pharmaceutical composition.

The anthracycline topoisomerase 2 inhibitors, hypomethylating agents and FLT3 inhibitors

[00220] Any suitable anthracycline topoisomerase 2 inhibitors, hypomethylating agents and FLT3 inhibitors may be used in this combination therapy of the present invention.

[00221] Suitably, the anthracycline topoisomerase 2 inhibitor is selected from daunorubicin, doxorubicin, epirubicin or idarubicin. Most suitably, the anthracycline topoisomerase 2 inhibitor is selected from daunorubicin and doxorubicin. In an embodiment, the anthracycline topoisomerase 2 inhibitor is daunorubicin.

[00222] Suitably, the hypomethylating agent is selected from 5-azacitidine or decitabine. In an embodiment, the hypomethylating agent is 5-azacitidine. In another embodiment, the hypomethylating agent is decitabine.

[00223] Suitably, the FLT3 inhibitor is selected from sorafenib, lestaurtinib, midostaurin, quizartinib, crenolanib, or gilteritinib. More suitably, the FLT3 inhibitor is selected from midostaurin, quizartinib or gilteritinib. In an embodiment, the FLT3 inhibitor is midostaurin. In another embodiment, the FLT3 inhibitor is quizartinib. In another embodiment, the FLT3 inhibitor is gilteritinib.

Therapeutic Uses

[00224] The present invention also relates to a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, wherein the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, is administered in combination with one or more additional agents selected from:

(i) an anthracycline topoisomerase 2 inhibitor (e.g. daunorubicin);

(ii) cytarabine;

(iii) a hypomethylating agent (e.g. 5-azacitidine or decitabine); or

(iv) a FLT3 inhibitor (e.g. quizartinib);

or a pharmaceutically-acceptable salt thereof.

[00225] The present invention also relates to the use of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of cancer, wherein the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, is administered in combination with one or more additional agents selected from

(i) an anthracycline topoisomerase 2 inhibitor (e.g. daunorubicin);

(ii) cytarabine;

(iii) a hypomethylating agent (e.g. 5-azacitidine or decitabine); or

(iv) a FLT3 inhibitor (e.g. quizartinib);

or a pharmaceutically-acceptable salt thereof.

[00226] The present invention also relates to a method of treating cancer, the method comprising administering a therapeutically effective amount of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, to a patient in combination with one or more additional agents selected from:

(i) an anthracycline topoisomerase 2 inhibitor (e.g. daunorubicin);

(ii) cytarabine;

(iii) a hypomethylating agent (e.g. 5-azacitidine or decitabine); or

(iv) a FLT3 inhibitor (e.g. quizartinib);

or a pharmaceutically-acceptable salt thereof.

[00227] Suitably, the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, is administered simultaneously, sequentially or separately with the:

(i) an anthracycline topoisomerase 2 inhibitor (e.g. daunorubicin);

(ii) cytarabine;

(iii) a hypomethylating agent (e.g. 5-azacitidine or decitabine); or

(iv) a FLT3 inhibitor (e.g. quizartinib);

or a pharmaceutically-acceptable salt thereof.

[00228] In another aspect the present invention relates to a pharmaceutical product comprising a combination as defined above.

[00229] In another aspect, the present invention relates to a pharmaceutical composition comprising a combination as defined above, and one or more pharmaceutically acceptable excipients.

[00230] In another aspect, the present invention relates to a combination as defined above, or a pharmaceutical product as defined above, or a pharmaceutical composition as defined above for use in therapy.

[00231] In another aspect, the present invention relates to a combination as defined above, or a pharmaceutical product as defined above, or a pharmaceutical composition as defined above for use in the treatment of cancer.

[00232] In another aspect, the present invention relates to the use of a combination as defined above in the manufacture of a medicament for the treatment of cancer.

[00233] In another aspect, the present invention relates to a method of treating of cancer in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a combination as defined above.

[00234] In another aspect, the present invention relates to a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, wherein the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, is for simultaneous, separate or sequential administration with one or more additional agents selected from:

(i) an anthracycline topoisomerase 2 inhibitor (e.g. daunorubicin);

(ii) cytarabine;

(iii) a hypomethylating agent (e.g. 5-azacitidine or decitabine); or

(iv) a FLT3 inhibitor (e.g. quizartinib);

or a pharmaceutically-acceptable salt thereof.

[00235] In another aspect, the present invention relates to an agent selected from:

(i) an anthracycline topoisomerase 2 inhibitor (e.g. daunorubicin);

(ii) cytarabine;

(iii) a hypomethylating agent (e.g. 5-azacitidine or decitabine); or

(iv) a FLT3 inhibitor (e.g. quizartinib);

or a pharmaceutically-acceptable salt thereof, for use in the treatment of cancer, wherein the agent, or a pharmaceutically acceptable salt thereof, is for simultaneous, separate or sequential administration with a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof.

[00236] In another aspect, the present invention relates to a use of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer, wherein the medicament is for simultaneous, separate or sequential administration with one or more additional agents selected from:

(i) an anthracycline topoisomerase 2 inhibitor (e.g. daunorubicin);

(ii) cytarabine;

(iii) a hypomethylating agent (e.g. 5-azacitidine or decitabine); or

(iv) a FLT3 inhibitor (e.g. quizartinib);

or a pharmaceutically-acceptable salt thereof.

[00237] In another aspect, the present invention relates to a use of an agent selected from:

(i) an anthracycline topoisomerase 2 inhibitor (e.g. daunorubicin);

(ii) cytarabine;

(iii) a hypomethylating agent (e.g. 5-azacitidine or decitabine); or

(iv) a FLT3 inhibitor (e.g. quizartinib);

or a pharmaceutically-acceptable salt thereof, in the manufacture of a medicament for treating cancer, wherein the medicament is for simultaneous, separate or sequential administration with a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof.

[00238] In another aspect, the present invention relates to a method of treating cancer comprising adminstering to a subject in need thereof a therapeutically effective amount of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, and an agent selected from:

(i) an anthracycline topoisomerase 2 inhibitor (e.g. daunorubicin);

(ii) cytarabine;

(iii) a hypomethylating agent (e.g. 5-azacitidine or decitabine); or

(iv) a FLT3 inhibitor (e.g. quizartinib);

or a pharmaceutically-acceptable salt thereof,

wherein the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, and the agent, or a pharmaceutically acceptable salt thereof, are administered sequentially, separately or simultaneously with one another.

[00239] In another aspect, the present invention relates to a method of treating cancer, or potentiating the effect of an agent selected from:

(i) an anthracycline topoisomerase 2 inhibitor (e.g. daunorubicin);

(ii) cytarabine;

(iii) a hypomethylating agent (e.g. 5-azacitidine or decitabine); or

(iv) a FLT3 inhibitor (e.g. quizartinib);

or a pharmaceutically-acceptable salt thereof, the method comprising administering to a patient in need of such treatment a therapeutically effective amount the agent, or a pharmaceutically acceptable salt thereof, separately, sequentially or simultaneously with a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof.

[00240] In another aspect, the present invention relates to a method of treating cancer, or potentiating the effect of a METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, the method comprising administering to a patient in need of such treatment a therapeutically effective amount of the METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, separately, sequentially or simultaneously with an agent selected from:

(i) an anthracycline topoisomerase 2 inhibitor (e.g. daunorubicin);

(ii) cytarabine;

(iii) a hypomethylating agent (e.g. 5-azacitidine or decitabine); or

(iv) a FLT3 inhibitor (e.g. quizartinib);

or a pharmaceutically-acceptable salt thereof.

[00241] The anti-proliferative effects of the combination therapy of the present invention has particular application in the treatment of human cancers.

[00242] Suitably, the cancer is selected from acute myeloid leukaemia (AML), chronic lymphocytic leukaemia (CLL), small lymphocytic lymphoma (SLL) and myelodysplastic syndromes (MDS).

[00243] In an embodiment, this combination therapy of the invention is suitable for the treatment of acute myeloid leukaemia (AML), chronic lymphocytic leukaemia (CLL), small lymphocytic lymphoma (SLL).

[00244] The anti-cancer effect may arise through one or more mechanisms, including but not limited to, the promotion of an antitumour immune response, the regulation of cell

proliferation, the inhibition of angiogenesis (the formation of new blood vessels), the inhibition of metastasis (the spread of a tumour from its origin), the inhibition of invasion (the spread of tumour cells into neighbouring normal structures or within an organ), or the promotion of apoptosis (programmed cell death).

[00245] As indicated above, any suitable anthracycline topoisomerase 2 inhibitor, hypomethylating agent and FLT3 inhibitor may be used in the combination therapy of the present invention.

[00246] In an embodiment, the METTL3 inhibitor is as defined herein and the second agent is selected from daunorubicin, doxorubicin, epirubicin, idarubicin, 5-azacitidine, decitabine, sorafenib, lestaurtinib, midostaurin, quizartinib, crenolanib, gilteritinib or cytarabine.

[00247] In an embodiment, the METTL3 inhibitor is selected any compound of the formulae I, II, VI or VII defined above, or a pharmaceutically acceptable salt thereof and the second agent is selected from daunorubicin, doxorubicin, epirubicin, idarubicin, 5-azacitidine, decitabine, sorafenib, lestaurtinib, midostaurin, quizartinib, crenolanib, gilteritinib or cytarabine.

[00248] In an embodiment, the METTL3 inhibitor is selected any compound of the formulae I, II, VI or VII defined above, or a pharmaceutically acceptable salt thereof and the second agent is selected from daunorubicin, doxorubicin, 5-azacitidine, decitabine, midostaurin, quizartinib, gilteritinib or cytarabine.

[00249] In an embodiment, the METTL3 inhibitor is selected any compound of the formulae I, II, VI or VII defined above, or a pharmaceutically acceptable salt thereof and the second agent is selected from daunorubicin, 5-azacitidine, decitabine, quizartinib, or cytarabine.

[00250] In an embodiment, the METTL3 inhibitor is selected from STM3006, STM3480 or STM3675, or a pharmaceutically-acceptable salt thereof, and the second agent is selected from daunorubicin, doxorubicin, epirubicin, idarubicin, 5-azacitidine, decitabine, sorafenib, lestaurtinib, midostaurin, quizartinib, crenolanib, gilteritinib or cytarabine.

[00251] In an embodiment, the METTL3 inhibitor is selected from STM3006, STM3480 or STM3675, or a pharmaceutically-acceptable salt thereof, and the second agent is selected from daunorubicin, doxorubicin, 5-azacitidine, decitabine, midostaurin, quizartinib, gilteritinib or cytarabine.

[00252] In an embodiment, the METTL3 inhibitor is selected from STM3006, STM3480 or STM3675, or a pharmaceutically-acceptable salt thereof, and the second agent is selected from daunorubicin, 5-azacitidine, decitabine, quizartinib, or cytarabine.

[00253] In an embodiment, the METTL3 inhibitor is STM3480, or a pharmaceutically-acceptable salt thereof, and the second agent is selected from daunorubicin, doxorubicin, epirubicin, idarubicin, 5-azacitidine, decitabine, sorafenib, lestaurtinib, midostaurin, quizartinib, crenolanib, gilteritinib or cytarabine.

[00254] In an embodiment, the METTL3 inhibitor is STM3480, or a pharmaceutically-acceptable salt thereof, and the second agent is selected from daunorubicin, doxorubicin, 5-azacitidine, decitabine, midostaurin, quizartinib, gilteritinib or cytarabine.

[00255] In an embodiment, the METTL3 inhibitor is STM3480, or a pharmaceutically-acceptable salt thereof, and the second agent is selected from daunorubicin, 5-azacitidine, decitabine, quizartinib, or cytarabine.

Pharmaceutical Compositions

[00256] In one aspect the present invention relates to a pharmaceutical composition comprising a combination of METTL3 inhibitor as defined herein, or a pharmaceutically acceptable salt thereof, and the other agent present in the combination as defined above, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

[00257] The pharmaceutical compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular, intraperitoneal or intramuscular dosing or as a suppository for rectal dosing).

[00258] The pharmaceutical compositions of the invention will typically be for parenteral administration, especially when the inhibitors are antibodies.

[00259] The pharmaceutical compositions may be obtained by conventional procedures using conventional pharmaceutical excipients well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

[00260] An effective amount of each component of the combination therapy will be present. Such an amount is an amount sufficient to treat or prevent a cancer condition referred to herein, slow its progression and/or reduce the symptoms associated with the condition.

[00261] The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the individual treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 0.5 g of active agent (more suitably from 0.5 to 100 mg, for example from 1 to 30 mg) compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

[00262] The size of the dose for therapeutic or prophylactic purposes of a combination of the invention will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well-known principles of medicine.

[00263] In using a combination of the invention for therapeutic or prophylactic purposes it will generally be administered within a therapeutically effective dose of the particular agent concerned. These dosages are known in the art and will vary from one agent to another. The dosage may, for example, be in the range of 0.1 mg/kg to 30 mg/kg body weight. The dosing schedule will also vary from one immune checkpoint inhibitor to another. Suitable dosing schedules are known in the art.

Routes of Administration

[00264] The combination of the invention or pharmaceutical compositions comprising said combination may be administered to a subject by any appropriate or convenient route of administration, whether systemically/peripherally or topically (i.e., at the site of desired action).

[00265] Depending on the nature of the agent, routes of administration include, but are not limited to, oral (e.g., by ingestion); buccal; sublingual; transdermal (including, e.g., by a patch, plaster, etc.); transmucosal (including, e.g., by a patch, plaster, etc.); intranasal (e.g., by nasal spray); ocular (e.g., by eye drops); pulmonary (e.g., by inhalation or insufflation

therapy using, e.g., via an aerosol, e.g., through the mouth or nose); rectal (e.g., by suppository or enema); vaginal (e.g., by pessary); parenteral, for example, by injection, including subcutaneous, intradermal, intramuscular, intravenous, intra-arterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrasternal; by implant of a depot or reservoir, for example, subcutaneously or intramuscularly.

Combinations with additional therapeutic agents

[00266] The combination treatments defined herein may be applied as a sole therapy for the treatment of the specified condition or it may involve, in addition to the combination therapy of the present invention, one or more additional therapies (including treatment with another therapeutic agent, surgery or other therapeutic interventions such as radiotherapy in the oncology setting).

[00267] Typically, the other therapeutic agent used in combination with the combination therapy of the present invention will be one or more therapeutic agents used as the standard of care for the treatment of the disease or condition concerned. The other therapeutic agent may include, for example, another drug used for the treatment of the condition concerned, or an agent that modulates the biological response to the combination therapy of the invention, such as, for example, an immunomodulatory agent.

[00268] Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of this invention within the dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

[00269] For example, the combination therapies defined hereinbefore may be applied as a sole therapy or may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may further include one or more of the following categories of anti-tumour agents:-

other antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan, temozolamide and nitrosoureas); antimetabolites (for example gemcitabine and antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, and hydroxyurea); antitumour antibiotics (for example anthracyclines like

adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere and polokinase inhibitors); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

cytostatic agents such as antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and iodoxyfene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5α-reductase such as finasteride;

anti-invasion agents [for example c-Src kinase family inhibitors like 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline (AZD0530; International Patent Application WO 01/94341), *N*-(2-chloro-6-methylphenyl)-2-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-ylamino}thiazole-5-carboxamide (dasatinib, BMS-354825; J. Med. Chem., 2004, 47, 6658-6661) and bosutinib (SKI-606), and metalloproteinase inhibitors like marimastat, inhibitors of urokinase plasminogen activator receptor function or antibodies to Heparanase];

inhibitors of growth factor function: for example such inhibitors include growth factor antibodies and growth factor receptor antibodies (for example the anti-erbB2 antibody trastuzumab [Herceptin™], the anti-EGFR antibody panitumumab, the anti-erbB1 antibody cetuximab [Erbitux, C225] and any growth factor or growth factor receptor antibodies disclosed by Stern *et al.* (Critical reviews in oncology/haematology, 2005, Vol. 54, pp11-29); such inhibitors also include tyrosine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, ZD1839), *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-*N*-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)-quinazolin-4-amine (CI 1033), erbB2 tyrosine kinase inhibitors such as lapatinib); inhibitors of the hepatocyte growth factor family; inhibitors of the insulin growth factor family; inhibitors of the platelet-derived growth factor family such as imatinib and/or nilotinib (AMN107); inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006), tipifarnib (R115777) and lonafarnib (SCH66336)), inhibitors of cell signalling through MEK and/or AKT kinases, c-kit inhibitors, abl kinase inhibitors, PI3 kinase inhibitors, Plt3 kinase inhibitors, CSF-1R kinase inhibitors, IGF receptor

(insulin-like growth factor) kinase inhibitors; aurora kinase inhibitors (for example AZD1152, PH739358, VX-680, MLN8054, R763, MP235, MP529, VX-528 AND AX39459) and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors;

antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, [for example the anti-vascular endothelial cell growth factor antibody bevacizumab (Avastin™) and for example, a VEGF receptor tyrosine kinase inhibitor such as vandetanib (ZD6474), vatalanib (PTK787), sunitinib (SU11248), axitinib (AG-013736), pazopanib (GW 786034) and 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171; Example 240 within WO 00/47212), compounds such as those disclosed in International Patent Applications WO97/22596, WO 97/30035, WO 97/32856 and WO 98/13354 and compounds that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function and angiostatin)];

vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213;

an endothelin receptor antagonist, for example zibotentan (ZD4054) or atrasentan;

antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

immunotherapy approaches, including for example *ex-vivo* and *in-vivo* approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

[00270] In a particular embodiment, the combination therapies defined hereinbefore may involve, in addition to the combination therapy of the invention, conventional surgery or radiotherapy or chemotherapy.

[00271] Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the combination therapy of this invention within the dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

[00272] According to this aspect of the invention there is provided a combination as defined herinbefore for use in the treatment of a cancer as defined herein, comprising a combination therapy of the invention as defined hereinbefore, and another anti-tumour agent.

[00273] According to this aspect of the invention there is provided a combination for use in the treatment of cancer as defined herein, comprising a combination therapy of the invention as defined hereinbefore, and any one of the anti-tumour agents listed herein above.

[00274] In a further aspect of the invention there is provided a combination product of the invention for use in the treatment of cancer in combination with another anti-tumour agent, optionally selected from one listed herein above.

[00275] In a particular aspect, the present invention provides a combination of a METTL3 inhibitor and a BCL2 inhibitor as defined above for use in the treatment of acute myeloid leukaemia (AML), chronic lymphocytic leukaemia (CLL), small lymphocytic lymphoma (SLL) or myelodysplastic syndromes (MDS), wherein the METTL3 inhibitor and BCL2 inhibitor are administered in combination with an additional anti-tumour agent.

[00276] In a further aspect, the present invention provides a combination of STM3480 and venetoclax for use in the treatment of acute myeloid leukaemia (AML), chronic lymphocytic leukaemia (CLL), small lymphocytic lymphoma (SLL) or myelodysplastic syndromes (MDS), wherein STM3480 and venetoclax are administered in combination with another anti-tumour agent.

[00277] Suitably, the additional anti-tumour agent is selected from an agent that is the standard of care for the treatment of AML, CLL, SLL or MDS. In particular, the additional anti-tumour agent may be selected from:

(i) an anthracycline topoisomerase 2 inhibitor (e.g. daunorubicin);

(ii) cytarabine;

(iii) a hypomethylating agent (e.g. 5-azacitidine or decitabine); or

(iv) a FLT3 inhibitor (e.g. quizartinib);

or a pharmaceutically-acceptable salt thereof.

[00278] More particularly, the additional anti-tumour agent may be selected from daunorubicin, doxorubicin, epirubicin, idarubicin, 5-azacitidine, decitabine, sorafenib, lestaurtinib, midostaurin, quizartinib, crenolanib, gilteritinib or cytarabine. Suitably, the combination is for the treatment of AML, CLL or SLL, especially AML.

[00279] In one particular aspect, the present invention provides a combination of STM3480 and venetoclax for use in the treatment of acute myeloid leukaemia (AML), wherein STM3480 and venetoclax are administered in combination with another anti-tumour agent. Suitably, the additional anti-tumour agent is selected from an agent that is the standard of care for the treatment of AML. In particular, the additional anti-tumour agent may be selected from:

(i) an anthracycline topoisomerase 2 inhibitor (e.g. daunorubicin);

(ii) cytarabine;

(iii) a hypomethylating agent (e.g. 5-azacitidine or decitabine); or

(iv) a FLT3 inhibitor (e.g. quizartinib);

or a pharmaceutically-acceptable salt thereof. More particularly, the additional anti-tumour agent may be selected from daunorubicin, doxorubicin, epirubicin, idarubicin, 5-azacitidine, decitabine, sorafenib, lestaurtinib, midostaurin, quizartinib, crenolanib, gilteritinib or cytarabine. Suitably, the combination is for the treatment of AML, CLL or SLL, especially AML.

DESCRIPTION OF DRAWINGS

[00280] Embodiments of the invention will be described, by way of example only, with reference to the accompanying drawings, in which:

Figure 1 - The combination of STM3480 and pembrolizumab leads to the strongest reduction in SKOV3 tumour survival (NLR intensity) and an enhanced effect relative to either agent alone.

Figure 2 - The combination of STM3480 and avelumab leads to the strongest reduction in SKOV3 tumour survival (NLR intensity) and an enhanced effect relative to either agent alone.

Figure 3 - Mean tumour volume of A20 lymphomas shown after treatments indicated, with Standard Error of the Mean indicated (SEM). Vehicle treatment (solid black lines, open circles) shows rapid progressive tumour growth. STM3480 treatment (dotted grey lines, open squares) shows a reduction of tumour growth compared to the vehicle control. Anti-PD1 treatment (grey dashed lines, open circles) shows a modest reduction in tumour growth. Combination of STM3480 and anti-PD1 (black dashed lines, closed triangles) shows complete tumour regressions in 6/10 animals. Abbreviations: TV – tumour volume; BID – twice daily dosing; BIW – twice weekly dosing.

Figure 4 - Tumour growth of A20 lymphomas shown for individual tumours after treatments indicated. Vehicle treatment (solid black lines, upper left panel) shows progressive tumour growth in 9/10 animals. STM3480 treatment (dashed grey lines, upper right panel) shows progressive tumour growth in 8/10 animals. Anti-PD1 treatment (black dotted lines, lower left panel) shows progressive tumour growth in 8/10 animals. Combination of STM3480 and anti-PD1 (black dotted and dashed lines, lower right panel) shows progressive tumour growth in 2/10 animals, tumour regressions in 8/10 and complete tumour regressions in 6/10 animals. Abbreviations: TV – tumour volume; BID – twice daily dosing; BIW – twice weekly dosing

Figure 5 - No adverse effects of treatments on body weight were observed in any group. Note decline in body weight of vehicle treated group from day 25 was a result of progression of disease and large tumour burden, and not due to the treatment per se.

Figure 6 - STM3480 shows a synergistic interaction with venetoclax in the Kasumi1 AML cell line, with increasing concentrations of STM3480 leading to decreasing IC50 of venetoclax as shown in the table below.

Figure 7 - STM3480 shows a synergistic interaction with venetoclax in the MOLM13 AML cell line, with increasing concentrations of STM3480 leading to decreasing IC50 of venetoclax as shown in the table below.

Figure 8 - STM3006 shows a synergistic interaction with venetoclax in the Kasumi1 AML cell line, with increasing concentrations of STM3006 leading to decreasing IC50 of venetoclax as shown in the table below.

Figure 9 - STM3006 shows a synergistic interaction with venetoclax in the MOLM13 AML cell line, with increasing concentrations of STM3006 leading to decreasing IC50 of venetoclax as shown in the table below.

Figure 10 - STM3675 shows a synergistic interaction with venetoclax in the Kasumi1 AML cell line, with increasing concentrations of STM3675 leading to decreasing IC50 of venetoclax as shown in the table below.

Figure 11 - STM3675 shows a synergistic interaction with venetoclax in the MOLM13 AML cell line, with increasing concentrations of STM3675 leading to decreasing IC50 of venetoclax as shown in the table below.

Figure 12 - STM3480 shows an additive interaction with daunorubicin in the Kasumi1 AML cell line, with increasing concentrations of STM3480 leading to decreasing viability. No change in IC50 of daunorubicin is observed, indicating an additive interaction.

Figure 13 - STM3006 shows an additive interaction with daunorubicin in the Kasumi1 AML cell line, with increasing concentrations of STM3006 leading to decreasing viability. No change in IC50 of daunorubicin is observed, indicating an additive interaction.

Figure 14 - STM3480 shows an additive interaction with cytarabine in the Kasumi1 AML cell line, with increasing concentrations of STM3480 leading to decreasing viability. No change in IC50 of cytarabine is observed, indicating an additive interaction.

Figure 15 - STM3006 shows an additive interaction with cytarabine in the Kasumi1 AML cell line, with increasing concentrations of STM3006 leading to decreasing viability. No change in IC50 of cytarabine is observed, indicating an additive interaction.

Figure 16 - STM3480 shows an additive interaction with 5'-azacitidine in the Kasumi1 AML cell line, with increasing concentrations of STM3480 leading to decreasing viability. No change in IC50 of 5'-azacitidine is observed, indicating an additive interaction.

Figure 17 - STM3006 shows an additive interaction with 5'-azacitidine in the Kasumi1 AML cell line, with increasing concentrations of STM3006 leading to decreasing viability. No change in IC50 of 5'-azacitidine is observed, indicating an additive interaction.

Figure 18 - STM3480 shows an additive interaction with quizartinib in the FLT3-mutant MOLM-14 AML cell line, with increasing concentrations of STM3480 leading to decreasing viability. No change in IC50 of quizartinib is observed, indicating an additive interaction.

Figure 19 - STM3006 shows an additive interaction with quizartinib in the FLT3-mutant MOLM-14 AML cell line, with increasing concentrations of STM3006 leading to decreasing viability. No change in IC50 of quizartinib is observed, indicating an additive interaction.

EXAMPLES

Preparation of compounds STM3480, STM3675 and STM3006

The following abbreviations have been used:

AIBN – Azobisisobutyronitrile

DBU – 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCE – Dichloroethane

DCM – Dichloromethane

DIBAL – Diisobutylaluminium hydride

DIPEA - N-ethyl-N-isopropyl-propan-2-amine

DMAP – 4-Dimethylaminopyridine

DMF – Dimethylformamide

DMSO – Dimethyl sulfoxide

DPPA – Diphenylphosphoryl azide

HATU - [dimethylamino(triazolo[4,5-b]pyridin-3-yloxy)methylene]-dimethyl-ammonium ;hexafluorophosphate

HPLC – High performance liquid chromatography

IPA – Isopropanol

LCMS – Liquid chromatograph mass spectrometry

NBS – N-Bromosuccinimide

NMP – N-Methyl-2-pyrrolidone

Phase separation cartridge – Telos phase separator 6 mL

RBF- Round bottomed flask

RM – Reaction mixture

RT – Retention Time

STAB - Sodium triacetoxyborohydride

T3P – Propylphosphonic anhydride

TBAF – Tetra-n-butylammonium fluoride

TEA – Triethylamine

TFA – Trifluoroacetic acid

TFAA – Trifluoroacetic anhydride

THF – Tetrahydrofuran

The following methodologies have been used in the Examples:

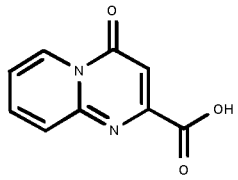
LCMS method A refers to low pH analysis using a mobile phase consisting of 0.1% formic acid in a gradient of 5-100% MeCN in water over 1.2 min at a flow rate of 1.2 mL/min. The stationary phase consisted of a Kinetex Core-Shell C18, 2.1mmx50mm, 5 µm. The experiment was run at 40°C.

LCMS Method B refers to high pH analysis using a mobile phase consisting of 2 mM ammonium bicarbonate, buffered to pH10 in a gradient of 5-100% MeCN in water over 2.1 min at a flow rate of 1.0 mL/min. The stationary phase consisted of a Phenomenex Gemini-NX C18, 2.0 x 50 mm, 3 µm. The experiment was run at 40°C.

LCMS Method C refers to high pH analysis using a mobile phase consisting of 2 mM ammonium bicarbonate, buffered to pH10 in a gradient of 5-100% MeCN in water over 5.8

min at a flow rate of 0.6 mL/min. The stationary phase consisted of a Waters UPLC® BEHTM C18, 2.1 x 100 mm, 1.7 µm. The experiment was run at 40°C.

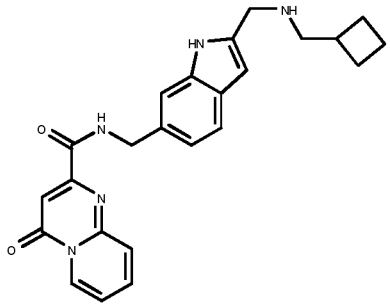
Intermediate 1: 4-Oxopyrido[1,2-a]pyrimidine-2-carboxylic acid



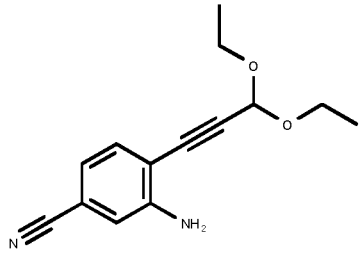
Methyl 4-oxopyrido[1,2-a]pyrimidine-2-carboxylate [Tetrahedron (2014), 70(17), 2761-2765] (3.94 g, 19.3 mmol) was dissolved in hydrogen chloride solution (8M, 7.5 mL) at room temperature (An exotherm was noted on addition) and the mixture was heated at reflux at for 2 h. The mixture was cooled to room temperature and the precipitate was collected by filtration and dried under vacuum to give the title compound (3.00 g, 81%) as a white solid.

Method A: LC-MS (electrospray): m/z = 191.1 $(M+H)^+$, RT = 0.32 min

Preparation of STM3480 - N-[(2-{[(cyclobutylmethyl)amino]methyl}-1H-indol-6-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide



Step 1: 3-amino-4-(3,3-diethoxyprop-1-yn-1-yl)benzonitrile

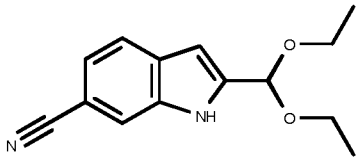


To a solution of 3-amino-4-iodobenzonitrile (8.00 g, 32.8 mmol) in THF-Anhydrous (40 mL) and triethylamine (80 mL, 0.574 mol) was added $Pd_2(PPh_3)_2Cl_2$ (230 mg, 0.328 mmol)

and triphenylphosphine (172 mg, 0.656 mmol) at ambient temperature. The solution was de-gassed by bubbling nitrogen into the solution for 20 minutes. Then copper (I) iodide (125 mg, 0.66 mmol) and 3,3-diethoxyprop-1-yne (5.04 g, 39.3 mmol) were added sequentially and the reaction was stirred under nitrogen atmosphere for 18 hours. The precipitate (triethylamine hydrochloride) was collected by filtration and washed with EtOAc (~20 mL). The filtrate was concentrated at reduced pressure and the residue was purified by chromatography on SiO_2 [Biotage KP-Sil 100 g, eluting with 0-50% EtOAc in heptane]. The product containing fractions were combined and concentrated in vacuo to afford the title compound (8.19 g, Quant) as an orange oil.

Method B: LC-MS (electrospray): m/z = 262.3 $(M+H)^+$, RT = 1.65 min.

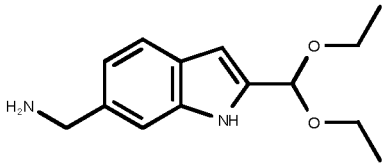
Step 2: 2-(diethoxymethyl)-1H-indole-6-carbonitrile



To a stirred solution of 3-amino-4-(3,3-diethoxyprop-1-ynyl)benzonitrile (8.00 g, 31.1 mmol) in NMP (99 mL) was added potassium tert-butoxide (6.98 g, 62.2 mmol) at 0°C (the colour of the solution turned from orange to dark red). After warming to RT, the solution was stirred at ambient temperature for 16 hours. Saturated aqueous ammonium chloride solution (25 mL) was added and the resulting mixture was partitioned between EtOAc (250 mL) and water (250 mL). The layers were separated and the organic layer washed twice more with water (2 x 200 mL). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to give a brown oil. The first aqueous layer was re-extracted with EtOAc (200 mL) and the layers separated. The organic layer was washed twice with water (2 x 200 mL). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to give an orange oil. The crude material was purified by chromatography on SiO_2 [BIOTAGE KP-Sil 100 g , eluting with 0-50% EtOAc in heptane]. The product containing fractions were combined and concentrated *in vacuo*. The residue (yellow solid) was recrystallised from EtOAc/heptane to afford the title compound (5.86 g, 24.0 mmol, 77%) as colourless crystalline solid.

Method B: LC-MS (electrospray): m/z = 262.3 $(M+H)^+$, RT = 1.69 min.

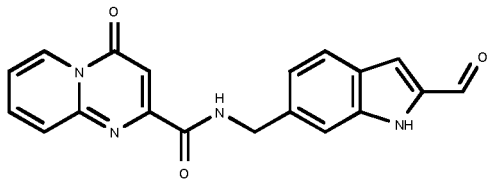
Step 3: [2-(diethoxymethyl)-1H-indol-6-yl]methanamine



To a degassed solution of 2-(diethoxymethyl)-1H-indole-6-carbonitrile (5.8 g, 24 mmol) in ethanol (70 mL) was added ammonia in MeOH (7M, 20 mL, 0.14 mmol) and the reaction was degassed and backfilled with nitrogen 3 times. Raney nickel (assumed 50%, about 5.4 g, 0.1 mmoL) was added and the reaction evacuated and backfilled with nitrogen 3 times. The flask was evacuated one final time and put under a hydrogen atmosphere and stirred at ambient temperature for 3 hours. More Raney nickel (about 2.7 g) was added and the reaction evacuated and placed under a hydrogen atmosphere and stirred at ambient temperature for 16 hours. The catalyst was removed by filtration (through Kieselguhr) and washed with methanol (50 mL). The filtrate was concentrated under reduced pressure to afford the title compound (5.96 g, 100%) as a colourless oil which crystallised upon standing.

Method C: LC-MS (electrospray): m/z = 247.3 $(M-H)^-$, RT = 2.74 min.

Step 4: N-[(2-formyl-1H-indol-6-yl)methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide



To a stirred solution of 4-oxopyrido[1,2-a]pyrimidine-2-carboxylic acid (455 mg, 2.39 mmol) (**Intermediate 1**) and DIPEA (1.0 mL, 5.98 mmol) in DMF (10 mL) was added HATU (910 mg, 2.39 mmol). A colour change was observed from colourless to green and a suspension formed. After a further 30 minutes of stirring at ambient temperature, a solution of [2-(diethoxymethyl)-1H-indol-6-yl]methanamine (500 mg, 1.99 mmol) in DMF (5 mL) was added dropwise to the reaction. A colour change of green to red was observed and the reaction became homogeneous and was stirred at ambient temperature overnight.

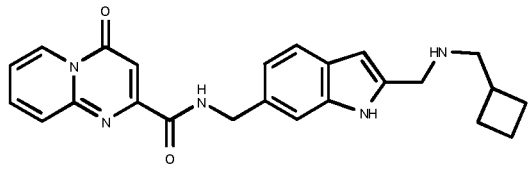
The mixture was partitioned between EtOAc (100 mL) and sat. $NaHCO_3$ solution (50 mL). The organic layer was separated, washed with water (80 mL) and brine (20 mL), dried (Na_2SO_4), filtered and concentrated at reduced pressure to give a viscous red oil.

The crude product was dissolved in THF (10 mL), water (1 mL) and acetic acid (0.5 mL) were added and the mixture was stirred at ambient temperature for 2 hours.

The THF was removed *in vacuo* and water (10 mL) was added to the resulting mixture causing further solid to precipitate out. The brown solid was collected by washed with water (2 x 5 mL) then ether (3 x 5 mL) and dried under vacuum to give the title compound (520 mg, 75%) as a brown solid.

Method C: LC-MS (electrospray): m/z = 347.2 $(M+H)^+$, RT = 2.37 min.

Step 5: N-[[2-[(Cyclobutylmethylamino)methyl]-1H-indol-6-yl]methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide

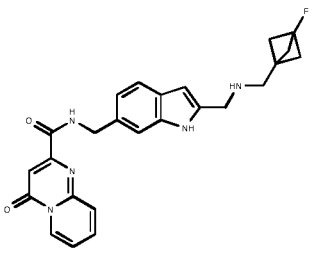


A pressure vial was charged with N-[(2-formyl-1H-indol-6-yl)methyl]-4-oxo-pyrido[1,2-a]pyrimidine-2-carboxamide (185 mg, 0.53 mmol), DCE (5 mL) and 1-cyclobutylmethanamine (0.13 mL, 1.0 mmol) at ambient temperature. The vial was sealed and the mixture was stirred at 65°C for 2 hours. After cooling to RT, sodium triacetoxyborohydride (340 mg, 1.85 mmol) was added and the mixture was heated to 65°C for 2 hours.

The mixture was partitioned between EtOAc (40 mL) and sat. sodium bicarbonate solution (30 mL). The organic layer was separated, washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated at reduced pressure. The residue (pale yellow oil) was purified by reverse phase chromatography (basic method, SNAP ULTRA 30 g Cartridge, eluting with MeCN+0.1% NH_3/H_2O + 0.1% NH_3, 10 to 90 %). The fractions containing desired product were freeze dried overnight to give the title compound (85 mg, 38%) as an off-white solid.

Method C: LC-MS (electrospray): m/z = 416.4 $(M+H)^+$, RT = 3.14 min.

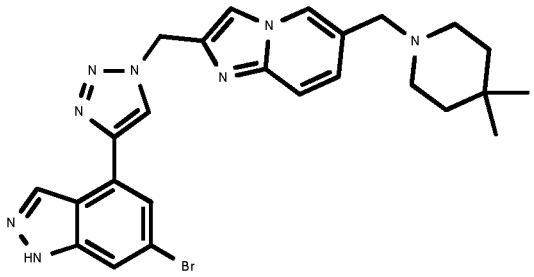
Preparation of STM3675 - N-[(2-{[({3-fluorobicyclo[1.1.1]pentan-1-yl}methyl)amino]methyl}-1H-indol-6-yl)methyl]-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide



This compound was prepared in the same manner as STM3480 described above using commercial amines or described intermediates.

Method C: LC-MS (electrospray): m/z = 446.4 $(M+H)^+$, RT = 3.01 min.

Preparation of STM3006 - (6-bromo-4-[1-({6-[(4,4-dimethylpiperidin-1-yl)methyl]imidazo[1,2-a]pyridin-2-yl}methyl)-1H-1,2,3-triazol-4-yl]-1H-indazole)



The preparation of STM3006 is described in Example 227 on page 285 of International Patent Publication No. WO2020/050898.

Example 1 - Combinations of METTL3 inhibitors (STM3480) with immune checkpoint inhibitors

Tumour Killing Assay (TKA)

This experiment evaluates the effects of human donor Peripheral Blood Mononuclear Cells (PBMCs) to attack and kill fluorescently-labelled tumour cells in a co-culture assay. Briefly, test agents are incubated at different concentrations with SKOV3 human ovarian cancer cells in the presence or absence of human donor PBMCs and tumour growth is monitored continuously by real time imaging of the NucLight Red-labelled SKOV3 cells for several days.

Tumour Killing Assay method

NucLight Red (Incucyte, Essen Biosciences) -transduced SK-OV-3 (SK-OV-3-NLR) cells were transferred into Ultra-low attachment 96 well plates with spontaneous spheroid formation occurring over 48 hours. Peripheral blood mononuclear cells (PBMC) were isolated from healthy single donor buffy coats by density separation. Prior to co-culture of SK-OV-3-NLR spheroids with PBMC, SK-OV-3-NLR spheroids were treated with 10ng/ml of interferon gamma (IFNγ). All treatments, including STM3480 and Pembrolizumab, were added at the point of co-culture in a final total volume of 200µl/ per well. Assay plates were

transferred into an IncuCyte S3 and images were collected every 2 hours for 7 days. Following experimental completion, an analysis definition was applied to quantify the Total NLR Integrated Intensity present on a per well basis. Changes in spheroid size were quantified by plotting Total NLR Integrated Intensity against time.

Table 1

Condition	Final concentration in assay	Cells	Readout
Untreated	N/A	SK-OV-3 spheroids +/- PBMC	Total NLR Integrated Intensity
DMSO (vehicle)	0.06%		
Pembrolizumab	20µg/mL		
IgG4 isotype control	20µg/mL		
STM3480	0.5, 0.1 & 0.05µM		
STM3480 + Pembrolizumab	0.5, 0.1 & 0.05µM (STM3480) + 20µg/ml (Pembrolizumab)		

Results

Figure 1 shows the changes of tumour viability (normalized NucLight Red [NLR] fluorescence on the y axis) against time (hours in the x axis). Vehicle-treated cells (closed black squares) show a steady modest decline in fluorescence intensity with time. Pembrolizumab (anti-PD1 antibody)-treated cells (closed grey circles) shows a greater decline in viable tumour cells at the end of the study. 0.05 micromolar STM3480 treatment (open triangles) yields a greater anti-tumour effect compared to vehicle, whereas the combination of STM3480 and pembrolizumab (open circles) gives the greatest reduction in tumour cell viability, beyond the effects seen with the individual agents.

Similarly, the treatment of SKOV3/PBMC co-cultures with STM3480 and/or avelumab (anti-PD-L1 antibody; open circles) leads to the greatest anti-tumour activity, greater than that seen with either single agent alone (grey circles, open triangles), demonstrating the surprising and beneficial effect of this combination treatment (see Figure 2).

Example 2 - Combinations of METTL3 inhibitors (STM3480) with immune checkpoint inhibitors - *in vivo* studies

The *in vivo* effect of METTL3 inhibition in combination with anti-PD1 immune checkpoint inhibitor was investigated using syngeneic mouse tumour models in immune-competent hosts. Mouse tumour models can be grown in appropriate host strains and are widely used to investigate the effects of therapeutic agents on the immune system and cancer growth. There are a limited range of mouse syngeneic tumour models available, far fewer than human cell lines, and they are widely used in the art to support potential clinical utility of immune stimulatory approaches across multiple indications. We exemplify the potential role of STM3480 and combinations with immune checkpoint inhibitors such as anti-PD-1 antibodies in multiple tumour models including A20 (murine B cell lymphoma), EMT-6 (murine breast cancer) and CT-26 (murine colorectal cancer).

1. A20 lymphoma model

Protocol

The objective of this study is to assess the anti-tumour efficacy of STM3480 in combination with anti-PD1 in subcutaneous A20 mouse B cell lymphoma cancer model in female BALB/c mice.

A20 (#ATCC TIB-208) mouse B cell lymphoma cells were cultured in (RPMI-1640 + 10% non H.I. FBS + 0.05mM 2-mercaptoethanol) media. 5 x 10^5 viable cells in 0.1 ml PBS were injected subcutaneously into the left flank of 7-9 week old female BALB/cN (BALB/cAnNCrl) Crl mice utilising 27 gauge needles following skin disinfection with 70% ethanol.

Tumours were measured three times a week and tumour volumes estimated using the formula 0.5 (LxW^2) by measuring the tumour in two dimensions using electronic callipers for the duration of the study.

Mice were randomly allocated to four treatment groups and treatment commenced when tumours reached a mean volume of ~50-100mm^3. Mice were allocated to their treatment groups with uniform mean tumour volume between groups. Treatment was continued for up to 3 weeks, or until individual mice were sacrificed for humane reasons according to Home Office licence regulations (e.g. body weight loss >20%; tumour volume >1500mm3; tumour ulceration; loss of clinical condition). The final dose was given on day 32 after implantation.

Formulation

Vehicle for STM3480 - Hydroxypropyl-β-Cyclodextrin (HPBCD)/ Sodium Acetate buffer pH:4,6 50 mM (10%/90%; w/v) : Weigh 1.025g of sodium acetate anhydrous. Add 700 µl of glacial acetic acid then make up to 500.0 ml with ultrapurified water. pH:4,6 50 mM.

For 1ml volume 5mg/ml STM3480 dosing solution: Weigh 5.0 mg of STM00003480 compound (Batch: EV-WZM001-421-002). Add 1.0 mL of HPBCD/Acetate buffer pH:4.6 50 mM (10%/90%; w/v). Magnetic stirring at high speed at ambient temperature; Overnight stirring may be required if there are any signs of precipitation. The formulation is a slight yellow solution with very few particles in suspension. Homogenize with a vortex before administration.

For PD-1 treatments, a mouse-specific anti-PD1 antibody (clone ID RMP1-14) was used, dissolved in PBS as described in the table below.

Table 2

Group (No per group)	Compound ID	Dose (mg/kg)	Dose Volume (ml/kg)	Dose Concentration (mg/ml)	Route/ N/A	Dosing Frequency
1 (10)	Vehicle (HPBCD+Acetate)	0	10	0	p.o	BID x up to 3 weeks
2 (10)	STM3480	50	^10	5	p.o	QD x up to 3 weeks
3 (10)	Anti PD1	10	10	1	i.p.	BIW x up to 3weeks
4 (10)	STM3480	50	^10	5	p.o	QD x up to 3 weeks
	Anti PD1	10	10	1	i.p.	BIW x up to 3weeks

p.o. = oral route (by gavage) – maximum volume 20 mL/kg

i.p. = Intraperitoneal – maximum volume 20 mL/kg

BID= ~8h apart

^For STM3480 the total dosing volume is 20 ml/kg per day so it was 10 ml/kg per dose for BID dosing

Animal welfare for this study complies with the UK Animals Scientific Procedures Act 1986 (ASPA) in line with Directive 2010/63/EU of the European Parliament and the Council of 22 September 2010 on the protection of animals used for scientific purposes.

Data

Vehicle treatment (solid black lines, upper left panel) shows progressive tumour growth in 9/10 animals. STM3480 treatment (dashed grey lines, upper right panel) shows progressive tumour growth in 8/10 animals. Anti-PD1 treatment (black dotted lines, lower left panel) shows progressive tumour growth in 8/10 animals. Combination of STM3480 and anti-PD1 (black dotted and dashed lines, lower right panel) shows progressive tumour growth in 2/10 animals, tumour regressions in 8/10 and complete tumour regressions in 6/10 animals.

Animals treated with the combination of STM3480 and anti-PD1 antibodies showed complete tumour regressions (i.e. no measurable tumour remaining) in the majority of treated animals. 6/10 animals remained tumour-free for 29 days after treatment ceased, indicating that these animals had all been cured.

Results

See Table 5 below and Figure 3 [A20 B cell lymphoma *in vivo* model (mean tumour volume)]; Figure 4 [A20 B cell lymphoma in vivo model (individual tumour curves)] and Figure 5 [A20 B cell lymphoma in vivo model (survival)].

2. EMT6 breast cancer model

Protocol

The objective of this study is to assess the anti-tumour efficacy of STM3480 in combination with anti-PD1 in subcutaneous EMT6 mouse breast cancer model in female BALB/c mice.

EMT6 (#ATCC CRL-2755) mouse breast cancer cells were cultured in (Waymouth's MB 752/1 Medium with 2mM L-glutamine, 85%; foetal bovine serum (non-heat inactivated), 15%) media. 5 x 10^4 viable cells in 0.1 ml PBS were injected subcutaneously into the left flank of 8-9 week old female BALB/cN (BALB/cAnNCrl) Crl mice utilising 27 gauge needles following skin disinfection with 70% ethanol.

Tumours were measured three times a week and tumour volumes estimated using the formula 0.5 (LxW^2) by measuring the tumour in two dimensions using electronic callipers for the duration of the study.

Mice were randomly allocated to four treatment groups and treatment commenced when tumours reached a mean volume of ~50-100mm^3. Mice were allocated to their treatment groups with uniform mean tumour volume between groups. Treatment was continued for up to 3 weeks, or until individual mice were sacrificed for humane reasons according to Home

Office licence regulations (e.g. body weight loss >20%; tumour volume >1500mm3; tumour ulceration; loss of clinical condition). The final dose was given on day 32 after implantation.

Table 3

Group (No per group)	Compound ID	Dose (mg/kg)	Dose Volume (ml/kg)	Dose Concentration (mg/ml)	Route/ N/A	Dosing Frequency
1 (10)	Vehicle (HPBCD+Acetate)	0	10	0	p.o	BID x up to 3 weeks
2 (10)	STM3480	50	^10	5	p.o	QD x up to 3 weeks
3 (10)	Anti PD1	10	10	1	i.p.	BIW x up to 3weeks
4 (10)	STM3480	50	^10	5	p.o	QD x up to 3 weeks
	Anti PD1	10	10	1	i.p.	BIW x up to 3weeks

p.o. = oral route (by gavage) – maximum volume 20 mL/kg

i.p. = Intraperitoneal – maximum volume 20 mL/kg

BID= ~8h apart

^For STM3480 the total dosing volume is 20 ml/kg per day so it was 10 ml/kg per dose for BID dosing

Animal welfare for this study complies with the UK Animals Scientific Procedures Act 1986 (ASPA) in line with Directive 2010/63/EU of the European Parliament and the Council of 22 September 2010 on the protection of animals used for scientific purposes.

Results

See Table 5 below.

3. CT26 colorectal cancer model

Protocol

The objective of this study is to assess the anti-tumour efficacy of STM3480 in combination with anti-PD1 in subcutaneous CT26 mouse colorectal cancer model in female BALB/c mice.

CT26.WT (CRL-2638) mouse breast cancer cells were cultured in (RPMI – 1640 + 10% FBS + 2mM L-Glutamine) media. 1 x 10^5 viable cells in 0.1 ml PBS were injected subcutaneously into the left flank of 8-9 week old female BALB/cN (BALB/cAnNCrl) Crl mice utilising 27 gauge needles following skin disinfection with 70% ethanol.

Tumours were measured three times a week and tumour volumes estimated using the formula 0.5 (LxW^2) by measuring the tumour in two dimensions using electronic callipers for the duration of the study.

Mice were randomly allocated to four treatment groups and treatment commenced when tumours reached a mean volume of ~50-100mm^3. Mice were allocated to their treatment groups with uniform mean tumour volume between groups. Treatment was continued for up to 3 weeks, or until individual mice were sacrificed for humane reasons according to Home Office licence regulations (e.g. body weight loss >20%; tumour volume >1500mm3; tumour ulceration; loss of clinical condition). The final dose was given on day 32 after implantation.

Table 4

Group (No per group)	Compound ID	Dose (mg/kg)	Dose Volume (ml/kg)	Dose Concentration (mg/ml)	Route/ N/A	Dosing Frequency
1 (10)	Vehicle (HPBCD+Acetate)	0	10	0	p.o	BID x up to 3 weeks
2 (10)	STM3480	50	^10	5	p.o	QD x up to 3 weeks
3 (10)	Anti PD1	10	10	1	i.p.	BIW x up to 3weeks
4 (10)	STM3480	50	^10	5	p.o	QD x up to 3 weeks
	Anti PD1	10	10	1	i.p.	BIW x up to 3weeks

p.o. = oral route (by gavage) – maximum volume 20 mL/kg

i.p. = Intraperitoneal – maximum volume 20 mL/kg

BID= ~8h apart

^For STM3480 the total dosing volume is 20 ml/kg per day so it was 10 ml/kg per dose for BID dosing

Animal welfare for this study complies with the UK Animals Scientific Procedures Act 1986 (ASPA) in line with Directive 2010/63/EU of the European Parliament and the Council of 22 September 2010 on the protection of animals used for scientific purposes.

Results

See Table 5 below.

Table 5 – summary of A20, EMT6, CT26 efficacy

Tumour model	Indication		Vehicle	STM3480	aPD1	STM3480 + aPD1
A20	Lymphoma	Mean tumour volume d24 (mm3)	1309	425	694	229
		No. mice with complete regressions	1	1	1	6
EMT6	Breast	Mean tumour volume d21 (mm3)	234	141	104	105
		No. mice with complete regressions	0	1	2	4
CT26	Colorectal	Mean tumour volume d28 (mm3)	1086	768	1095	641
		No. mice with regressions	0	0	0	2

The combination of STM3480 and anti-PD-1 antibody was highly efficacious in multiple in vivo syngeneic cancer models derived from a range of cancer indications (Table). In each case, the combination treatment caused the greatest number of tumour regressions compared to single agents, and in two models (A20 and EMT6), these regressions were

complete and no tumour was detected after treatment, indicating a profound anti-tumour response.

Example 3 - Combinations of METTL3 inhibitors (STM3480 / STM3006 / STM3675) with venetoclax

The sensitivity of AML cell lines to combinations of METTL3 inhibitor and standards of care was determined as described. Dose response curves of venetoclax were determined either alone or in the presence of different concentrations of METTL3 inhibitor that are known to be active in cells.

Synergistic interactions occur when the IC50 value decreases in the presence of METTL3 inhibitor. Additive interactions occur when the IC50 value does not change in the presence of METTL3 inhibitor. Antagonistic interactions occur when the IC50 value increases in the presence of METTL3 inhibitor.

Results

See Figures 6 to 11.

Figure 6 - STM3480 shows a synergistic interaction with venetoclax in the Kasumi1 AML cell line, with increasing concentrations of STM3480 leading to decreasing IC50 of venetoclax as shown in the table below.

In Figure 6, the IC50 of venetoclax in Kasumi1 cells was 238.5nM. In the presence of 316.2nM STM3480, the venetoclax IC50 dropped to 50.93nM, and in the presence of 1000nM STM3480, the venetoclax IC50 dropped further to 22.23nM. This increase potency indicates a synergistic interaction.

The same synergistic interaction and decrease in IC50 values were observed in the Kasumi1 cell line with additional METTL3 inhibitors, and in other AML cell lines (see figures 7 to 11).

Figure 7 - STM3480 shows a synergistic interaction with venetoclax in the MOLM13 AML cell line, with increasing concentrations of STM3480 leading to decreasing IC50 of venetoclax as shown in the table below.

Figure 8 - STM3006 shows a synergistic interaction with venetoclax in the Kasumi1 AML cell line, with increasing concentrations of STM3006 leading to decreasing IC50 of venetoclax as shown in the table below.

Figure 9 - STM3006 shows a synergistic interaction with venetoclax in the MOLM13 AML cell line, with increasing concentrations of STM3006 leading to decreasing IC50 of venetoclax as shown in the table below.

Figure 10 - STM3675 shows a synergistic interaction with venetoclax in the Kasumi1 AML cell line, with increasing concentrations of STM3675 leading to decreasing IC50 of venetoclax as shown in the table below.

Figure 11 - STM3675 shows a synergistic interaction with venetoclax in the MOLM13 AML cell line, with increasing concentrations of STM3675 leading to decreasing IC50 of venetoclax as shown in the table below.

Example 4 Combinations with other AML Standards of Care drugs

Materials

- RPMI 1640 Medium, no glutamine (Gibco #31870-025)
- Fetal Bovine Serum (Sigma F7524-500ML)
- GlutaMAX™ Supplement (Gibco #35050038)
- Sodium Pyruvate (100 mM) (Gibco #11360039)
- DMSO (Sigma #D2650)
- DPBS 1X (Gibco #14190-094)
- IFN gamma (R/D Systems, ref 285-IF) (200 µg/ml)
- Cell culture 384 well plate SBIO ultra low attachment (SBio, MS-9384WZ)
- Grip Tips Viaflo 384, sterile (Integra 6464)
- CellTiter-Glo Luminescent cell viability assay (Promega #G7571)
- T8+ dispensehead cassettes HP (Fisher #15429293)
- D4+ dispensehead cassettes HP (Fisher # 15577409)

Table 6 : Cell lines:

Cell line	Culture medium	Cell seeding	Treatment time
Kasumi-1	RPMI 1640 media 20% FBS, Glutamax and Sodium Pyruvate	333 000 cells/ml 250 000 cells/ml	3 days 5 days

MOLM-13	RPMI 1640 media 10% FBS, Glutamax and Sodium Pyruvate	266 000cells/ml	3 days
MOLM-14	RPMI 1640 media 10% FBS, Glutamax and Sodium Pyruvate	250 000 cells/ml	3 days

Table 7: Compounds

Compound	Supplier	Reference	Top dose
Venetoclax (ABT-199)	Interchim	1L2752-10MG	10µM
Quizartinib	MedChemExpress	HY13001	0.1µM
Daunorubicin	Sigma-Aldrich	30450-5MG	10µM
Cytarabine	Bio-Techne	4520/50mg	10µM
5-azacitidine	Sigma-Aldrich	A2385-100MG	10µM

A. Cell preparation

24h before cell treatment, homogenize, stain with Trypan blue and count viable cells using CellOMeter Auto T4. Dilute cells in media at 400 000 cells/ml to ensure an exponential growth the day after.

On treatment day, homogenize, stain with Trypan blue and count viable cells using CellOMeter Auto T4. Dilute to the proper cell seeding density according to Table 6 in cell media.

B. Cell treatment

- Dispense drug (see Table 7) and METTL3 inhibitor in semi-log dose-response matrix and DMSO in 384-well plates using D300e Nanodispenser (Tecan).
- 6X compound solution preparation : add 40µL of cell medium in compound-containing plates and homogenize using the ViaFlo device (Integra)
- Dispense 30 µl of cell suspension per well in three replicate 384-well white Ultra-Low-Attachment plates (Sbio) using ViaFlow device (Integra)
- Transfer 6µL of the 6X compound solution in each 30µL cell suspension-containing plate.

- Incubate at 37°C 5% CO2 for 3 to 5 days.

C. Cell Titer Glo assay

- Add 35µL CellTiter-Glo (Promega) in wells (vol/vol) using ViaFlo device (Integra).
- Incubate at RT 10 min in the dark, with agitation the first minute, and read luminescence on the Ensight device (Perkin Elmer).

D. Data analysis

Raw data were converted to % viability by normalization to DMSO controls. IC50 determination was performed using GraphPad Prism and fitting curves to the standard nonlinear regression four parameter equation (Y=Bottom + (Top-Bottom)/(1+(IC50/X)^HillSlope)) least squares method, and synergy was assessed by comparison of IC50 values of the standard of care in the presence or absence of different concentrations of METTL3 inhibitor (see Figures 12 to 19).

1. Daunorubicin (anthracycline topoisomerase 2 inhibitor)

Daunorubicin is a major component of the standard of care for AML treatment.

Additive interactions occur when the combination leads to an enhanced decrease in tumour cell viability with the addition of METTL3 inhibitor, yet the IC50 value does not change.

Results

Figure 12 - STM3480 shows an additive interaction with daunorubicin in the Kasumi1 AML cell line, with increasing concentrations of STM3480 leading to decreasing viability. No change in IC50 of daunorubicin is observed, indicating an additive interaction.

In Figure 12, the addition of STM3480 leads to a dose-dependent decrease in Kasumi1 cell viability. In the presence of 400nM or 1265nM STM3480, the daunorubicin IC50 did not significantly change, indicating an additive interaction.

The same additive interaction was observed in the Kasumi1 cell line with additional METTL3 inhibitor STM3006 (see Figure 13).

Figure 13 - STM3006 shows an additive interaction with daunorubicin in the Kasumi1 AML cell line, with increasing concentrations of STM3006 leading to decreasing viability. No change in IC50 of daunorubicin is observed, indicating an additive interaction.

2. Cytarabine (nucleoside analogue)

Cytarabine is a major component of the standard of care for AML treatment.

Results

Figure 14 - STM3480 shows an additive interaction with cytarabine in the Kasumi1 AML cell line, with increasing concentrations of STM3480 leading to decreasing viability. No change in IC50 of cytarabine is observed, indicating an additive interaction.

Figure 15 - STM3006 shows an additive interaction with cytarabine in the Kasumi1 AML cell line, with increasing concentrations of STM3006 leading to decreasing viability. No change in IC50 of cytarabine is observed, indicating an additive interaction.

3. 5'-azacitidine (hypomethylating agent)

Results

Figure 16 - STM3480 shows an additive interaction with 5'-azacitidine in the Kasumi1 AML cell line, with increasing concentrations of STM3480 leading to decreasing viability. No change in IC50 of 5'-azacitidine is observed, indicating an additive interaction.

Figure 17 - STM3006 shows an additive interaction with 5'-azacitidine in the Kasumi1 AML cell line, with increasing concentrations of STM3006 leading to decreasing viability. No change in IC50 of 5'-azacitidine is observed, indicating an additive interaction.

4. Quizartinib (FLT3 inhibitor)

MOLM-14 cells have a FLT3 mutation and are known to be highly dependent on FLT3 activity for survival and are highly sensitive to FLT3 inhibitors such as quizartinib.

Results

Figure 18 - STM3480 shows an additive interaction with quizartinib in the FLT3-mutant MOLM-14 AML cell line, with increasing concentrations of STM3480 leading to decreasing viability. No change in IC50 of quizartinib is observed, indicating an additive interaction.

Figure 19 - STM3006 shows an additive interaction with quizartinib in the FLT3-mutant MOLM-14 AML cell line, with increasing concentrations of STM3006 leading to decreasing viability. No change in IC50 of quizartinib is observed, indicating an additive interaction.

All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference in their entirety and to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein (to the maximum extent permitted by law).

All headings and sub-headings are used herein for convenience only and should not be construed as limiting the invention in any way.

The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise paragraphed. No language in the specification should be construed as indicating any non-paragraphed element as essential to the practice of the invention.

The citation and incorporation of patent documents herein is done for convenience only and does not reflect any view of the validity, patentability, and/or enforceability of such patent documents.

This invention includes all modifications and equivalents of the subject matter recited in the paragraphs appended hereto as permitted by applicable law.

CLAIMS

1. A combination comprising a METTL3 inhibitor, or a pharmaceutically acceptable salt thereof, and:

(i) an immune oncology agent or therapy;
(ii) a BCL2 inhibitor, or a pharmaceutically acceptable salt thereof;
(iii) an anthracycline topoisomerase 2 inhibitor, or a pharmaceutically acceptable salt thereof;
(iv) cytarabine, or a pharmaceutically acceptable salt thereof;
(v) a hypomethylating agent, or a pharmaceutically acceptable salt thereof; or
(vi) a FLT3 inhibitor, or a pharmaceutically acceptable salt thereof.

2. A combination according to claim 1, wherein the immune oncology agent or therapy is selected from the group conisting of immune checkpoint inhibitors (e.g. a PD1, PD-L1 inhibitor, LAG3, CTLA-4, TIGIT, TIM3, or VISTA inhibitor), STING agonists, TLR agonists, anti-CD137 antibodies, CD28 antibodies, OX40 stimulators, CD40 antibodies, ICOS agonists, GITR agonists, A2AR antagonists, Bispecific T cell engagers (BiTE), oncolytic viruses, cancer vaccines, and/or CAR-T cell therapy.

3. A combination according to claim 1 or claim 2, wherein the immune oncology agent or therapy is treatment with an immune checkpoint inhibitor, or a pharmaceutically acceptable salt thereof.

4. A combination according to claim 2 or claim 3, wherein the immune checkpoint inhibitor is selected from a PD1, PD-L1 inhibitor, a LAG3 inhibitor and a CTLA-4 inhibitor.

5. A combination according to any one of claims 2 to 4, wherein the immune checkpoint inhibitor is selected from a PD1 or PD-L1 inhibitor.

6. A combination according to any one of claims 2 to 4, wherein the immune checkpoint inhibitor is selected from BMS-986016/Relatlimab, TSR-033, REGN3767, MGD013 (bispecific DART binding PD-1 and LAG-3), GSK2831781, LAG525, MDX-010/Ipilimumab, AGEN1884, and CP-675,206/Tremelimumab, pembrolizumab, nivolumab, atezolizumab, avelumab and durvalumab, or a pharmaceutically acceptable salt thereof.

7. A combination according to claim 6, wherein the immune checkpoint inhibitor is selected from pembrolizumab, nivolumab, atezolizumab, avelumab and durvalumab, or a pharmaceutically acceptable salt thereof.

8. A combination according to claim 1, wherein the BCL2 inhibitor is venetoclax, or a pharmaceutically acceptable salt thereof.

9. A combination according to claim 1, wherein:

the anthracycline topoisomerase 2 inhibitor is selected from daunorubicin, doxorubicin, epirubicin or idarubicin, or a pharmaceutically acceptable salt thereof;

the hypomethylating agent is selected from 5-azacitidine or decitabine, or a pharmaceutically acceptable salt thereof;

the FLT3 inhibitor is selected from sorafenib, lestaurtinib, midostaurin, quizartinib, crenolanib, or gilteritinib, or a pharmaceutically acceptable salt thereof.

10. A combination according to any one of claims 1 to 9, wherein the METTL3 inhibitor is a compound of formula I, II, VI or VII defined herein, or a pharmaceutically acceptable salt thereof.

11. A combination according to any one of claims 1 to 9, wherein the METTL3 inhibitor is selected from STM3480, STM3675 or STM3006, or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical product comprising a combination according to any one of claims 1 to 11.

13. A pharmaceutical composition comprising a combination according to any one of claims 1 to 11, and one or more pharmaceutically acceptable excipients.

14. A METTL3 inhibitor, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, wherein the METTL3 inhibitor, or a pharmaceutically acceptable salt thereof, is administered in combination with:

(i) an immune oncology agent or therapy as claimed in any one of claims 1 to 7;
(ii) a BCL2 inhibitor, or a pharmaceutically acceptable salt thereof, as claimed in claim 1 or claim 8;
(iii) an anthracycline topoisomerase 2 inhibitor, or a pharmaceutically acceptable salt thereof as claimed in claim 1 or claim 9;
(iv) cytarabine, or a pharmaceutically acceptable salt thereof as claimed in claim 9;
(v) a hypomethylating agent, or a pharmaceutically acceptable salt thereof as claimed in claim 1 or claim 9; or

(vi) a FLT3 inhibitor, or a pharmaceutically acceptable salt thereof as claimed in claim 1 or claim 9.

15. A METTL3 inhibitor, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to claim 14, wherein the METTL3 inhibitor, or a pharmaceutically acceptable salt thereof, is administered in combination with an immune checkpoint inhibitor.

16. A METTL3 inhibitor, or a pharmaceutically acceptable salt thereof, for use in the treatment of a solid tumour, wherein the METTL3 inhibitor, or a pharmaceutically acceptable salt thereof, is administered in combination with an immune checkpoint inhibitor.

17. A METTL3 inhibitor, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to claim 15 or a solid tumour according to claim 16, wherein the METTL3 inhibitor is selected from STM3480, STM3675 or STM3006, or a pharmaceutically acceptable salt thereof, and is administered in combination with an immune checkpoint inhibitor, or a pharmaceutically acceptable salt thereof, as defined in any one of claims 4 to 7.

18. A METTL3 inhibitor, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to claim 14, wherein the METTL3 inhibitor, or a pharmaceutically acceptable salt thereof, is administered in combination with a BCL2 inhibitor, or a pharmaceutically acceptable salt thereof, as claimed in claim 1 or claim 8.

19. A METTL3 inhibitor, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to claim 18, wherein the METTL3 inhibitor is selected from STM3480, STM3675 or STM3006, or a pharmaceutically acceptable salt thereof, and is administered in combination with venetoclax, or a pharmaceutically acceptable salt thereof.

20. STM3480, or a pharmaceutically acceptable salt thereof, for use in the treatment of acute myeloid leukaemia (AML), chronic lymphocytic leukaemia (CLL), small lymphocytic lymphoma (SLL) or myelodysplastic syndromes (MDS), wherein STM3480 is administered in combination with venetoclax, or a pharmaceutically acceptable salt thereof.

21. STM3480, or a pharmaceutically acceptable salt thereof, for use in the treatment of acute myeloid leukaemia (AML), wherein STM3480 is administered in combination with venetoclax, or a pharmaceutically acceptable salt thereof.

22. A METTL3 inhibitor, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to claim 14, wherein the METTL3 inhibitor, or a pharmaceutically acceptable salt thereof, is administered in combination with

(i) an anthracycline topoisomerase 2 inhibitor, or a pharmaceutically acceptable salt thereof as claimed in claim 1 or claim 9;

(ii) cytarabine, or a pharmaceutically acceptable salt thereof, as claimed in claim 9;

(iii) a hypomethylating agent, or a pharmaceutically acceptable salt thereof, as claimed in claim 1 or claim 9; or

(iv) a FLT3 inhibitor, or a pharmaceutically acceptable salt thereof, as claimed in claim 1 or claim 9.

23. A METTL3 inhibitor, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to claim 22, wherein the METTL3 inhibitor is STM3480.

24. A METTL3 inhibitor, or a pharmaceutically acceptable salt thereof, for use as an immune-sensitiser.

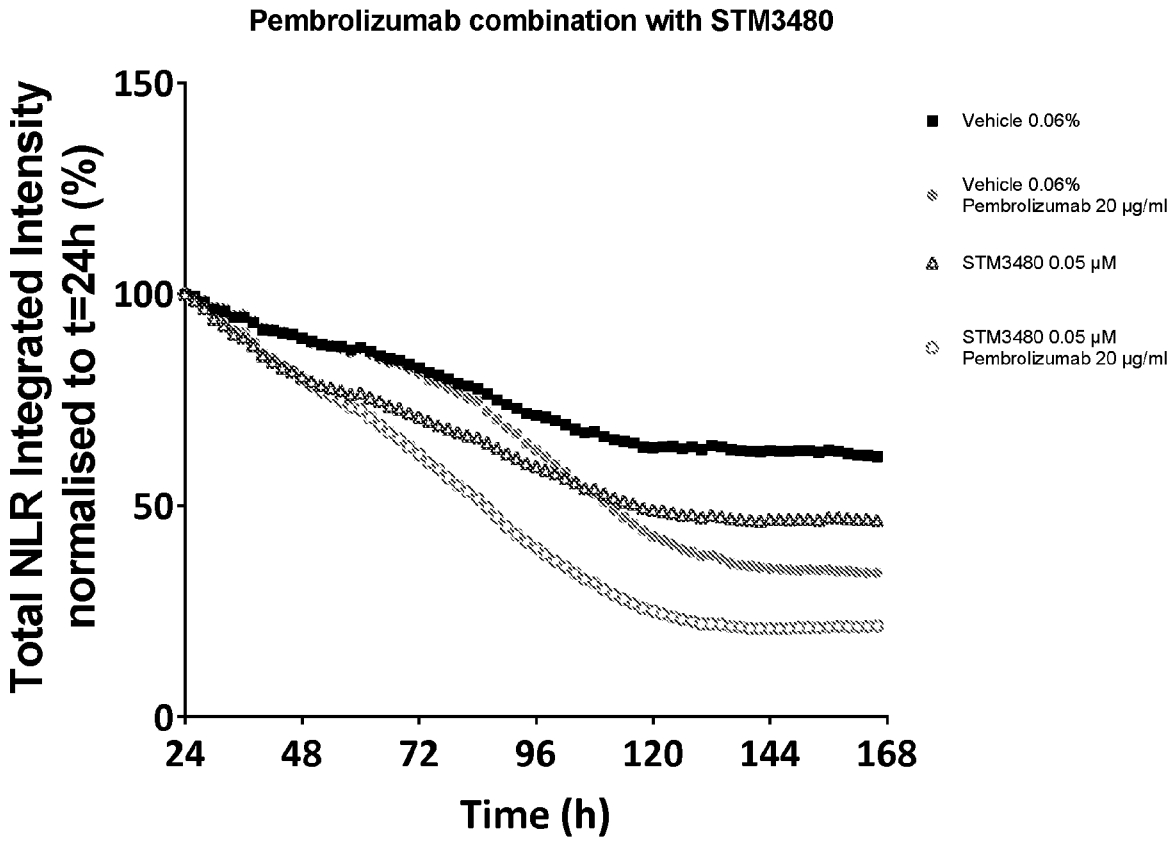

Pembrolizumab combination with STM3480
Total NLR Integrated Intensity normalised to t=24h (%)
150
100
50
0
24
48
72
96
120
144
168
Time (h)
Vehicle 0.06%
Vehicle 0.06% Pembrolizumab 20 µg/ml
STM3480 0.05 µM
STM3480 0.05 µM Pembrolizumab 20 µg/ml

FIGURE 1

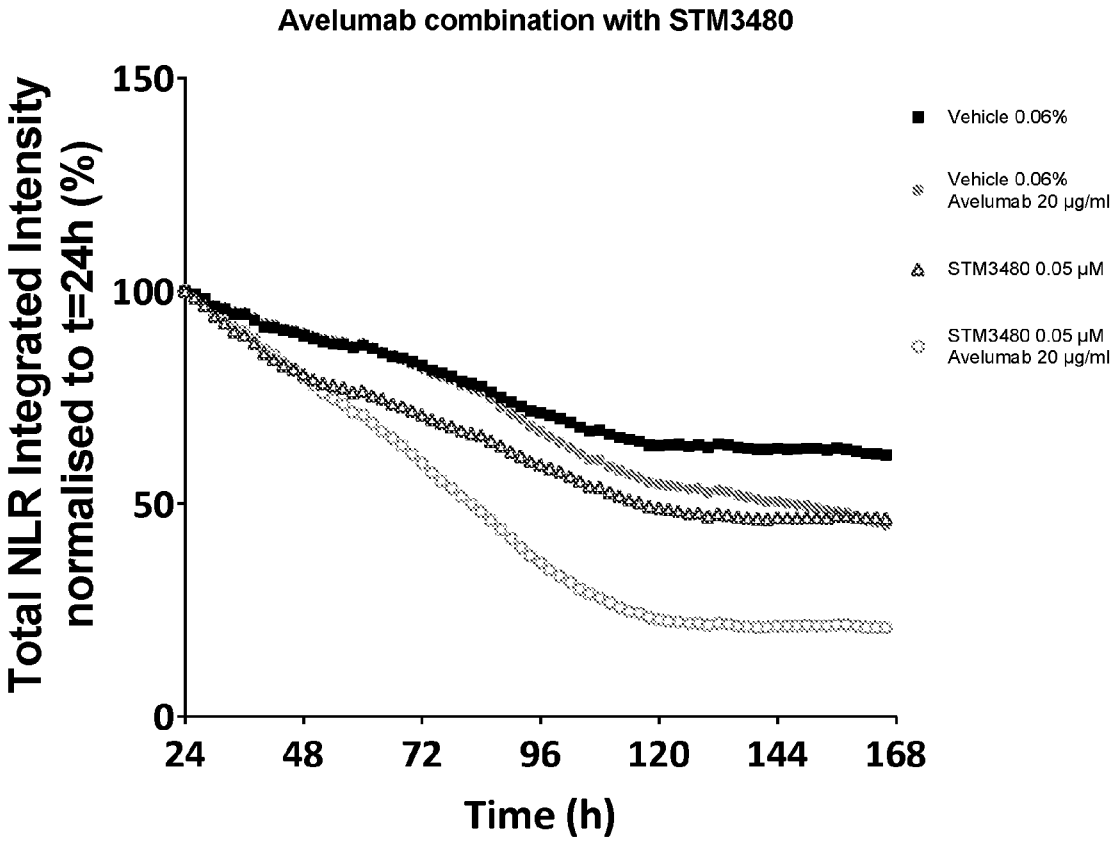

Avelumab combination with STM3480
Total NLR Integrated Intensity normalised to t=24h (%)
150
100
50
0
24
48
72
96
120
144
168
Time (h)
Vehicle 0.06%
Vehicle 0.06% Avelumab 20 µg/ml
STM3480 0.05 µM
STM3480 0.05 µM Avelumab 20 µg/ml

Figure 2

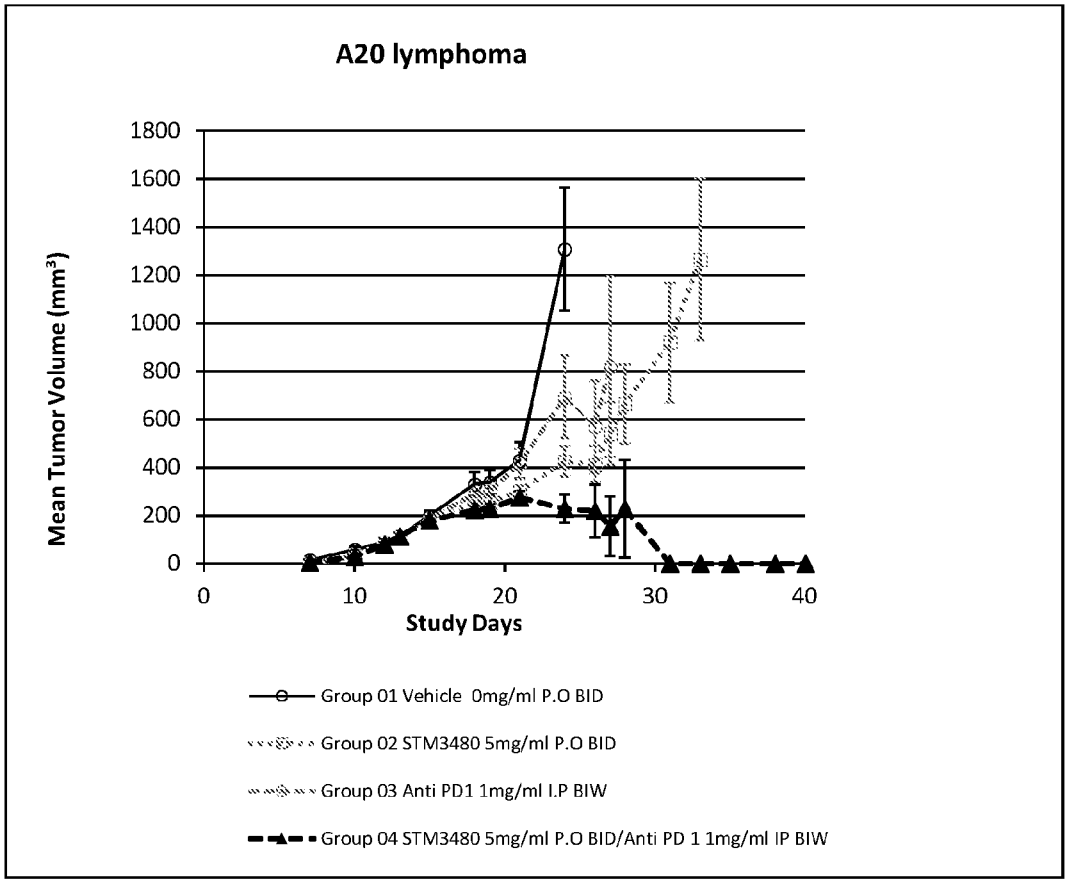

A20 lymphoma
Mean Tumor Volume (mm³)
1800
1600
1400
1200
1000
800
600
400
200
0
0
10
20
30
40
Study Days
Group 01 Vehicle 0mg/ml P.O BID
Group 02 STM3480 5mg/ml P.O BID
Group 03 Anti PD1 1mg/ml I.P BIW
Group 04 STM3480 5mg/ml P.O BID/Anti PD 1 1mg/ml IP BIW

Figure 3

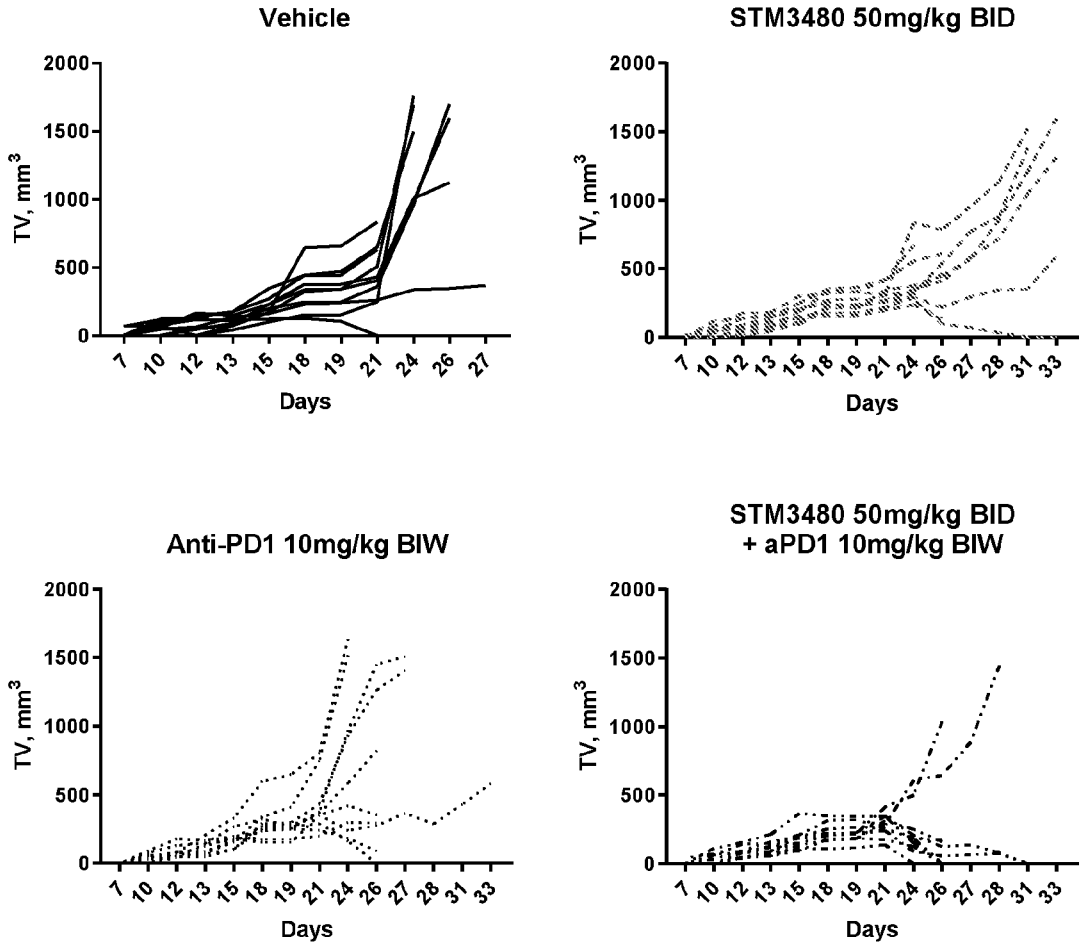
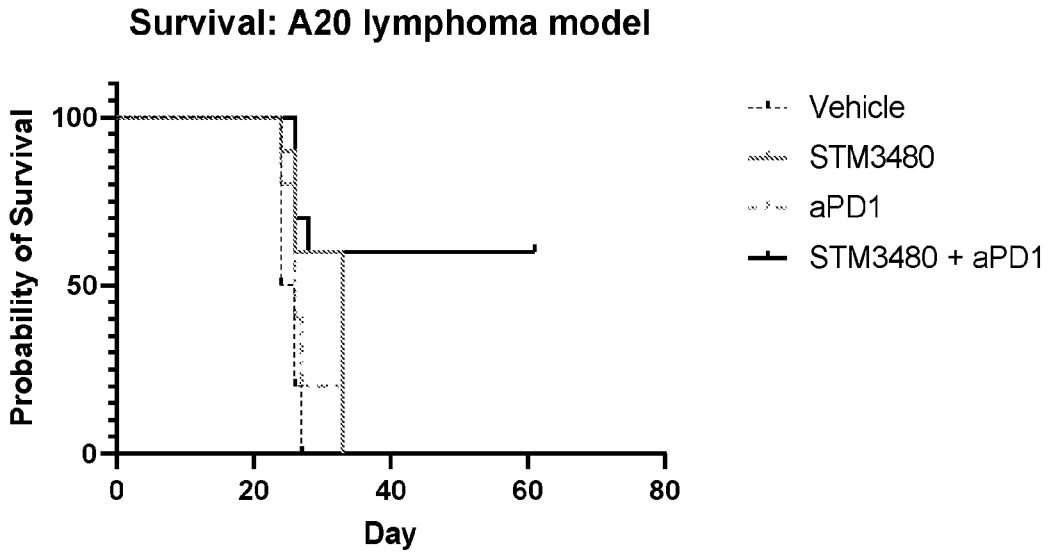

Vehicle
STM3480 50mg/kg BID
Anti-PD1 10mg/kg BIW
STM3480 50mg/kg BID
+ aPD1 10mg/kg BIW
TV, mm3
Days
0
500
1000
1500
2000
7 10 12 13 15 18 19 21 24 26 27
7 10 12 13 15 18 19 21 24 26 27 28 31 33

Figure 4


Survival: A20 lymphoma model
Probability of Survival
100
50
0
0
20
40
60
80
Day
Vehicle
STM3480
aPD1
STM3480 + aPD1

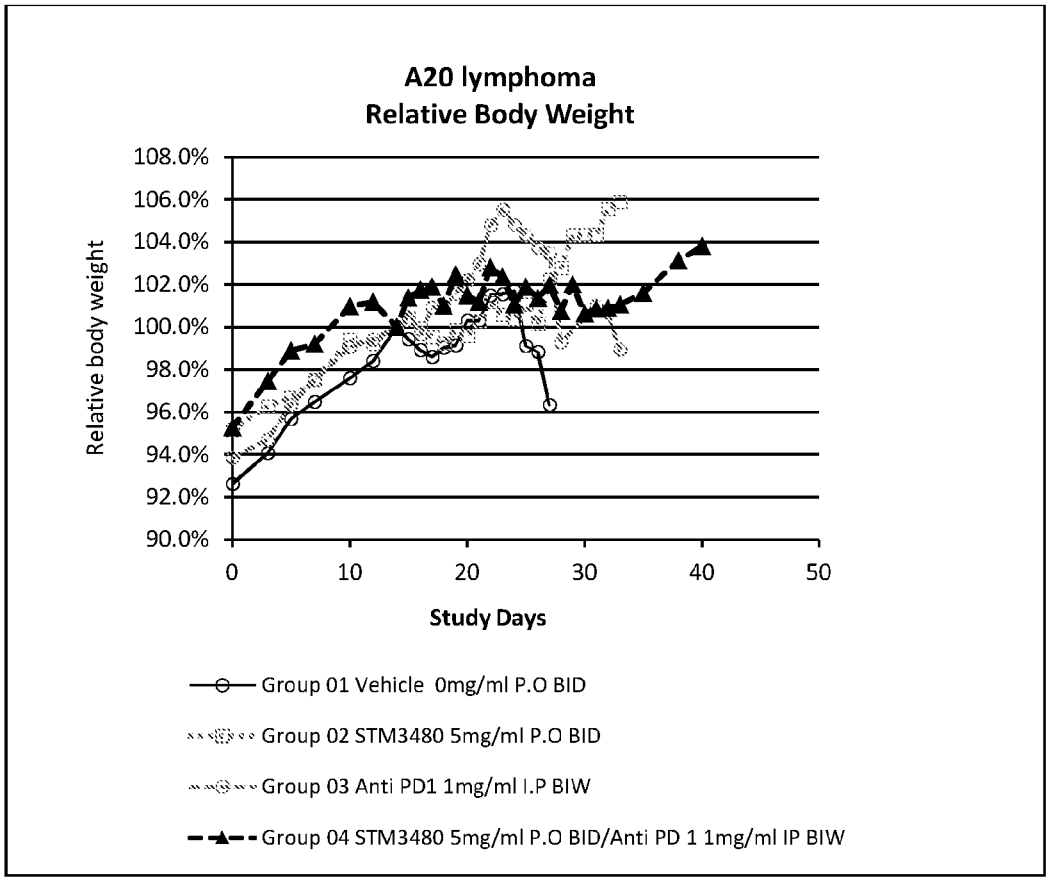
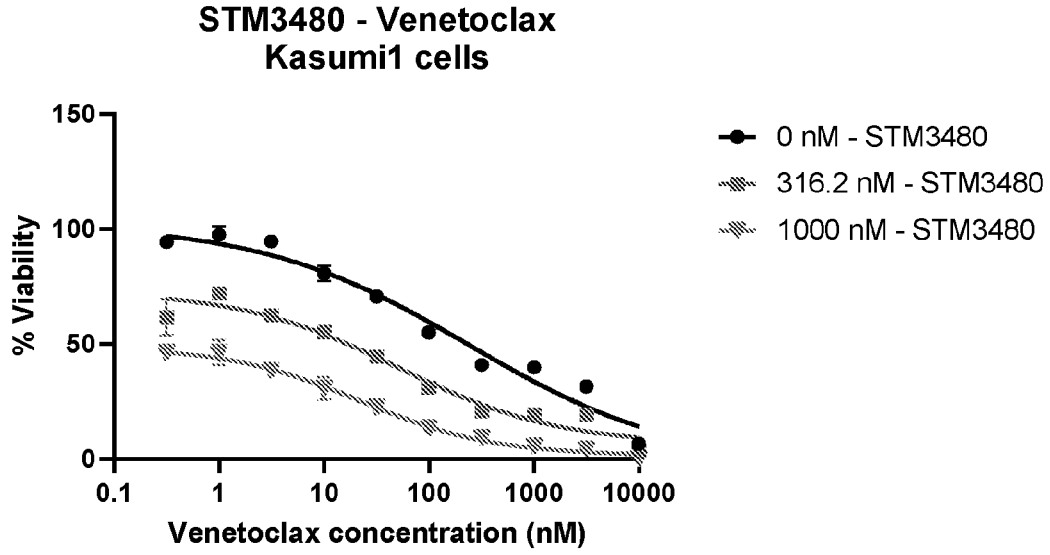
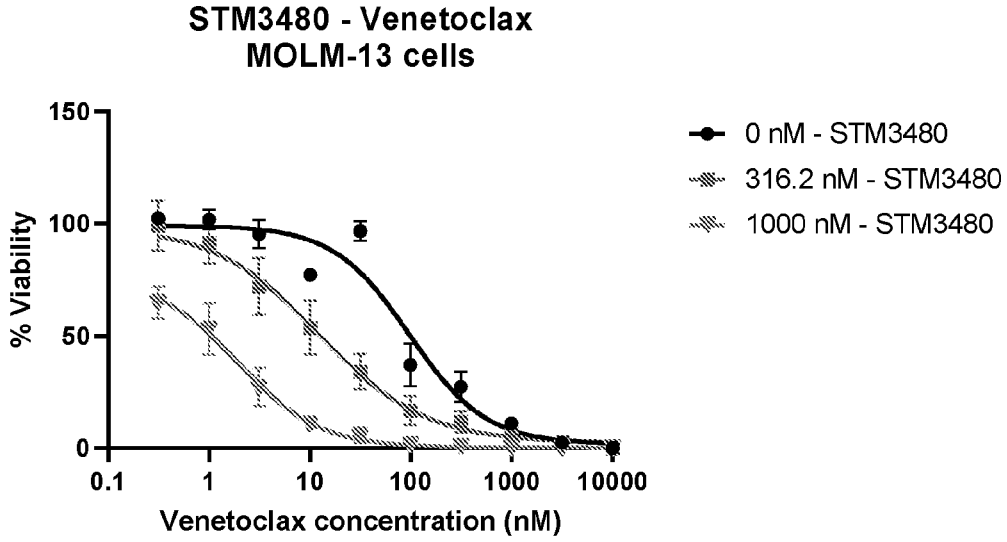

A20 lymphoma
Relative Body Weight
Relative body weight
108.0%
106.0%
104.0%
102.0%
100.0%
98.0%
96.0%
94.0%
92.0%
90.0%
0
10
20
30
40
50
Study Days
Group 01 Vehicle 0mg/ml P.O BID
Group 02 STM3480 5mg/ml P.O BID
Group 03 Anti PD1 1mg/ml I.P BIW
Group 04 STM3480 5mg/ml P.O BID/Anti PD 1 1mg/ml IP BIW

Figure 5



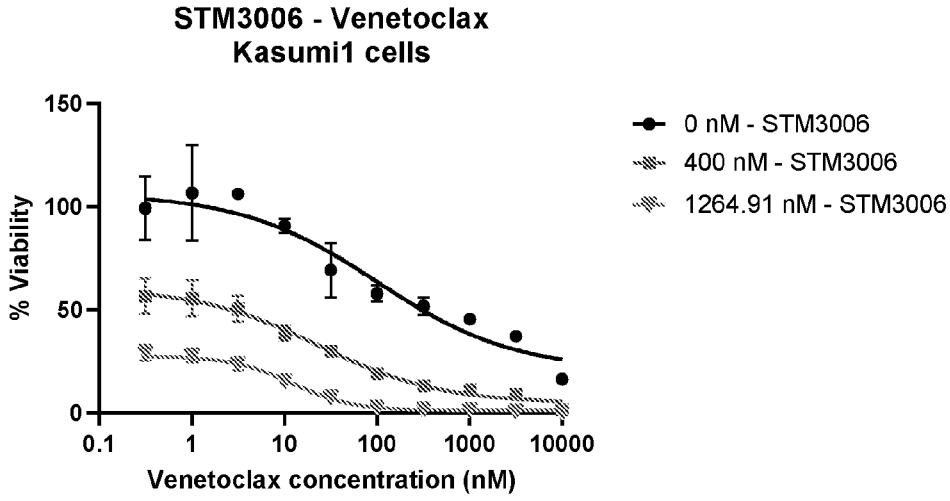
	0 nM - STM3480	316.2 nM - STM3480	1000 nM - STM3480
IC50	238.3	50.93	22.23

Figure 6



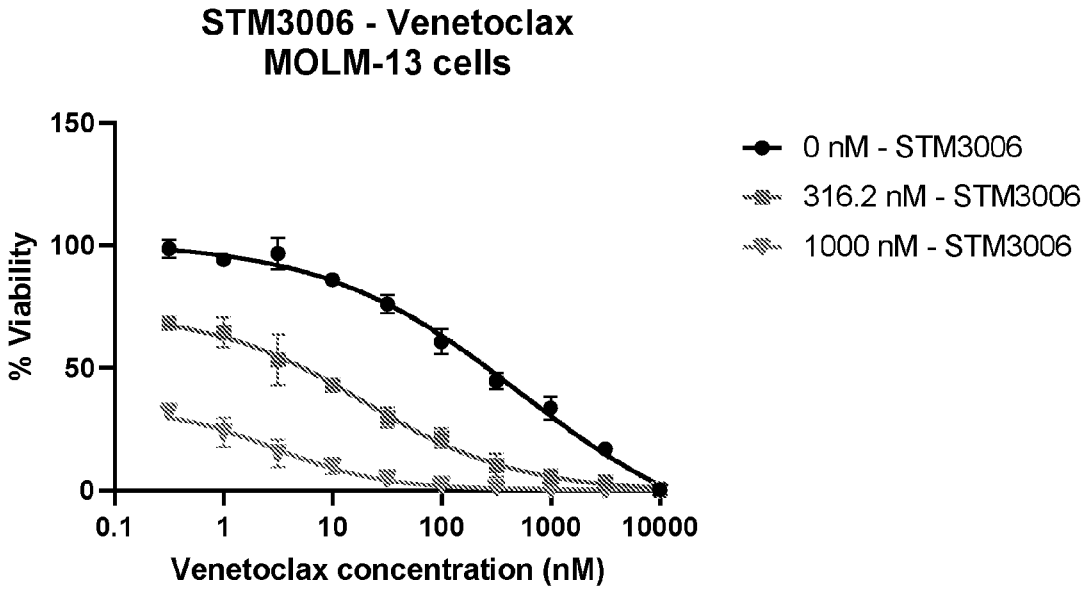
	0 nM - STM3480	316.2 nM - STM3480	1000 nM - STM3480
IC50	97.25	12.41	1.938

Figure 7



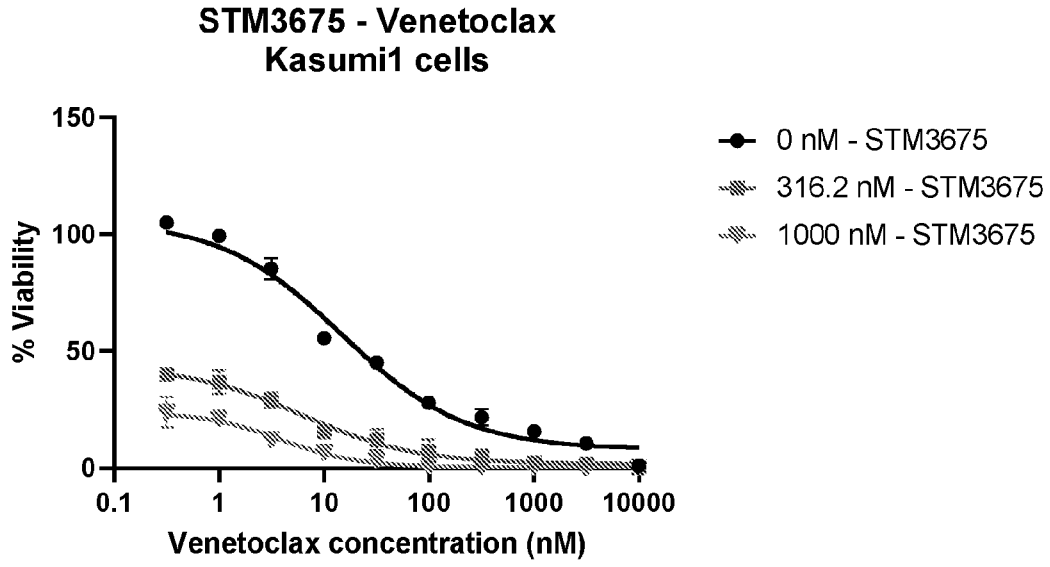
	0 nM - STM3006	400 nM - STM3006	1264.91 nM - STM3006
IC50	100.7	23.34	12.14

Figure 8



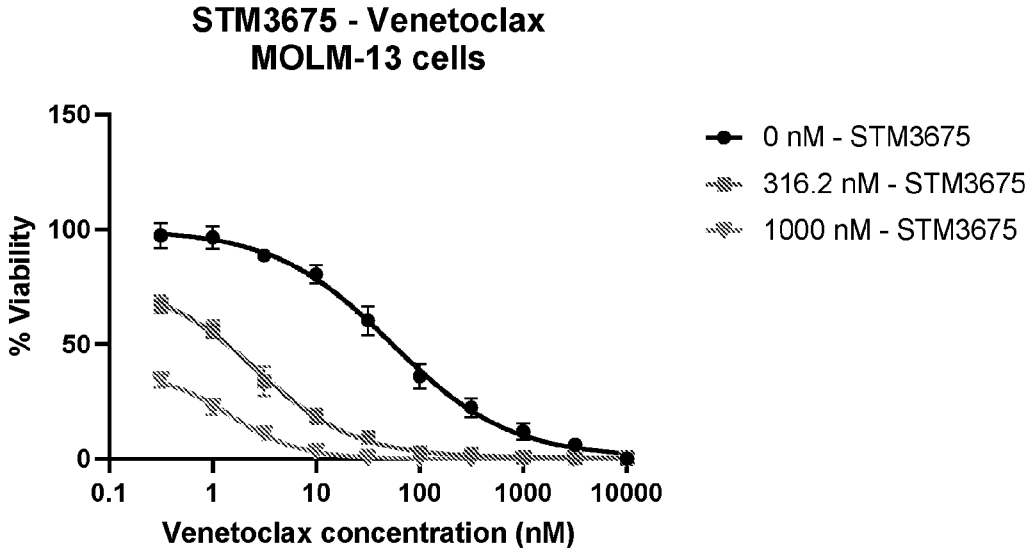
	0 nM - STM3006	316.2 nM - STM3006	1000 nM - STM3006
IC50	527.9	19.43	2.937

Figure 9



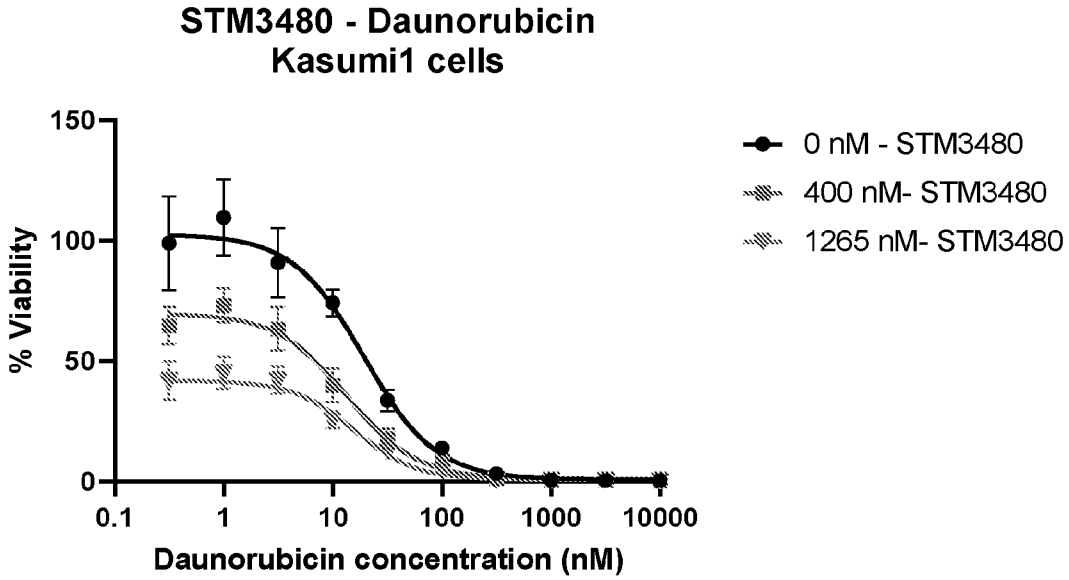
	0 nM - STM3675	316.2 nM - STM3675	1000 nM - STM3675
IC50	14.87	6.135	3.824

Figure 10



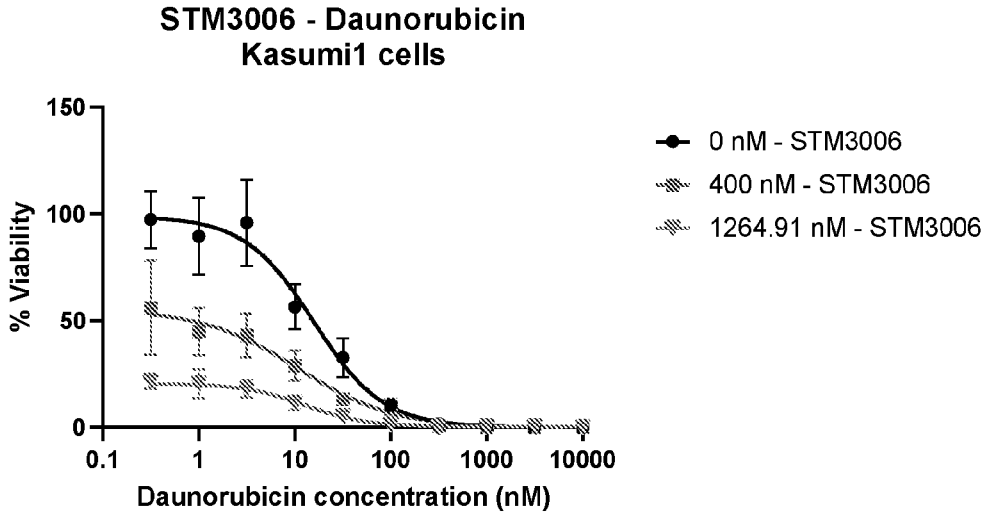
	0 nM - STM3675	316.2 nM - STM3675	1000 nM - STM3675
IC50	53.33	2.645	1.478

Figure 11



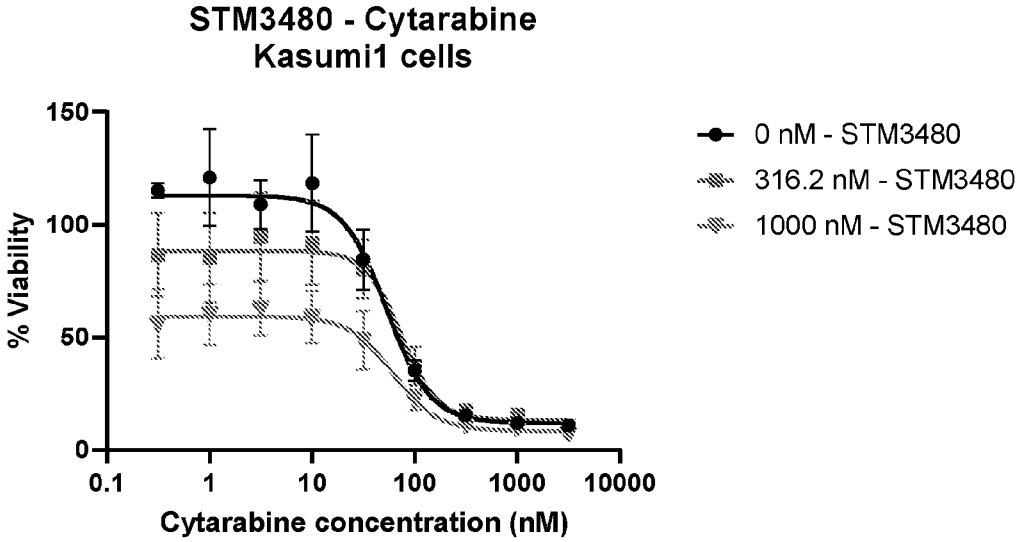
	0 nM - STM3480	400 nM- STM3480	1265 nM- STM3480
IC50	19.30	13.42	15.58

Figure 12



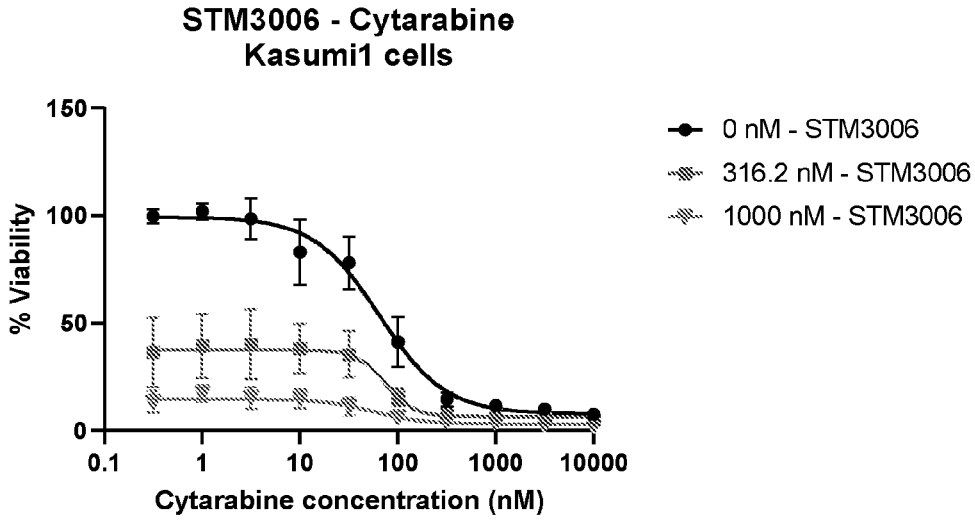
	0 nM - STM3006	400 nM - STM3006	1264.91 nM - STM3006
IC50	15.75	10.91	12.71

Figure 13



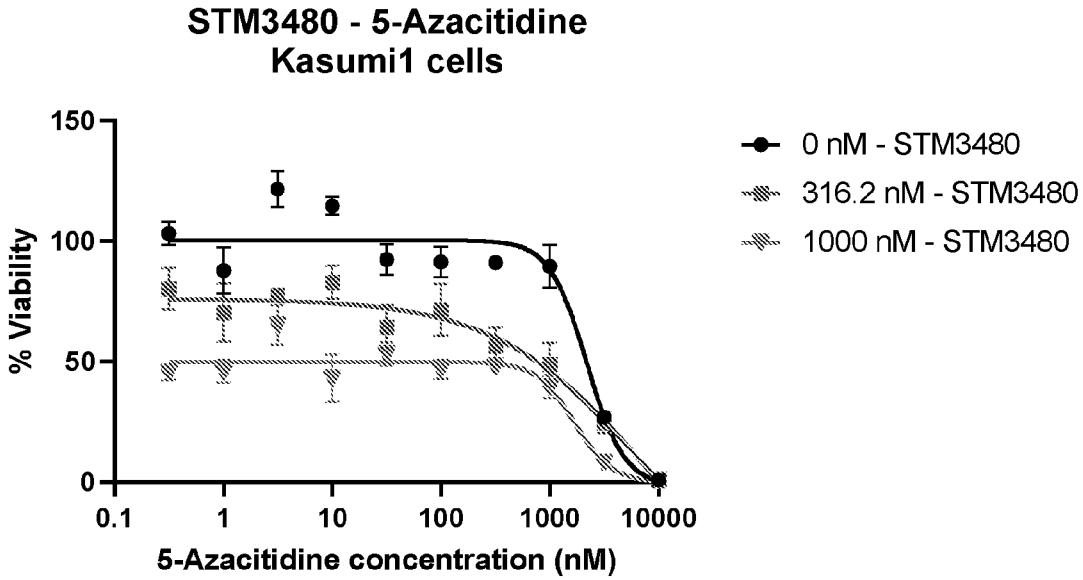
	0 nM - STM3480	316.2 nM - STM3480	1000 nM - STM3480
IC50	53.24	74.04	61.45

Figure 14



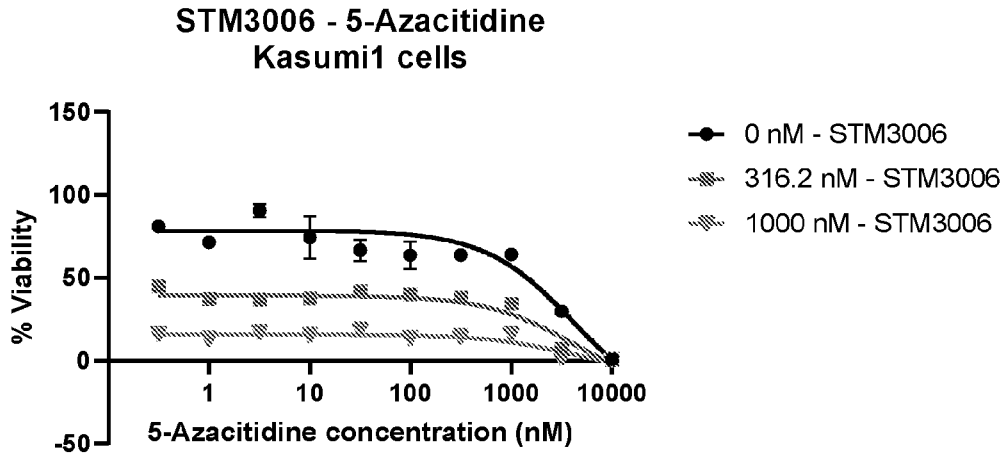
	0 nM - STM3006	316.2 nM - STM3006	1000 nM - STM3006
IC50	65.03	74.60	56.53

Figure 15



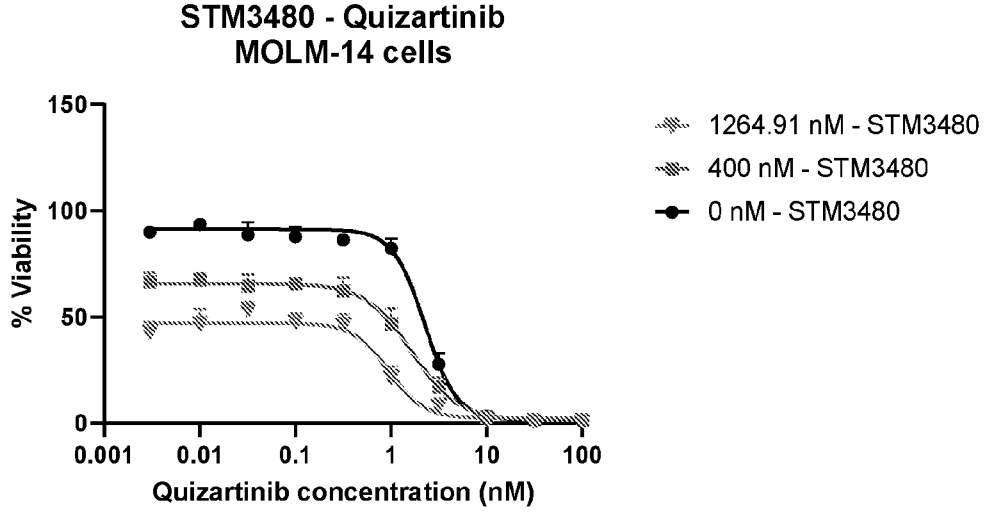
	0 nM - STM3480	316.2 nM - STM3480	1000 nM - STM3480
IC50	2194	7114	1669

Figure 16



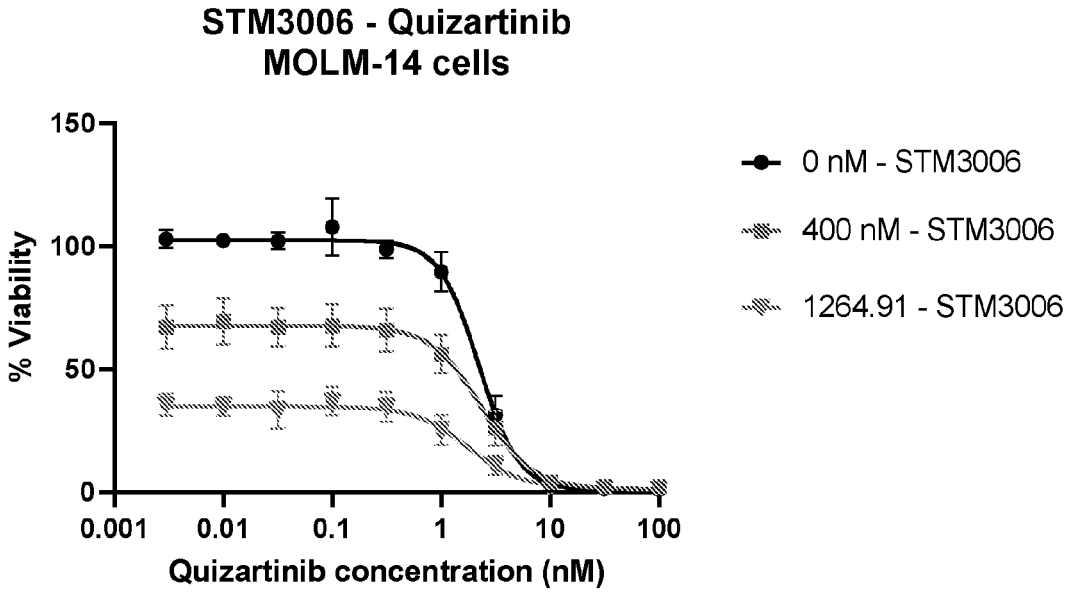
	0 nM - STM3006	316.2 nM - STM3006	1000 nM - STM3006
IC50	4077	4105	3894

Figure 17



	0 nM - STM3480	400 nM - STM3480	1264.91 nM - STM3480
IC50	2.264	1.658	0.9408

Figure 18



	0 nM - STM3006	400 nM - STM3006	1264.91 - STM3006
IC50	2.217	2.347	1.773

Figure 19