which are involved in the post-translational modification and recruitment of histones and non-histone proteins. There is high sequence similarity between CBP and p300 in the conserved functional domains (see Duncan A. Hay et al, JACS 2014, 135, 9308-9319). Modulation of CBP function therefore provides a promising route to the treatment of certain cancers. Accordingly, compounds that can modulate, e.g. inhibit, the function of p300 and/or CBP are of interest in cancer therapy.

Tumors which harbor loss of function mutations in CBP become addicted to p300 and are uniquely sensitive to p300 inhibition (see Ogiwara et al. 2016 Cancer Discovery. 6; 430-445). Conversely tumors with mutations in p300 are uniquely sensitive to CBP inhibition. Genetic analysis reveals that up to 15% of both non-small cell and small cell lung tumors have these loss of function mutations. Similar mutations are also found in up to 25% of bladder cancers. Accordingly, compounds that can modulate, e.g. inhibit, the function of p300 and/or CBP are of interest in cancer therapy for tumors with these molecular changes.

Furthermore, CBP/p300 regulates the expression of key tumor immune checkpoint proteins such as CTLA4/PD-L1 (see Casey et al., Science. 352; p227-231, 2016) and plays an important role in the differentiation and function of T-regulatory cells which are involved in immune evasion by tumors. Accordingly, compounds that can modulate, e.g. inhibit, the function of p300 and/or CBP are of interest for cancer therapy in combination with agents that target the onco-immune system.

In view of the above, there is a need for compounds targeting p300 and/or CBP. Such compounds are expected to be able to treat cancer and/or to prevent the development of drug resistance.

OBJECTS AND SUMMARY

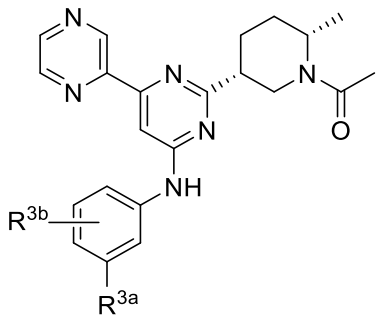
It is an object of the present disclosure to provide compounds, which have activity in modulating, e.g. inhibiting, p300 and CBP function, and accordingly, provide a therapeutic effect in the treatment of cancer and/or the prevention of resistance. It is another object of the present disclosure to provide compounds, which are suitable for use as a medicament. It is another object of the present disclosure to provide compounds, which are suitable for use in the treatment of cancer, preferably selected from melanoma, non-small cell lung cancer, prostate cancer, bile duct cancer, bladder cancer, pancreatic cancer, thyroid cancer, ovarian cancer, colorectal tumor, hairy cell leukemia, acute myeloid leukemia, multiple myeloma, liver cancer, breast cancer, esophageal cancer, head and neck cancer and glioma, in particular selected from multiple myeloma, acute myeloid leukemia, prostate cancer, and non-small cell lung cancer. It is another object of the present disclosure to provide compounds, which are suitable for use in the prevention of drug resistance in cancer patients, in particular in the prevention of resistance to EGFR inhibitors or in the prevention of resistance to KRAS inhibitors. It is yet another object of the present disclosure to provide compounds, which can be

used in combination with drugs, such as EGFR inhibitors or KRAS inhibitors, and preferably prevent the development of resistance to these drugs. It is yet another

object of the present disclosure to provide compounds, which are suitable for use in the treatment or amelioration of a fibrotic diseases.

At least some of the above objects can be achieved by the compounds of formula (I) or salts, solvates, cocrystals, tautomers, or mixtures thereof as defined herein, or the pharmaceutical compositions comprising the same, and by the medical uses thereof. The inventors of the present disclosure have surprisingly found that the compounds of formula (I) or the salts, solvates, cocrystals, tautomers, or mixtures thereof have activity in modulating, in particular inhibiting, p300 and CBP function. In preferred examples of the disclosure, the compounds exhibit a selectivity over other bromodomain-containing proteins. In certain particularly preferred examples of the disclosure, the compounds are selective over the BET protein family. Accordingly, the compounds of formula (I) or salts, solvates, cocrystals, tautomers, or mixtures thereof as defined herein, or the pharmaceutical compositions comprising the same, are suitable for use as a medicament, in particular for the treatment of cancer, either alone or in combination with another drug, preferably preventing resistance against said drug.

Thus, in a first example, the present disclosure relates to a compound of formula (I)

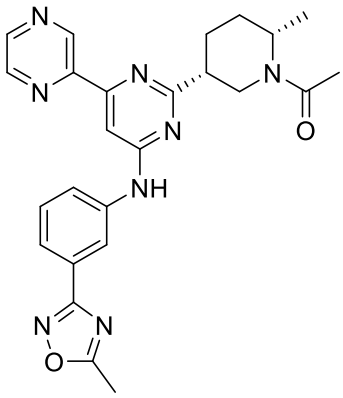


or a pharmaceutically acceptable salt, solvate, cocrystal, tautomer, or a mixture thereof, wherein

R^{3a} is a 5-membered heterocyclic ring, wherein the heterocyclic ring comprises one or more, same or different heteroatoms selected from O and N, and wherein each substitutable carbon or heteroatom is independently unsubstituted or substituted with one or more, same or different substituents selected from C_1-C_3-alkyl and a 4-membered heterocyclic ring, wherein the heterocyclic ring comprises one or more, same or different heteroatoms selected from O, N, or S;

R^{3b} is selected from H, F, Cl, and CH_3;

and wherein the compound is not any one of: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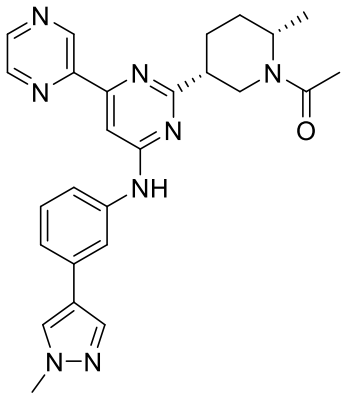
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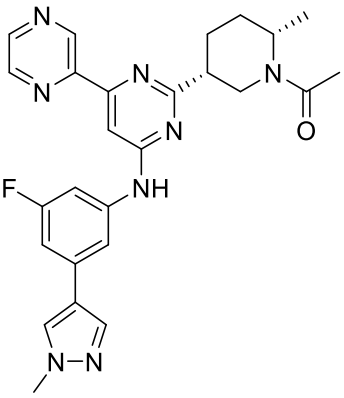
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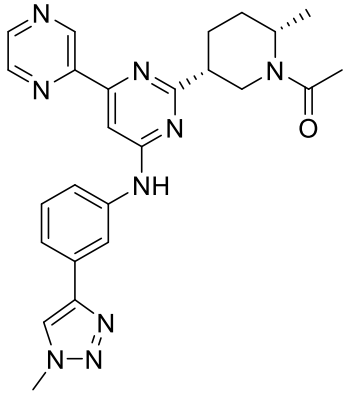
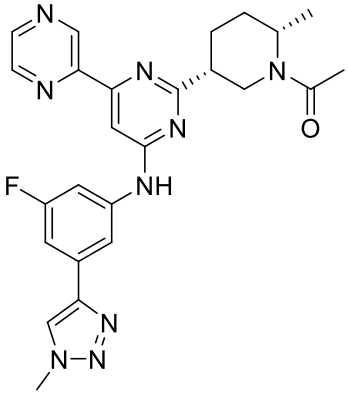

, or

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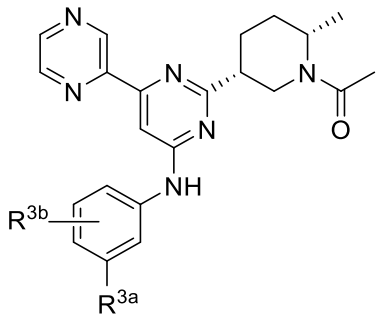
In one aspect, the present disclosure refers to a compound of formula (I)

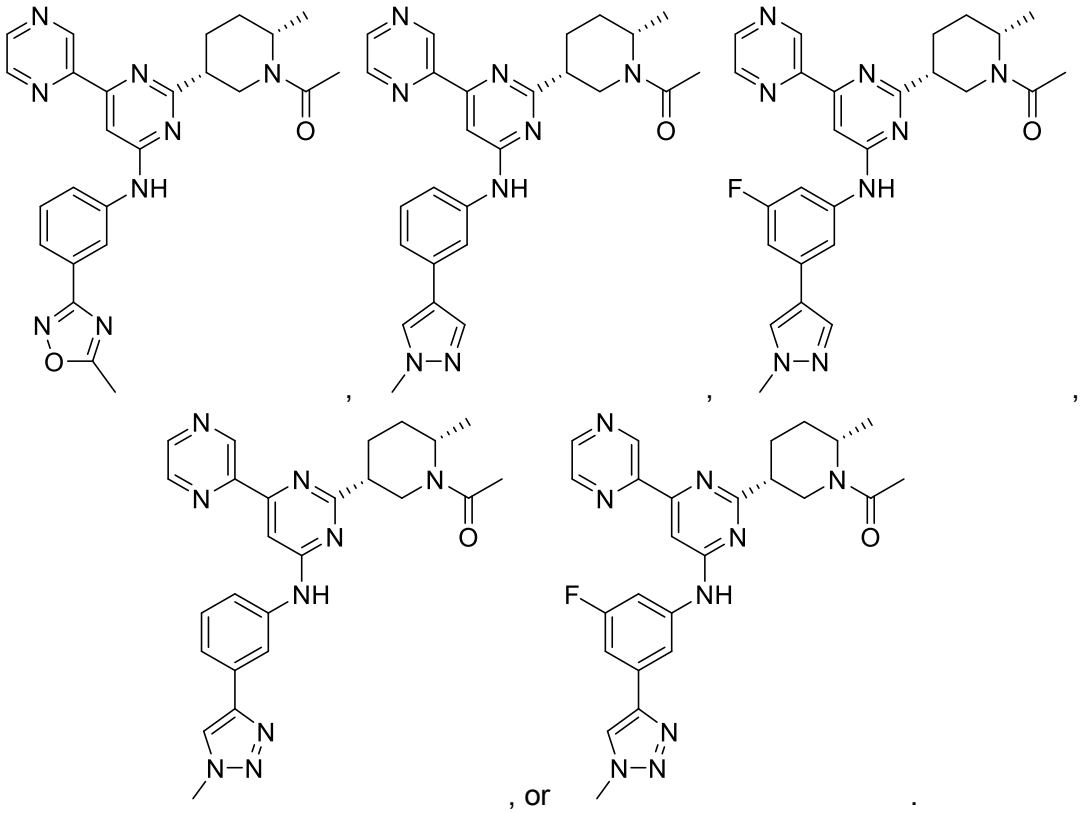

(I)

or a pharmaceutically acceptable salt, solvate, cocrystal, tautomer, or a mixture thereof, wherein

R^{3a} is a 5-membered heterocyclic ring, wherein the heterocyclic ring comprises one or more, same or different heteroatoms selected from O and N, and wherein each substitutable carbon or heteroatom is independently unsubstituted or substituted with one or more, same or different substituents selected from C_1-C_3-alkyl and a 4-membered heterocyclic ring, wherein the heterocyclic ring comprises one or more, same or different heteroatoms selected from O, N, or S;

R^{3b} is selected from H, F, Cl, and CH_3;

and wherein the compound is not any one of:



, or .

In another aspect, the present disclosure refers to a pharmaceutical composition comprising a pharmaceutically effective amount of the compound as defined above and optionally a pharmaceutically acceptable carrier, diluent or excipient.

In another aspect, there is provided the use of a compound as defined above or a pharmaceutical composition as defined above in the manufacture of a medicament.

In another aspect, there is provided the use of a compound as defined above or a pharmaceutical composition as defined above in the manufacture of a medicament for the treatment or amelioration of cancer, wherein preferably the cancer is selected from melanoma, non-small cell lung cancer, prostate cancer, bile duct cancer, bladder cancer, pancreatic cancer, thyroid cancer, ovarian cancer, colorectal tumor, hairy cell leukemia, acute myeloid leukemia, multiple myeloma, liver cancer, breast cancer, esophageal cancer, head and neck cancer and glioma, in particular multiple myeloma, acute myeloid leukemia, prostate cancer and non-small cell lung cancer.

In another aspect, there is provided the use of a compound as defined above or a pharmaceutical composition as defined above in combination with a second therapeutic agent in the manufacture of a medicament for the treatment or amelioration of cancer, wherein preferably said therapeutic agent is an anti-cancer agent, and wherein preferably the cancer is selected from melanoma, non-small cell lung cancer, prostate cancer, bile duct cancer, bladder cancer, pancreatic cancer, thyroid cancer, ovarian cancer, colorectal tumor, hairy cell leukemia, acute myeloid leukemia, multiple myeloma, liver cancer, breast cancer, esophageal cancer, head and

neck cancer and glioma, in particular multiple myeloma, acute myeloid leukemia, prostate cancer and non-small cell lung cancer.

In another aspect, there is provided the use of a compound as defined above or a pharmaceutical composition as defined above in the manufacture of a first medicament and use of a second therapeutic agent in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy for the treatment or amelioration of cancer, wherein preferably said therapeutic agent is an anti-cancer agent,
and wherein preferably the cancer is selected from melanoma, non-small cell lung cancer, prostate cancer, bile duct cancer, bladder cancer, pancreatic cancer, thyroid cancer, ovarian cancer, colorectal tumor, hairy cell leukemia, acute myeloid leukemia, multiple myeloma, liver cancer, breast cancer, esophageal cancer, head and neck cancer and glioma, in particular multiple myeloma, acute myeloid leukemia, prostate cancer and non-small cell lung cancer.

In another aspect, there is provided the use of a compound as defined above or a pharmaceutical composition as defined above in combination with an EGFR inhibitor in the manufacture of a medicament for the treatment of a patient suffering from non-small cell lung cancer (NSCLC), wherein the NSCLC exhibits an oncogenic alteration in the EGFR.

In another aspect, there is provided the use of a compound as defined above or a pharmaceutical composition as defined above in the manufacture of a first medicament and use of an EGFR inhibitor in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy for the treatment of a patient suffering from non-small cell lung cancer (NSCLC), wherein the NSCLC exhibits an oncogenic alteration in the EGFR.

In another aspect, there is provided the use of a compound as defined above or a pharmaceutical composition as defined above in the manufacture of a medicament for use in combinatorial therapy for the treatment of a patient suffering from non-small cell lung cancer (NSCLC),
wherein the NSCLC exhibits an oncogenic alteration in the EGFR, wherein said medicament is to be administered in combination with an EGFR inhibitor.

In another aspect, there is provided the use of a compound as defined above or a pharmaceutical composition as defined above in the manufacture of a medicament for treatment or amelioration of a fibrotic disease, wherein preferably the fibrotic disease is idiopathic pulmonary fibrosis (IPF) or non-alcoholic steatohepatitis (NASH).

Further examples regarding the compound of formula (I) are provided below.

In a further example, the present disclosure relates to pharmaceutical composition comprising a pharmaceutically effective amount of the compound of formula (I) or a pharmaceutically acceptable salt, solvate, cocrystal, tautomer, or a mixture thereof as defined

above, and optionally a pharmaceutically acceptable carrier, diluent or excipient. Still further optionally, the pharmaceutical composition of the present example comprises a KRAS inhibitor. In a related example, the present disclosure relates to a kit comprising (i) a pharmaceutical composition according to the present example and (ii) a pharmaceutical composition comprising a KRAS inhibitor.

In yet a further example, the present disclosure relates to a compound of formula (I) or a pharmaceutically acceptable salt, solvate, cocrystal, tautomer, or a mixture thereof as defined above or a pharmaceutical composition as defined above for use in medicine.

In a further example, the present disclosure relates to a compound of formula (I) or a pharmaceutically acceptable salt, solvate, cocrystal, tautomer, or a mixture thereof as defined above or a pharmaceutical composition as defined above for use in the treatment or amelioration of cancer, wherein preferably the cancer is selected from melanoma, non-small cell lung cancer, prostate cancer, bile duct cancer, bladder cancer, pancreatic cancer, thyroid cancer, ovarian cancer, colorectal tumor, hairy cell leukemia, acute myeloid leukemia, multiple myeloma, liver cancer, breast cancer, esophageal cancer, head and neck cancer and glioma, in particular multiple myeloma, acute myeloid leukemia, prostate cancer and non-small cell lung cancer. In one example in this connection, the compound of formula (I) or a pharmaceutically acceptable salt, solvate, cocrystal, tautomer, or a mixture thereof as defined above or the pharmaceutical composition as

defined above is used in combination with a second therapeutic agent, wherein preferably said therapeutic agent is an anti-cancer agent.

In a further example, the present disclosure relates to a compound of formula (I) or a pharmaceutically acceptable salt, solvate, cocrystal, tautomer, or a mixture thereof as defined above or a pharmaceutical composition as defined above in combination with an EGFR inhibitor for use in the treatment of a patient suffering from non-small cell lung cancer (NSCLC), wherein the NSCLC exhibits an oncogenic alteration in the EGFR.

In still a further example, the present disclosure relates to a compound of formula (I) or a pharmaceutically acceptable salt, solvate, cocrystal, tautomer, or a mixture thereof as defined above or a pharmaceutical composition as defined above in combination with a KRAS inhibitor for use in the treatment of a patient suffering from cancer, wherein the cancer exhibits an oncogenic alteration in the KRAS.

In yet a further example, the present disclosure relates to a compound of formula (I) or a pharmaceutically acceptable salt, solvate, cocrystal, tautomer, or a mixture thereof as defined above or a pharmaceutical composition as defined above for use in the treatment or amelioration of a fibrotic disease, wherein preferably the fibrotic disease is idiopathic pulmonary fibrosis (IPF) or non-alcoholic steatohepatitis (NASH).

DETAILED DESCRIPTION OF THE INVENTION

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. The herein described and disclosed embodiments, preferred embodiments and very preferred embodiments should apply to all aspects and other embodiments, preferred embodiments and very preferred embodiments irrespective of whether it is specifically again referred to or its repetition is avoided for the sake of conciseness.

The articles “a” and “an”, as used herein, refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. The term “or”, as used herein, should be understood to mean “and/or”, unless the context clearly indicates otherwise.

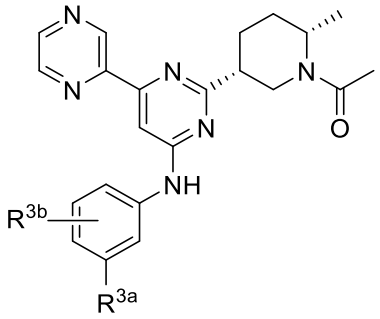
The term "preferably" is used to describe features or embodiments which are not required in the present invention but may lead to improved technical effects.

As used herein, the term "about" preferably refers to ±10% of the indicated numerical value, more preferably to ±5% of the indicated numerical value, and in particular to the exact numerical value indicated.

The term “compound(s) of the present invention" is to be understood as equivalent to the term "compound(s) according to the invention", and covers the compound(s) of formula (I) or a salt, solvate, cocrystal, or tautomer or a mixture thereof.

CLAIMS

1. A compound of formula (I)



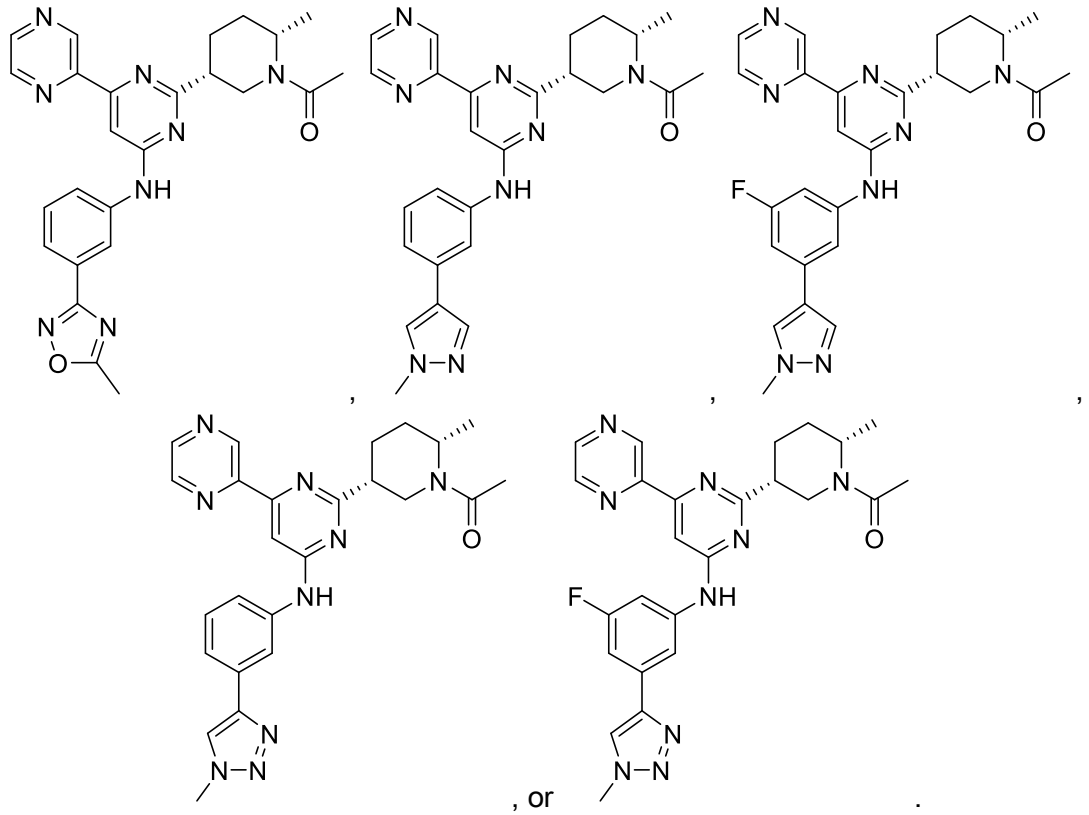
(I)

or a pharmaceutically acceptable salt, solvate, cocrystal, tautomer, or a mixture thereof, wherein

R^{3a} is a 5-membered heterocyclic ring, wherein the heterocyclic ring comprises one or more, same or different heteroatoms selected from O and N, and wherein each substitutable carbon or heteroatom is independently unsubstituted or substituted with one or more, same or different substituents selected from C_1-C_3-alkyl and a 4-membered heterocyclic ring, wherein the heterocyclic ring comprises one or more, same or different heteroatoms selected from O, N, or S;

R^{3b} is selected from H, F, Cl, and CH_3;

and wherein the compound is not any one of:



, or .

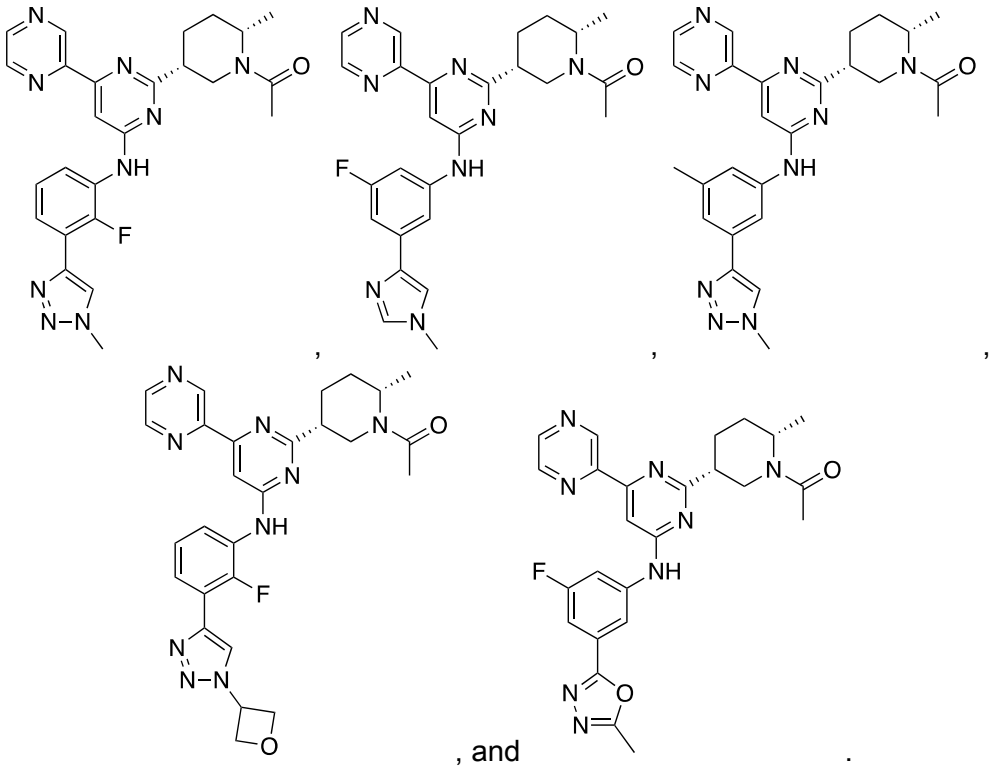
2. The compound according to claim 1, wherein

R^{3a} is a 5-membered heteroaryl ring, wherein the heteroaryl ring comprises one or more, same or different heteroatoms selected from O and N, and wherein each substitutable carbon or heteroatom is independently unsubstituted or substituted with one or more, same or different substituents selected from CH_3 and oxetanyl.

3. The compound according to claim 1 or 2, wherein

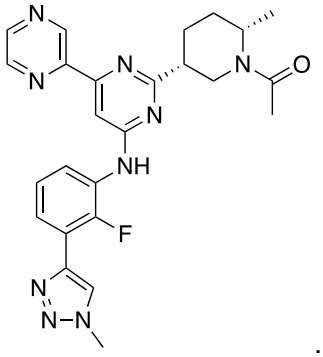
R^{3b} is selected from H, F, and CH_3.

4. The compound according to any one of claims 1 to 3, wherein the compound of formula (I) is selected from the group consisting of



, and .

5. The compound according to any one of claims 1 to 4, wherein the compound of formula (I) is:



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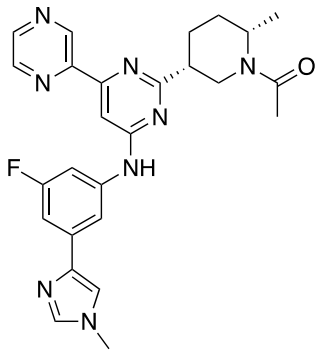
6. The compound according to any one of claims 1 to 4, wherein the compound of formula (I) is



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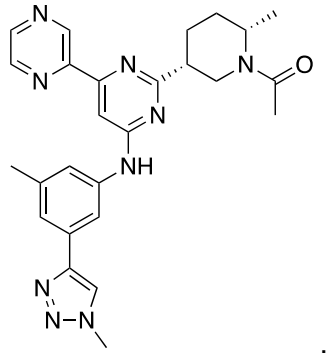
7. The compound according to any one of claims 1 to 4, wherein the compound of formula (I) is



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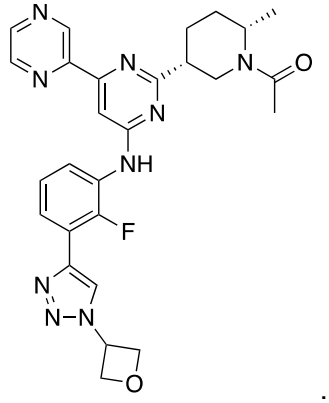
8. The compound according to any one of claims 1 to 4, wherein the compound of formula (I) is



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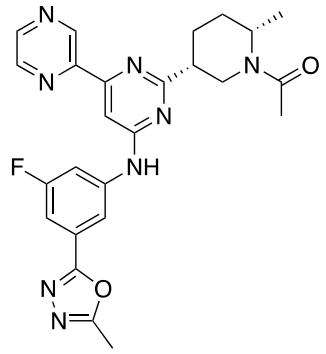
9. The compound according to any one of claims 1 to 4, wherein the compound of formula (I) is



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10. A pharmaceutical composition comprising a pharmaceutically effective amount of the compound according to any one of claims 1 to 9 and optionally a pharmaceutically acceptable carrier, diluent or excipient.

11. Use of a compound according to any one of claims 1 to 9 or a pharmaceutical composition according to claim 10 in the manufacture of a medicament.

12. Use of a compound according to any one of claims 1 to 9 or a pharmaceutical composition according to claim 10 in the manufacture of a medicament for the treatment or amelioration of cancer, wherein preferably the cancer is selected from melanoma, non-small cell lung cancer, prostate cancer, bile duct cancer, bladder cancer, pancreatic cancer, thyroid cancer, ovarian cancer, colorectal tumor, hairy cell leukemia, acute myeloid leukemia, multiple myeloma, liver cancer, breast cancer, esophageal cancer, head and neck cancer and glioma, in particular multiple myeloma, acute myeloid leukemia, prostate cancer and non-small cell lung cancer.

13. Use of a compound according to any one of claims 1 to 9 or a pharmaceutical composition according to claim 10, in combination with a second therapeutic agent in the manufacture of a medicament for the treatment or amelioration of cancer,
wherein preferably said therapeutic agent is an anti-cancer agent,
and wherein preferably the cancer is selected from melanoma, non-small cell lung cancer, prostate cancer, bile duct cancer, bladder cancer, pancreatic cancer, thyroid cancer, ovarian cancer, colorectal tumor, hairy cell leukemia, acute myeloid leukemia, multiple myeloma, liver cancer, breast cancer, esophageal cancer, head and neck cancer and glioma, in particular multiple myeloma, acute myeloid leukemia, prostate cancer and non-small cell lung cancer.

14. Use of a compound according to any one of claims 1 to 9 or a pharmaceutical composition according to claim 10 in the manufacture of a first medicament and use of a second therapeutic agent in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy for the treatment or amelioration of cancer,
wherein preferably said therapeutic agent is an anti-cancer agent,
and wherein preferably the cancer is selected from melanoma, non-small cell lung cancer, prostate cancer, bile duct cancer, bladder cancer, pancreatic cancer, thyroid cancer, ovarian cancer, colorectal tumor, hairy cell leukemia, acute myeloid leukemia, multiple myeloma, liver cancer,

breast cancer, esophageal cancer, head and neck cancer and glioma, in particular multiple myeloma, acute myeloid leukemia, prostate cancer and non-small cell lung cancer.

15. Use of a compound according to any one of claims 1 to 9 or a pharmaceutical composition according to claim 10 in the manufacture of a medicament for use in combinatorial therapy for the treatment or amelioration of cancer, wherein said medicament is to be administered in combination with a second therapeutic agent,
wherein preferably said therapeutic agent is an anti-cancer agent,
and wherein preferably the cancer is selected from melanoma, non-small cell lung cancer, prostate cancer, bile duct cancer, bladder cancer, pancreatic cancer, thyroid cancer, ovarian cancer, colorectal tumor, hairy cell leukemia, acute myeloid leukemia, multiple myeloma, liver cancer, breast cancer, esophageal cancer, head and neck cancer and glioma, in particular multiple myeloma, acute myeloid leukemia, prostate cancer and non-small cell lung cancer.

16. Use of a compound according to any one of claims 1 to 9 or a pharmaceutical composition according to claim 10 in combination with an EGFR inhibitor in the manufacture of a medicament for the treatment of a patient suffering from non-small cell lung cancer (NSCLC), wherein the NSCLC exhibits an oncogenic alteration in the EGFR.

17. Use of a compound according to any one of claims 1 to 9 or a pharmaceutical composition according to claim 10 in the manufacture of a first medicament and use of an EGFR inhibitor in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy for the treatment of a patient suffering from non-small cell lung cancer (NSCLC), wherein the NSCLC exhibits an oncogenic alteration in the EGFR.

18. Use of a compound according to any one of claims 1 to 9 or a pharmaceutical composition according to claim 10 in the manufacture of a medicament for use in combinatorial therapy for the treatment of a patient suffering from non-small cell lung cancer (NSCLC), wherein the NSCLC exhibits an oncogenic alteration in the EGFR, wherein said medicament is to be administered in combination with an EGFR inhibitor.

19. Use of a compound according to any one of claims 1 to 9 or a pharmaceutical composition according to claim 10 in the manufacture of a medicament for the treatment or amelioration of a fibrotic disease, wherein preferably the fibrotic disease is idiopathic pulmonary fibrosis (IPF) or non-alcoholic steatohepatitis (NASH).