

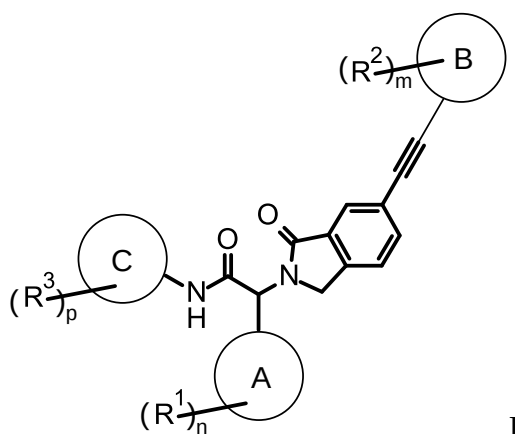
Recent studies suggest that purposefully targeting allosteric sites might lead to mutant-selective inhibitors (Jia *et al.*)

There is just a need in the generation of selective molecules that specifically inhibit TMLR, TMLRCS, LR, LRCS containing EGFR mutants useful for the therapeutic and/or prophylactic treatment of cancer, in particular T790M and C797S containing EGFR mutants.

WO2009158369 describes certain heterocyclic antibacterial agents. WO2016183534 describes certain heterocyclic compounds suitable as EBNA1 inhibitors. WO2011128279 describes certain heterocyclic compounds suitable as mGluR5 modulators.

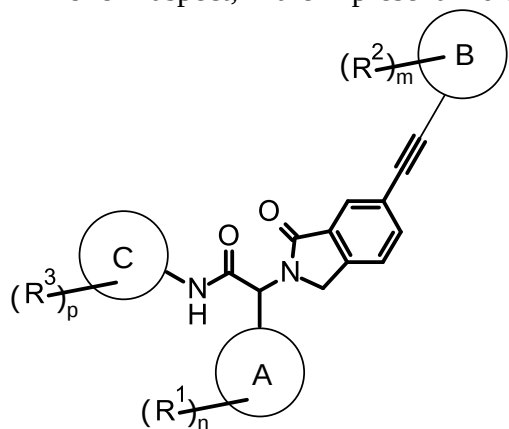
Summary

The present disclosure provides an isoindoline-acetylene of formula I, or a pharmaceutically acceptable salt thereof,



wherein the substituents and variables are as described below and in the claims, or a pharmaceutically acceptable salt thereof.

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



wherein

A is aryl or heteroaryl,

B is aryl or heteroaryl,

C is heteroaryl,

5 R¹ is each independently selected from the group consisting of

i) amino,

ii) C₁₋₆-alkyl,

iii) C₁₋₆-alkoxy,

iv) cyano,

10 v) halogen,

vi) halogen-C₁₋₆-alkyl,

vii) halogen-C₁₋₆-alkoxy, and

viii) hydroxy;

R² is each independently selected from the group consisting of

15 i) -(CH₂)_k-N(R⁴,R⁵),

ii) -(C=O)-N(R⁴,R⁵),

iii) halogen,

iv) -NH-(C=O)-C₁₋₆-alkyl, and

v) C₁₋₆-alkyl;

20 R³ is each independently selected from the group consisting of

i) amino,

ii) C₁₋₆-alkyl,

iii) C₁₋₆-alkoxy,

iv) cyano,

25 v) halogen,

vi) halogen-C₁₋₆-alkyl,

vii) halogen-C₁₋₆-alkoxy, and

viii) hydroxy;

R⁴ is each independently selected from the group consisting of

30 i) H, and

ii) C₁₋₆-alkyl;

R⁵ is each independently selected from the group consisting of

i) H,

ii) C₁₋₆-alkyl, and

35 iii) -(C=O)-C₁₋₆-alkyl;

or R⁴ and R⁵ form together with the N they are attached to a heterocyclyl, which heterocyclyl is optionally be substituted by R⁶.

R⁶ is each independently selected from the group consisting of

- i) -OH,
- ii) C₁₋₆-alkyl, and
- iii) -(C=O)-C₁₋₆-alkyl;

k is 0, 1 or 2,

n is 0, 1, 2 or 3;

m is 0, 1 or 2

p is 0 or 1;

or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure provides the compound of formula I, or a pharmaceutically acceptable salt thereof, as described herein, for use as therapeutically active substance.

In another aspect, the present disclosure provides the compound of formula I, or a pharmaceutically acceptable salt thereof, as described herein, for the use in the therapeutic and/or prophylactic treatment of cancer, in particular non-small-cell lung cancer.

In another aspect, the present disclosure provides the compound of formula I, or a pharmaceutically acceptable salt thereof, as described herein, for the use in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of cancer, in particular non-small-cell lung cancer.

In another aspect, the present disclosure provides a pharmaceutical composition comprising the compound of formula I, or a pharmaceutically acceptable salt thereof, as described herein and a pharmaceutically acceptable auxiliary substance

In another aspect, the present disclosure provides the use of the compound of formula I, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of cancer, in particular non-small-cell lung cancer.

In another aspect, the present disclosure provides the compound of formula I, or a pharmaceutically acceptable salt thereof as described herein for the use as a medicament in therapeutic and/or prophylactic treatment of a patient with EGFR activating mutations suffering from cancer, in particular non-small-cell lung cancer, wherein the EGFR activating mutations status in said patient is to be determined before administration of the compound of formula I, or
5 a pharmaceutically acceptable salt thereof as described herein.

The present compounds are useful for the therapeutic and/or prophylactic treatment of cancer.

Detailed Description of the Invention

10 The present invention provides a compound of formula I and their pharmaceutically acceptable salts thereof, the preparation of the above-mentioned compounds, medicaments containing them and their manufacture as well as the use of the above-mentioned compounds in the therapeutic and/or prophylactic treatment of cancer, in particular non-small-cell lung cancer.

The following definitions of the general terms used in the present description apply
15 irrespectively of whether the terms in question appear alone or in combination with other groups.

A is aryl or heteroaryl,

C is heteroaryl,

i) amino,

iii) C₁₋₆-alkoxy,

iv) cyano,

v) halogen,

vi) halogen-C₁₋₆-alkyl,

vii) halogen-C₁₋₆-alkoxy, and

viii) hydroxy;

R^2 is each independently selected from the group consisting of

i) $-(\text{CH}_2)_k-\text{N}(\text{R}^4, \text{R}^5),$

ii) $-(\text{C}=\text{O})-\text{N}(\text{R}^4, \text{R}^5)$,

iii) halogen,

iv) -NH-(C=O)-C₁₋₆-alkyl, and

v) C₁₋₆-alkyl;

$\mathbf{R}^3$ is each independently selected from the group consisting of

i) amino,

ii) C₁₋₆-alkyl,

iii) C₁₋₆-alkoxy,

iv) cyano,

v) halogen,

vi) halogen-C₁₋₆-alkyl,

vii) halogen-C₁₋₆-alkoxy, and

viii) hydroxy;

R^4 is each independently selected from the group consisting of

i) H, and

ii) C_{1-6} -alkyl;

5 R^5 is each independently selected from the group consisting of

i) H,

ii) C_{1-6} -alkyl, and

iii) $-(C=O)-C_{1-6}$ -alkyl;

or R^4 and R^5 form together with the N they are attached to a heterocyclyl, which heterocyclyl is

10 optionally be substituted by R^6 .

R^6 is each independently selected from the group consisting of

i) $-OH$,

ii) C_{1-6} -alkyl, and

iii) $-(C=O)-C_{1-6}$ -alkyl;

15 k is 0, 1 or 2,

n is 0, 1, 2 or 3;

m is 0, 1 or 2

p is 0 or 1;

or a pharmaceutically acceptable salt thereof.

20 2. The compound of formula I, or a pharmaceutically acceptable salt thereof, according to claim 1, wherein

A is aryl or heteroaryl,

B is aryl or heteroaryl,

C is heteroaryl,

25 R^1 is each independently selected from the group consisting of

i) amino,

ii) C_{1-6} -alkyl,

iii) C_{1-6} -alkoxy,

iv) cyano,

30 v) halogen,

vi) halogen- C_{1-6} -alkyl,

vii) halogen- C_{1-6} -alkoxy, and

viii) hydroxy;

R^2 is each independently selected from the group consisting of

35 i) $-(CH_2)_k-N(R^4, R^5)$,

ii) $-(C=O)-N(R^4, R^5)$,

iii) $-NH-(C=O)-C_{1-6}$ -alkyl, and

iv) C_{1-6} -alkyl;

R³ is each independently selected from the group consisting of

- i) amino,
- ii) C₁₋₆-alkyl,
- iii) C₁₋₆-alkoxy,
- iv) cyano,
- v) halogen,
- vi) halogen-C₁₋₆-alkyl,
- vii) halogen-C₁₋₆-alkoxy, and
- viii) hydroxy;

5

10 R⁴ is each independently selected from the group consisting of

- i) H, and
- ii) C₁₋₆-alkyl;

R⁵ is each independently selected from the group consisting of

- i) H,
- ii) C₁₋₆-alkyl, and
- iii) -(C=O)-C₁₋₆-alkyl;

15

or R⁴ and R⁵ form together with the N they are attached to a heterocyclyl;

k is 0, 1 or 2;

n is 0, 1, 2 or 3;

20 m is 0, 1 or 2;

p is 0 or 1.

3. The compound of formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-2, wherein A is aryl, in particular phenyl.

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4. The compound of formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-3, wherein B is aryl, in particular phenyl.

5. The compound of formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-4, wherein B is heteroaryl, in particular pyridinyl.

6. The compound of formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-5, wherein C is heteroaryl, in particular thiazolyl.

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7. The compound of formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-6, wherein n is 0, 1 or 2, in particular 0 or 2, more particularly 2.

8. The compound of formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-7, wherein m is 1.

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9. The compound of formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-8, wherein R² is -(C=O)-morpholinyl, -(C=O)N(H,CH₃), -CH₂-(4-

methylpiperazinyl), -CH₂-(4-acetylpiperazinyl), -CH₂-(4-ethylpiperazinyl), -CH₂-(4-hydroxy-piperidyl), -CH₂-(morpholinyl), -CH₂NH₂, -CH₂-piperazinyl, Cl, -N(H,C=OCH₃), or -NH₂, in particular -C=O-morpholinyl, -(C=O)N(H,CH₃), -CH₂-(4-acetylpiperazinyl), -CH₂-(4-ethylpiperazinyl), -CH₂-morpholinyl, -CH₂-NH₂, -CH₂-piperazinyl, -N(H,(C=O)CH₃) or -NH₂.

10. The compound of formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-9, that is selected from the group consisting of

(2RS)-2-(5-Fluoro-2-hydroxy-phenyl)-2-[1-oxo-6-(2-phenylethynyl)isoindolin-2-yl]-N-thiazol-2-yl-acetamide,

10 (2RS)-2-(5-Fluoro-2-hydroxy-phenyl)-2-[1-oxo-6-[2-(3-pyridyl)ethynyl]isoindolin-2-yl]-N-thiazol-2-yl-acetamide,

(2RS)-2-(5-Fluoro-2-hydroxy-phenyl)-2-[1-oxo-6-[2-[4-(piperazin-1-ylmethyl)phenyl]ethynyl]isoindolin-2-yl]-N-thiazol-2-yl-acetamide,

15 (2RS)-2-(5-Fluoro-2-hydroxy-phenyl)-2-[6-[2-[4-(morpholinomethyl)phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide,

(2RS)-2-(5-Fluoro-2-hydroxy-phenyl)-2-[6-[2-[4-[(4-hydroxy-1-piperidyl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide,

(2RS)-2-(5-Fluoro-2-hydroxy-phenyl)-2-[6-[2-[4-[(4-methylpiperazin-1-yl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide,

20 (2RS)-2-(5-Fluoro-2-hydroxy-phenyl)-2-[7-fluoro-1-oxo-6-[2-(3-pyridyl)ethynyl]isoindolin-2-yl]-N-thiazol-2-yl-acetamide,

(2RS)-2-[1-Oxo-6-(2-phenylethynyl)isoindolin-2-yl]-2-phenyl-N-thiazol-2-yl-acetamide,

(2RS)-2-[1-oxo-6-[2-(3-pyridyl)ethynyl]isoindolin-2-yl]-2-phenyl-N-thiazol-2-yl-acetamide,

25 (2RS)-2-[1-Oxo-6-[2-[4-(piperazin-1-ylmethyl)phenyl]ethynyl]isoindolin-2-yl]-2-phenyl-N-thiazol-2-yl-acetamide ,

(2RS)-2-[6-[2-(2-Aminopyrimidin-5-yl)ethynyl]-1-oxo-isoindolin-2-yl]-2-(5-fluoro-2-hydroxy-phenyl)-N-thiazol-2-yl-acetamide,

(2RS)-2-[6-[2-(2-Chloro-4-pyridyl)ethynyl]-1-oxo-isoindolin-2-yl]-2-(5-fluoro-2-hydroxy-phenyl)-N-thiazol-2-yl-acetamide,

(2RS)-2-[6-[2-(6-Acetamido-3-pyridyl)ethynyl]-1-oxo-isoindolin-2-yl]-2-phenyl-N-thiazol-2-yl-acetamide,

(2RS)-2-[6-[2-(6-Amino-3-pyridyl)ethynyl]-1-oxo-isoindolin-2-yl]-2-phenyl-N-thiazol-2-yl-acetamide,

5 (2RS)-2-[6-[2-(6-Amino-3-pyridyl)ethynyl]-1-oxo-isoindolin-2-yl]-2-(3-fluorophenyl)-N-thiazol-2-yl-acetamide,

(2RS)-2-[6-[2-(6-Amino-3-pyridyl)ethynyl]-1-oxo-isoindolin-2-yl]-2-(2,5-difluorophenyl)-N-thiazol-2-yl-acetamide,

10 (2RS)-2-[6-[2-(6-Amino-3-pyridyl)ethynyl]-1-oxo-isoindolin-2-yl]-2-(1,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-N-thiazol-2-yl-acetamide,

(2RS)-2-[6-[2-(6-Amino-3-pyridyl)ethynyl]-1-oxo-isoindolin-2-yl]-2-(5-fluoro-2-hydroxyphenyl)-N-thiazol-2-yl-acetamide,

(2RS)-2-[6-[2-(6-Amino-3-pyridyl)ethynyl]-1-oxo-isoindolin-2-yl]-2-(5-fluoro-2-hydroxyphenyl)-N-(2-pyridyl)acetamide,

15 (2RS)-2-[6-[2-(6-Amino-3-pyridyl)ethynyl]-1-oxo-isoindolin-2-yl]-2-(5-chloro-2-hydroxyphenyl)-N-thiazol-2-yl-acetamide,

(2RS)-2-[6-[2-(6-Amino-3-pyridyl)ethynyl]-1-oxo-isoindolin-2-yl]-2-(2-hydroxyphenyl)-N-thiazol-2-yl-acetamide,

20 (2RS)-2-[6-[2-(6-Amino-3-pyridyl)ethynyl]-1-oxo-isoindolin-2-yl]-2-(3-hydroxy-2-pyridyl)-N-thiazol-2-yl-acetamide trifluoroacetate,

(2RS)-2-[6-[2-(6-Amino-3-pyridyl)ethynyl]-7-methyl-1-oxo-isoindolin-2-yl]-2-(5-fluoro-2-hydroxyphenyl)-N-thiazol-2-yl-acetamide,

(2RS)-2-[6-[2-(6-Amino-3-pyridyl)ethynyl]-7-methyl-1-oxo-isoindolin-2-yl]-2-(5-fluoro-2-hydroxyphenyl)-N-(2-pyridyl)acetamide,

25 (2RS)-2-[6-[2-[4-(Aminomethyl)phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-2-phenyl-N-thiazol-2-yl-acetamide,

(2RS)-2-[6-[2-[4-(Morpholinomethyl)phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-2-phenyl-N-thiazol-2-yl-acetamide,

30 (2RS)-2-[6-[2-[4-[(4-acetylpiperazin-1-yl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-2-phenyl-N-thiazol-2-yl-acetamide,

(2RS)-2-[6-[2-[4-[(4-Ethylpiperazin-1-yl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-2-phenyl-N-thiazol-2-yl-acetamide,

(2RS)-2-[6-[2-[4-[(4-Ethylpiperazin-1-yl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-2-(5-fluoro-2-hydroxy-phenyl)-N-thiazol-2-yl-acetamide,

- 5 (2RS)-2-[6-[2-[6-(Morpholine-4-carbonyl)-3-pyridyl]ethynyl]-1-oxo-isoindolin-2-yl]-2-phenyl-N-thiazol-2-yl-acetamide, and

N-Methyl-5-[2-[3-oxo-2-[(1RS)-2-oxo-1-phenyl-2-(thiazol-2-ylamino)ethyl]isoindolin-5-yl]ethynyl]pyridine-2-carboxamide.

- 10 11. The compound of formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-10, for use as therapeutically active substance.
12. The compound of formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-10, for the use in the therapeutic and/or prophylactic treatment of cancer, in particular non-small-cell lung cancer.
- 15 13. The compound of formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-10, for the use in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of cancer, in particular non-small-cell lung cancer.
14. A pharmaceutical composition comprising the compound of formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-10 and a pharmaceutically acceptable auxiliary substance.
- 20 15. Use of the compound of formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-10 in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of cancer, in particular non-small-cell lung cancer .
- 25 16. The compound of formula I, or a pharmaceutically acceptable salt thereof according to any one of claims 1-10 for the use as a medicament in therapeutic and/or prophylactic treatment of a patient with EGFR activating mutations suffering from cancer, in particular non-small-cell lung cancer, wherein the EGFR activating mutations status in said patient is to be determined before administration of the compound of formula I, or a pharmaceutically acceptable salt thereof according to any one of claims 1-10.