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(54) Titre : COMPOSES
(54) Title: COMPOUNDS

(57) Abrégé/Abstract:

The present invention provides compounds which are selective allosteric inhibitors of T790M/L858R, T790M/L858R/C797S, L858R, L858R/C797S containing EGFR mutants, their manufacture, pharmaceutical compositions containing them and their use as therapeutically active substances.

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(54) Title: COMPOUNDS

(57) Abstract: The present invention provides compounds which are selective allosteric inhibitors of T790M/L858R, T790M/L858R/C797S, L858R, L858R/C797S containing EGFR mutants, their manufacture, pharmaceutical compositions containing them and their use as therapeutically active substances.

**WO 2020/002487 A1**

COMPOUNDS

Field of the Invention

The present invention provides compounds which are selective allosteric inhibitors of T790M/L858R, T790M/L858R/C797S, L858R, L858R/C797S containing EGFR mutants, their
5 manufacture, pharmaceutical compositions containing them and their use as therapeutically active substances.

Background of the Invention

The HER family receptor tyrosine kinases are mediators of cell growth, differentiation and survival. The receptor family includes four distinct members, i.e. epidermal growth factor receptor
10 (EGFR, ErbB1, or HER1) HER2 (ErbB2), HER3 (ErbB3) and HER4 (ErbB4). Upon ligand binding the receptors form homo and heterodimers and subsequent activation of the intrinsic tyrosine kinase activity leads to receptor auto-phosphorylation and the activation of downstream signaling molecules (Yarden *et al.*¹). De-regulation of EGFR by overexpression or mutation has been implicated in many types of human cancer including colorectal, pancreatic, gliomas, head and neck
15 and lung cancer, in particular non-small cell lung cancer (NSCLC) and several EGFR targeting agents have been developed over the years (Ciardiello *et al.*²). Erlotinib (Tarceva®), a reversible inhibitor of the EGFR tyrosine kinase was approved in numerous countries for the treatment of recurrent NSCLC.

An impressive single agent activity of EGFR tyrosine kinase inhibitors is observed in a
20 subset of NSCLC patients whose tumors harbor somatic kinase domain mutations, whereas clinical benefit in wild-type EGFR patients is greatly diminished (Paez *et al.*³). The most common somatic mutations of EGFR are exon 19 deletions with delta 746-750 the most prevalent mutation and the exon 21 amino acid substitutions with L858R the most frequent mutation (Sharma *et al.*⁴).

Treatment resistance arises frequently, often due to the secondary T790M mutation within
25 the ATP site of the receptor. Some developed mutant-selective irreversible inhibitors are highly active against the T790M mutant, but their efficacy can be compromised by acquired mutation of C797S, that is the cysteine residue with which they form a key covalent bond (Thress *et al.*⁵). C797S mutation was further reported by Wang to be a major mechanism for resistance to T790M-targeting EGFR inhibitors (Wang *et al.*⁶). Additional mutations that cause resistance to
30 Osimertinib are described by Yang, for example L718Q.(Yang *et al.*⁷.) Lu *et al.*⁸ report in a review article on Targeting EGFR^{L858R/T790M} and EGFR^{L858R/T790M/C797S} resistance mutations in NSCLC treatment.

As most available EGFR tyrosine kinase inhibitors target the ATP-site of the kinase, there is a need for new therapeutic agents that work differently, for example through targeting drug-resistant EGFR mutants.

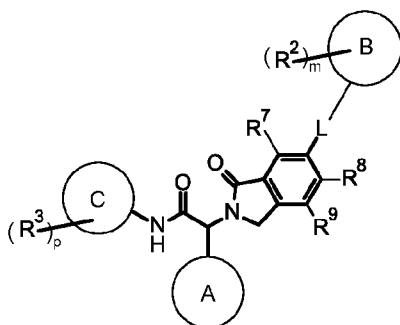
Recent studies suggest that purposefully targeting allosteric sites might lead to mutant-selective inhibitors (Jia *et al*⁹.)

There is just a need in the generation of selective molecules that specifically inhibit T790M/L858R, T790M/L858R/C797S, L858R, L858R/C797S containing EGFR mutants useful for the therapeutic and/or prophylactic treatment of cancer, in particular T790M and C797S containing EGFR mutants.

WO2009158369¹⁰ describes certain heterocyclic antibacterial agents. WO2016183534¹¹ describes certain heterocyclic compounds suitable as EBNA1 inhibitors. WO2011128279 describes certain heterocyclic compounds suitable as mGluR5 modulators.

Summary of the Invention

The present invention provides compounds of formula I, or a pharmaceutically acceptable salt thereof,



I

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

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

Detailed Description of the Invention

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 irrespective of whether the terms in question appear alone or in combination with other groups.

Unless otherwise stated, the following terms used in this Application, including the specification and claims, have the definitions given below. It must be noted that, as used in the
5 specification and the appended claims, the singular forms “a”, “an,” and “the” include plural referents unless the context clearly dictates otherwise.

The term “C₁₋₆-alkyl”, alone or in combination with other groups, stands for a hydrocarbon radical which may be linear or branched, with single or multiple branching, wherein the alkyl group in general comprises 1 to 6 carbon atoms, for example, methyl (Me), ethyl (Et), propyl,
10 isopropyl (i-propyl), n-butyl, i-butyl (isobutyl), 2-butyl (sec-butyl), t-butyl (*tert*-butyl), isopentyl, 2-ethyl-propyl (2-methyl-propyl), 1,2-dimethyl-propyl and the like. Specific groups are methyl and ethyl.

The term “halogen-C₁₋₆-alkyl”, alone or in combination with other groups, refers to C₁₋₆-alkyl as defined herein, which is substituted by one or multiple halogen, particularly 1-5 halogen,
15 more particularly 1-3 halogen. Particular halogen is fluoro. Particular “halogen-C₁₋₆-alkyl” is fluoro-C₁₋₆-alkyl and a particular “halogen-C₁₋₃-alkyl” is fluoro-C₁₋₃-alkyl. Examples are trifluoromethyl, difluoromethyl, fluoromethyl and the like.

The term “cyano”, alone or in combination with other groups, refers to N≡C-(NC-).

The term “amino”, alone or in combination with other groups, refers to NH₂.

20 The term “hydroxy”, alone or in combination with other groups, refers to OH.

The term “halogen”, alone or in combination with other groups, denotes chloro (Cl), iodo (I), fluoro (F) and bromo (Br). A specific group is F.

The term “heteroaryl”, alone or in combination with other groups, refers to an aromatic carbocyclic group of having a single 4 to 8 membered ring, in particular 5 to 8, or multiple
25 condensed rings comprising 6 to 14, in particular 6 to 10 ring atoms and containing 1, 2 or 3 heteroatoms individually selected from N, O and S, in particular 1N or 2N, in which group at least one heterocyclic ring is aromatic. The term “5-membered heteroaryl” refers to a single 5-membered aromatic ring, containing 1 or 2 heteroatoms selected from N, O and S, in particular one N and one S, for example thiazolyl. A specific group is thiazol-2-yl. The term “6-membered
30 heteroaryl” refers to a single 6-membered aromatic ring, containing 1 or 2 heteroatoms selected from N, O and S, in particular one N, for example pyridinyl. A specific group is 2-pyridyl. Examples of “heteroaryl” include benzofuryl, benzoimidazolyl, 1H-benzoimidazolyl, benzooxazinyl, benzoxazolyl, benzothiazinyl, benzothiazolyl, benzothienyl, benzotriazolyl, furyl, imidazolyl, indazolyl, 1H-indazolyl, indolyl, isoquinolinyl, isothiazolyl, isoxazolyl, oxazolyl,

pyrazinyl, pyrazolyl (pyrazyl), 1H-pyrazolyl, pyrazolo[1,5-a]pyridinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, quinolinyl, tetrazolyl, thiazolyl, thienyl, triazolyl, 6,7-dihydro-5H-[1]pyrindinyl and the like. Specific groups are pyridinyl and thiazolyl.

5 The term "C₁₋₆-alkoxy", alone or in combination with other groups, stands for an -O-C₁₋₆-alkyl radical which may be linear or branched, with single or multiple branching, wherein the alkyl group in general comprises 1 to 6 carbon atoms, for example, methoxy (OMe, MeO), ethoxy (OEt), propoxy, isopropoxy (i-propoxy), n-butoxy, i-butoxy (iso-butoxy), 2-butoxy (sec-butoxy), t-butoxy (*tert*-butoxy), isopentyloxy (i-pentyloxy) and the like. Particular "C₁₋₆-alkoxy" are groups with 1 to 4 carbon atoms. A specific group is methoxy.

10 The term "halogen-C₁₋₆-alkoxy", alone or in combination with other groups, refers to C₁₋₆-alkoxy as defined herein, which is substituted by one or multiple halogen, particularly 1-5 halogen, more particularly 1-3 halogen. Particular halogen is fluoro. Particular "halogen-C₁₋₆-alkoxy" is fluoro-C₁₋₆-alkoxy and a particular "halogen-C₁₋₃-alkoxy" is fluoro-C₁₋₃-alkoxy. A specific group is -O-CF₃.

15 The term "N-containing heterocyclyl" or "heterocyclyl" refers to a monovalent saturated or partly unsaturated mono- or bicyclic ring system of 4 to 9 ring atoms, comprising 1, 2, or 3 ring heteroatoms that are N, the remaining ring atoms being carbon. Bicyclic means consisting of two cycles having two ring atoms in common, i.e. the bridge separating the two rings is either a single bond or a chain of one or two ring atoms. Examples are piperidinyl and piperazinyl.

20 The term "aryl" denotes a monovalent aromatic carbocyclic mono- or bicyclic ring system comprising 6 to 10 carbon ring atoms. Examples of aryl moieties include phenyl and naphthyl. Specific "aryl" is phenyl.

The term "pharmaceutically acceptable" denotes an attribute of a material which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic, and neither biologically
25 nor otherwise undesirable and is acceptable for veterinary as well as human pharmaceutical use.

The term "a pharmaceutically acceptable salt" refers to a salt that is suitable for use in contact with the tissues of humans and animals. Examples of suitable salts with inorganic and organic acids are, but are not limited to acetic acid, citric acid, formic acid, fumaric acid, hydrochloric acid, lactic acid, maleic acid, malic acid, methane-sulfonic acid, nitric acid, phosphoric acid, p-
30 toluenesulphonic acid, succinic acid, sulfuric acid (sulphuric acid), tartaric acid, trifluoroacetic acid and the like. Particular acids are formic acid, trifluoroacetic acid and hydrochloric acid. Specific acids are hydrochloric acid, trifluoroacetic acid and fumaric acid.

The terms "pharmaceutically acceptable auxiliary substance" refer to carriers and auxiliary substances such as diluents or excipients that are compatible with the other ingredients of the
35 formulation.

The term "pharmaceutical composition" encompasses a product comprising specified ingredients in pre-determined amounts or proportions, as well as any product that results, directly or indirectly, from combining specified ingredients in specified amounts. Particularly it encompasses a product comprising one or more active ingredients, and an optional carrier comprising inert ingredients, as well as any product that results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients.

The term "inhibitor" denotes a compound which competes with, reduces or prevents the binding of a particular ligand to particular receptor or which reduces or prevents the function of a particular protein.

The term "half maximal inhibitory concentration" (IC_{50}) denotes the concentration of a particular compound required for obtaining 50% inhibition of a biological process in vitro. IC_{50} values can be converted logarithmically to pIC_{50} values ($-\log IC_{50}$), in which higher values indicate exponentially greater potency. The IC_{50} value is not an absolute value but depends on experimental conditions e.g. concentrations employed. The IC_{50} value can be converted to an absolute inhibition constant (K_i) using the Cheng-Prusoff equation¹².

"Therapeutically effective amount" means an amount of a compound that, when administered to a subject for treating a disease state, is sufficient to effect such treatment for the disease state. The "therapeutically effective amount" will vary depending on the compound, disease state being treated, the severity of the disease treated, the age and relative health of the subject, the route and form of administration, the judgment of the attending medical or veterinary practitioner, and other factors.

The term "as defined herein" and "as described herein" when referring to a variable incorporates by reference the broad definition of the variable as well as particularly, more particularly and most particularly definitions, if any.

The terms "treating", "contacting" and "reacting" when referring to a chemical reaction means adding or mixing two or more reagents under appropriate conditions to produce the indicated and/or the desired product. It should be appreciated that the reaction which produces the indicated and/or the desired product may not necessarily result directly from the combination of two reagents which were initially added, i.e., there may be one or more intermediates which are produced in the mixture which ultimately leads to the formation of the indicated and/or the desired product.

The term "aromatic" denotes the conventional idea of aromaticity as defined in the literature, in particular in IUPAC¹³.

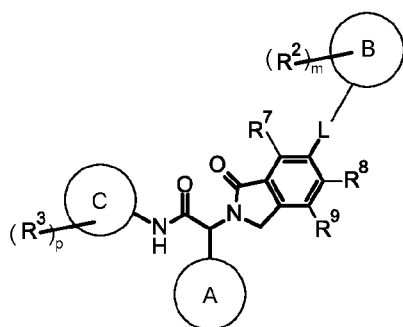
The term “pharmaceutically acceptable excipient” denotes any ingredient having no therapeutic activity and being non-toxic such as disintegrators, binders, fillers, solvents, buffers, tonicity agents, stabilizers, antioxidants, surfactants or lubricants used in formulating pharmaceutical products.

- 5 Whenever a chiral carbon is present in a chemical structure, it is intended that all stereoisomers associated with that chiral carbon are encompassed by the structure as pure stereoisomers as well as mixtures thereof.

The invention also provides pharmaceutical compositions, methods of using, and methods of preparing the aforementioned compounds.

- 10 All separate embodiments may be combined.

One embodiment of the invention provides a compound of formula I,

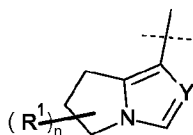


I

wherein

L is absent or $-(C\equiv C)-$,

- 15 A is



B is aryl or heteroaryl,

C is heteroaryl,

Y is N, C(OH) or CH,

- 20 R¹ 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 R² is each independently selected from the group consisting of

- i) -(CH₂)_k-N(R⁴,R⁵),
- ii) -(C=O)-N(R⁴,R⁵),
- iii) halogen,
- iv) halogen-C₁₋₆-alkyl,
- 10 v) -NH-(C=O)-C₁₋₆-alkyl, and
- vi) C₁₋₆-alkyl, optionally substituted by OH;

R³ is each independently selected from the group consisting of

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

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

- 25 i) H,
- ii) C₁₋₆-alkyl, and
- 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 one to three R⁶.

30 R⁶ is each independently selected from the group consisting of

- i) -OH,
- ii) halogen,
- iii) C₃₋₈-cycloalkyl,
- iv) halogen-C₁₋₆-alkyl,
- 35 v) C₁₋₆-alkoxy-C₁₋₆-alkyl,
- vi) cyano-C₁₋₆-alkyl,
- vii) C₁₋₆-alkyl, and
- viii) -(C=O)-C₁₋₆-alkyl;

R⁷ is each independently selected from the group consisting of

- 40 i) H,

B is aryl or heteroaryl,

C is heteroaryl,

Y is N, C(OH) or CH,

R¹ is each independently selected from the group consisting of

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

R² is each independently selected from the group consisting of

- i) $-(CH_2)_k-N(R^4, R^5)$,
- 15 ii) $-(C=O)-N(R^4, R^5)$,
- iii) halogen,
- iv) $-NH-(C=O)-C_{1-6}$ -alkyl, and
- v) C₁₋₆-alkyl, optionally substituted by OH;

R³ is each independently selected from the group consisting of

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

R⁴ is each independently selected from the group consisting of

- i) H, and
- 30 ii) C₁₋₆-alkyl;

R⁵ is each independently selected from the group consisting of

- i) H,
- ii) C₁₋₆-alkyl, and
- 35 iii) $-(C=O)-C_{1-6}$ -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) $-OH$,
- 40 ii) C₁₋₆-alkyl, and
- iii) $-(C=O)-C_{1-6}$ -alkyl;

R⁷ is each independently selected from the group consisting of

- i) H,
- ii) halogen,
- iii) halogen-C₁₋₆-alkoxy,
- 5 iv) C₁₋₆-alkoxy, and
- v) C₁₋₆-alkyl;

R⁸ is each independently selected from the group consisting of

- i) H,
- ii) halogen,
- 10 iii) C₁₋₆-alkoxy, and
- iv) C₁₋₆-alkyl;

R⁹ is each independently selected from the group consisting of

- i) H,
- ii) halogen,
- 15 iii) halogen-C₁₋₆-alkoxy,
- iv) C₁₋₆-alkoxy, and
- v) C₁₋₆-alkyl;

k is 0, 1 or 2,

n is 0, 1, 2, 3 or 4;

20 m is 0, 1 or 2;

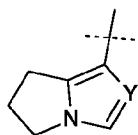
p is 0 or 1;

or a pharmaceutically acceptable salt thereof.

A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, wherein

25 L is absent or $-(C\equiv C)-$,

A is



B is aryl or heteroaryl,

C is heteroaryl,

30 Y is N or CH,

R² is each independently selected from the group consisting of

- i) $-(CH_2)_k-N(R^4, R^5)$,
- ii) halogen-C₁₋₆-alkyl, and
- iii) C₁₋₆-alkyl, optionally substituted by OH;

R^4 and R^5 form together with the N they are attached to a heterocyclyl, which heterocyclyl is optionally be substituted by one to three R^6 .

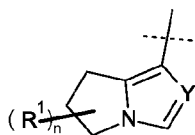
R^6 is each independently selected from the group consisting of

- i) $-\text{OH}$,
 - 5 ii) halogen,
 - iii) C_{3-8} -cycloalkyl,
 - iv) halogen- C_{1-6} -alkyl,
 - v) C_{1-6} -alkoxy- C_{1-6} -alkyl,
 - vi) cyano- C_{1-6} -alkyl, and
 - 10 vii) C_{1-6} -alkyl;
- R^7 is H or halogen;
- R^8 is H;
- R^9 is halogen;
- k is 0 or 1;
- 15 n is 0;
- m is 1;
- p is 0.

A certain embodiment of the invention relates to the compound of formula I as described
20 herein, or a pharmaceutically acceptable salt thereof, wherein

L is absent or $-(\text{C}\equiv\text{C})-$,

A is



- B is aryl or heteroaryl,
- 25 C is heteroaryl,
- Y is N or CH,
- R^2 is each independently selected from the group consisting of
- i) $-(\text{CH}_2)_k-\text{N}(\text{R}^4, \text{R}^5)$, and
 - ii) C_{1-6} -alkyl, optionally substituted by OH;
- 30 R^4 and R^5 form together with the N they are attached to a heterocyclyl, which heterocyclyl is optionally be substituted by R^6 .
- R^6 is each independently selected from the group consisting of
- i) $-\text{OH}$, and

- ii) C₁₋₆-alkyl;
 R⁷ is H or halogen;
 R⁸ is H;
 R⁹ is halogen;
 5 k is 0 or 1;
 n is 0;
 m is 1;
 p is 0.

A certain embodiment of the invention relates to the compound of formula I as described
 10 herein, or a pharmaceutically acceptable salt thereof, wherein A is



, in particular

wherein

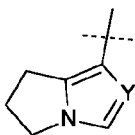
Y is N or CH, and

R^a, R^b, R^c or R^d is each independently selected from the group consisting of

- 15 i) H,
 ii) amino,
 iii) C₁₋₆-alkyl,
 iv) C₁₋₆-alkoxy,
 v) cyano,
 20 vi) halogen,
 vii) halogen-C₁₋₆-alkyl,
 viii) halogen-C₁₋₆-alkoxy, and
 ix) hydroxyl;

more particularly, wherein A is 6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl or 6,7-Dihydro-5H-
 25 pyrrolizin-1-yl.

A certain embodiment of the invention relates to the compound of formula I as described
 herein, or a pharmaceutically acceptable salt thereof, wherein A is



and Y is N or CH.

A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, wherein A is 6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl.

5 A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, wherein B is aryl, in particular phenyl.

A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, wherein B is aryl.

A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, wherein B is phenyl.

10 A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, wherein B is heteroaryl, in particular pyridinyl.

A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, wherein B is heteroaryl.

15 A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, wherein B is pyridinyl.

A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, wherein B is phenyl or pyridinyl.

20 A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, wherein C is heteroaryl, in particular thiazolyl.

A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, wherein C is heteroaryl.

25 A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, wherein C is thiazolyl.

A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, wherein n is 0, 1 or 2.

A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, wherein n is 0.

30 A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, wherein m is 1.

A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, wherein p is 0.

A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, wherein R^2 is $-(CH_2)_k-N(R^4, R^5)$, k is 0 or 1 and R^4 and R^5 form together with the N they are attached to a heterocyclyl, which heterocyclyl is optionally substituted by one or two R^6 .

A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, wherein R^2 is $-(CH_2)_k-N(R^4, R^5)$, k is 0 or 1 and R^4 and R^5 form together with the N they are attached to a heterocyclyl, which heterocyclyl is optionally substituted by one R^6 .

A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, wherein R^2 is $-(CH_2)_k-N(R^4, R^5)$, k is 0 or 1 and R^4 and R^5 form together with the N they are attached to a heterocyclyl, which heterocyclyl is optionally be substituted by methyl, ethyl or OH, in particular wherein R^2 is (ethyl)piperazinyl, (hydroxy)piperidinyl, $-CH_2$ -(hydroxy)-piperidinyl, $-CH_2$ -(methyl)piperazinyl, or $-piperazinyl$.

A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, wherein R^2 is $-(CH_2)_k-N(R^4, R^5)$, k is 0 or 1 and R^4 and R^5 form together with the N they are attached to a heterocyclyl, which heterocyclyl is optionally be substituted by methyl, ethyl or OH.

A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, wherein R^2 is $-(CH_2)_k-N(R^4, R^5)$, k is 0 and R^4 and R^5 form together with the N they are attached to a heterocyclyl, which heterocyclyl is optionally be substituted by methyl, ethyl or OH.

A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, wherein R^2 is $-(CH_2)_k-N(R^4, R^5)$, k is 1 and R^4 and R^5 form together with the N they are attached to a heterocyclyl, which heterocyclyl is optionally be substituted by methyl, ethyl or OH.

A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, wherein R^2 is $-(CH_2)_k-N(R^4, R^5)$, k is 0 or 1 and R^4 and R^5 form together with the N they are attached to piperazinyl, piperidinyl or morpholino, which piperazinyl, piperidinyl or morpholino are optionally substituted by one or two R^6 .

A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, wherein R^2 is $-(CH_2)_k-N(R^4, R^5)$, k is 0 or 1

and R⁴ and R⁵ form together with the N they are attached to piperazinyl, piperidinyl or morpholino, which piperazinyl, piperidinyl or morpholino are optionally substituted by one R⁶.

A certain embodiment of the invention relates to the compound of formula I as described
5 herein, or a pharmaceutically acceptable salt thereof, wherein R² is (ethyl)piperazinyl, (hydroxy)piperidinyl, -CH₂-(hydroxy)-piperidinyl, -CH₂-(methyl)piperazinyl, or -piperazinyl.

A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, wherein R⁹ is halogen.

A certain embodiment of the invention relates to the compound of formula I as described
10 herein, or a pharmaceutically acceptable salt thereof, wherein R⁹ is F.

A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, wherein R⁶ is selected from

- i) -OH,
- ii) halogen,
- 15 iii) C₃₋₈-cycloalkyl,
- iv) halogen-C₁₋₆-alkyl,
- v) C₁₋₆-alkoxy-C₁₋₆-alkyl,
- vi) cyano-C₁₋₆-alkyl, and
- vii) C₁₋₆-alkyl.

20 A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, wherein R⁶ is selected from

- i) C₃₋₈-cycloalkyl,
- ii) halogen-C₁₋₆-alkyl,
- iii) C₁₋₆-alkoxy-C₁₋₆-alkyl,
- 25 iv) cyano-C₁₋₆-alkyl, and
- v) C₁₋₆-alkyl.

A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, that is selected from the group consisting of

- (2*RS*)-2-(6,7-Dihydro-5H-pyrrolizin-1-yl)-2-[4-fluoro-6-[2-[4-[(4-hydroxy-1-
30 piperidyl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide,
- (2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-[4-fluoro-6-[2-[4-[(4-methylpiperazin-1-yl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide,
- (2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-[4-fluoro-6-[2-[4-[(4-hydroxy-1-
piperidyl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide,

- (2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-[4-fluoro-1-oxo-6-(4-piperazin-1-yl)phenyl]isoindolin-2-yl]-N-thiazol-2-yl-acetamide,
- (2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-[4-fluoro-6-[4-(4-hydroxy-1-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide,
- 5 (2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-[4-fluoro-6-[2-[4-(hydroxymethyl)phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide,
- (2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-[4-fluoro-1-oxo-6-[2-[4-(1-piperidylmethyl)phenyl]ethynyl]isoindolin-2-yl]-N-thiazol-2-yl-acetamide,
- (2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-[6-[4-(4-ethylpiperazin-1-yl)phenyl]-4-
10 fluoro-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide,
- (2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-[6-[6-(4-ethylpiperazin-1-yl)-3-pyridyl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide,
- (2*RS*)-2-[4-Chloro-6-[2-[4-[(4-hydroxy-1-piperidyl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide,
- 15 (2*RS*)-2-[4-Chloro-6-[4-(4-ethylpiperazin-1-yl)phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide,
- (2*RS*)-2-[4-Chloro-6-[4-(4-hydroxy-1-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide,
- (2*RS*)-2-[4-Chloro-6-[6-(4-hydroxy-1-piperidyl)-3-pyridyl]-1-oxo-isoindolin-2-yl]-2-(6,7-
20 dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide, and
- (2*RS*)-2-[7-chloro-4-fluoro-6-[2-[4-[(4-hydroxy-1-piperidyl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide.

A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, that is selected from the group consisting of

- 25 (2*RS*)-2-(6,7-Dihydro-5H-pyrrolizin-1-yl)-2-[4-fluoro-6-[2-[4-[(4-hydroxy-1-piperidyl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide,
- (2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-[4-fluoro-6-[2-[4-[(4-methylpiperazin-1-yl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide,
- (2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-[4-fluoro-6-[2-[4-[(4-hydroxy-1-
30 piperidyl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide,
- (2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-[4-fluoro-1-oxo-6-(4-piperazin-1-yl)phenyl]isoindolin-2-yl]-N-thiazol-2-yl-acetamide,
- (2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-[4-fluoro-6-[4-(4-hydroxy-1-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide,
- 35 (2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-[4-fluoro-1-oxo-6-[2-[4-(1-piperidylmethyl)phenyl]ethynyl]isoindolin-2-yl]-N-thiazol-2-yl-acetamide,
- (2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-[6-[4-(4-ethylpiperazin-1-yl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide,

- (2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-[6-[6-(4-ethylpiperazin-1-yl)-3-pyridyl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide,
 (2*RS*)-2-[4-Chloro-6-[2-[4-[(4-hydroxy-1-piperidyl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide,
 5 (2*RS*)-2-[4-Chloro-6-[4-(4-ethylpiperazin-1-yl)phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide,
 (2*RS*)-2-[4-Chloro-6-[4-(4-hydroxy-1-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide,
 (2*RS*)-2-[4-Chloro-6-[6-(4-hydroxy-1-piperidyl)-3-pyridyl]-1-oxo-isoindolin-2-yl]-2-(6,7-
 10 dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide, and
 (2*RS*)-2-[7-chloro-4-fluoro-6-[2-[4-[(4-hydroxy-1-piperidyl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide.

A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, that is selected from the group consisting of

- 15 2-[4-chloro-1-oxo-6-[2-[4-(1-piperidylmethyl)phenyl]ethynyl]isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide;
 2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-[6-[4-(1-ethyl-4-piperidyl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide;
 2-[4-fluoro-6-[2-[4-[(4-hydroxy-1-piperidyl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-
 20 yl]-2-[rac-(6*R*)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl]-N-thiazol-2-yl-acetamide;
 2-[6-[3-chloro-4-(4-ethylpiperazin-1-yl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide;
 2-[6-[3-chloro-4-[rac-(3*R*)-3-methylpiperazin-1-yl]phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide;
 25 2-[6-[3-chloro-4-[rac-(3*R*)-4-ethyl-3-methyl-piperazin-1-yl]phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide;
 2-[4-chloro-6-[4-[(1-ethyl-4-piperidyl)oxy]phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide;
 2-[6-(3-chloro-4-morpholino-phenyl)-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-
 30 pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide;
 2-[6-[3-chloro-4-(4-ethylpiperazin-1-yl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-[rac-(6*R*)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

2-[6-(3-chloro-4-morpholino-phenyl)-4-fluoro-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

2-[6-[3-chloro-4-[rac-(3R)-4-ethyl-3-methyl-piperazin-1-yl]phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

2-[6-[4-(1-ethyl-4-piperidyl)-3-fluoro-phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

2-[6-[4-(1-cyclopropyl-4-piperidyl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

10 2-[4-chloro-6-[4-(1-cyclopropyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

2-[4-chloro-6-[4-(1-ethyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

15 2-[6-[3-chloro-4-(1-ethyl-4-piperidyl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

2-[6-[4-(1-ethyl-4-piperidyl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-1-oxo-6-[4-[rac-(3R,4R)-1-ethyl-3-fluoro-4-piperidyl]phenyl]isoindolin-2-yl]-N-thiazol-2-yl-acetamide;

20 2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[6-[4-(1-ethyl-4-piperidyl)-3-fluoro-phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide;

2-[6-[4-[1-(2,2-difluoroethyl)-4-piperidyl]phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

25 2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-6-[4-[1-(2-methoxyethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide;

2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-6-[4-[1-(2-fluoroethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide;

2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[6-[3-ethyl-4-(1-ethyl-4-piperidyl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide;

2-[6-[4-(4-cyclopropylpiperazin-1-yl)-3-fluoro-phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

2-[6-[3-chloro-4-(4-cyclopropylpiperazin-1-yl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

5 2-[4-chloro-6-[4-(4-cyclopropylpiperazin-1-yl)-3-fluoro-phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

2-[6-[3-chloro-4-[4-(2,2-difluoroethyl)piperazin-1-yl]phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

10 2-[6-[4-(4-cyclopropylpiperazin-1-yl)-3-fluoro-phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

2-[6-[2-(2-chlorophenyl)ethynyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

2-[6-[2-[4-[(4,4-difluoro-1-piperidyl)methyl]phenyl]ethynyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

15 2-(6,7-dihydro-5H-pyrrolizin-1-yl)-2-[4-fluoro-6-(3-fluoro-4-morpholino-phenyl)-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide;

2-[6-[3-chloro-4-(4-cyclopropylpiperazin-1-yl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

20 2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-1-oxo-6-[2-[4-(trifluoromethyl)phenyl]ethynyl]isoindolin-2-yl]-N-thiazol-2-yl-acetamide;

2-(6,7-dihydro-5H-pyrrolizin-1-yl)-2-[6-[4-(1-ethyl-4-piperidyl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide;

2-[6-[3-chloro-4-[4-(2-fluoroethyl)piperazin-1-yl]phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

25 2-[6-[3-ethyl-4-(1-ethyl-4-piperidyl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

2-[7-chloro-4-fluoro-6-(4-morpholinophenyl)-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

30 2-[4-chloro-6-[3-ethyl-4-(1-ethyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

2-[4-chloro-6-[4-(1-ethyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

2-[4-chloro-6-[4-(1-cyclopropyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

5 2-[4-chloro-6-[4-[1-(2-fluoroethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

2-[4-chloro-6-[4-[1-(2-cyanoethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

10 2-[4-chloro-6-[3-ethyl-4-[1-(2-fluoroethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

2-[4-chloro-6-[4-[1-(2-fluoroethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

2-[4-chloro-6-[4-[1-(2,2-difluoroethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

15 2-[4,7-dichloro-6-[4-(1-ethyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

2-[4,7-dichloro-6-[4-(1-ethyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

20 2-[4,7-dichloro-6-[4-[1-(2-fluoroethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

2-[4,7-dichloro-6-[4-[1-(2-fluoroethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

2-[4,7-dichloro-6-(4-morpholinophenyl)-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

25 2-[4-chloro-1-oxo-6-[4-[rac-(3R,4R)-1-ethyl-3-fluoro-4-piperidyl]phenyl]isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

2-[4-fluoro-6-[2-[4-[4-(hydroxymethyl)-1-piperidyl]methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

2-[4-chloro-6-[4-(1-ethyl-3,3-difluoro-4-piperidyl)phenyl]-1-oxo-isindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

2-[4-chloro-6-[4-[1-(2-hydroxyethyl)-4-piperidyl]phenyl]-1-oxo-isindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide.

- 5 A more particular embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, that is selected from the group consisting of

2-[4-chloro-6-[3-ethyl-4-[1-(2-fluoroethyl)-4-piperidyl]phenyl]-1-oxo-isindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

- 10 2-[4-chloro-1-oxo-6-[4-[rac-(3R,4R)-1-ethyl-3-fluoro-4-piperidyl]phenyl]isindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide.

A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, for use as therapeutically active substance.

- 15 A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, for the use in the therapeutic and/or prophylactic treatment of cancer, in particular non-small-cell lung cancer.

A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, for the use in the therapeutic and/or prophylactic treatment of non-small-cell lung cancer.

- 20 A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the therapeutic and/or prophylactic treatment of cancer, in particular non-small-cell lung cancer.

- 25 A certain embodiment of the invention relates to a pharmaceutical composition comprising the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable auxiliary substance.

A certain embodiment of the invention relates to a method for the therapeutic and/or prophylactic treatment of cancer, in particular non-small-cell lung cancer by administering the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, to a patient.

- 30 A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, 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, comprising determining the EGFR activating mutations status in said patient and then administering the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, to said patient.

5 A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, for the use as a medicament in therapeutic and/or prophylactic treatment of a patient with EGFR mutations T790M/L858R, T790M/L858R/C797S, L858R and/or L858R/C797S suffering from cancer, in particular non-small-cell lung cancer, comprising determining the EGFR activating mutations status in said patient and then administering the compound of formula I as described herein, or a
10 pharmaceutically acceptable salt thereof, to said patient.

A certain embodiment of the invention relates to the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, for the use as a medicament in therapeutic and/or prophylactic treatment of a patient with EGFR activating mutations as determined with a cobas® EGFR Mutation Test v2 suffering from cancer, in particular non-small-cell lung cancer,
15 comprising determining the EGFR activating mutations status in said patient and then administering the compound of formula I as described herein, or a pharmaceutically acceptable salt thereof, to said patient.

Furthermore, the invention includes all substituents in its corresponding deuterated form, wherever applicable, of the compounds of formula I.

20 Furthermore, the invention includes all optical isomers, i.e. diastereoisomers, diastereomeric mixtures, racemic mixtures, all their corresponding enantiomers and/or tautomers as well as their solvates, wherever applicable, of the compounds of formula I.

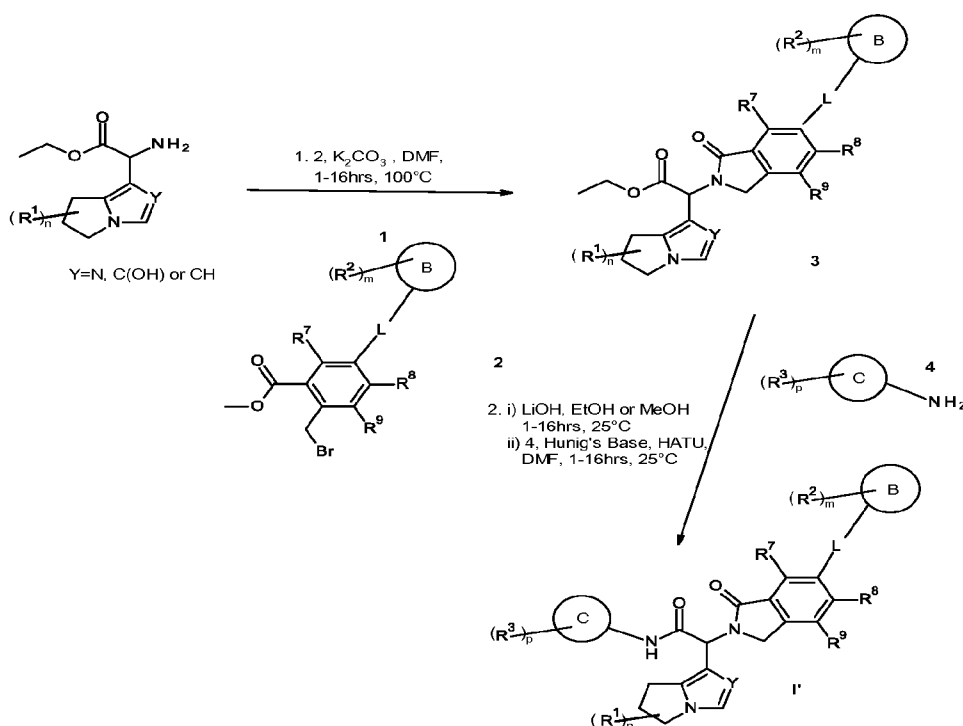
The compounds of formula I may contain one or more asymmetric centers and can therefore occur as racemates, racemic mixtures, single enantiomers, diastereomeric mixtures and individual
25 diastereomers. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within this invention. The present invention is meant to encompass all such isomeric forms of these compounds. The
30 independent syntheses of these diastereomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration. If desired, racemic mixtures of the
35 compounds may be separated so that the individual enantiomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of

compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography.

In the embodiments, where optically pure enantiomers are provided, optically pure enantiomer means that the compound contains > 90 % of the desired isomer by weight, particularly > 95 % of the desired isomer by weight, or more particularly > 99 % of the desired isomer by weight, said weight percent based upon the total weight of the isomer(s) of the compound. Chirally pure or chirally enriched compounds may be prepared by chirally selective synthesis or by separation of enantiomers. The separation of enantiomers may be carried out on the final product or alternatively on a suitable intermediate.

The compounds of formula I may be prepared in accordance with the schemes described in the examples. The starting material is commercially available or may be prepared in accordance with known methods.

Scheme 1



An isoindoline based compound of general formula I' can be obtained for example by ring cyclization of a previously prepared aminoester 1 with an appropriately substituted methyl 2-(bromomethyl)benzoate of formula 2 to yield the desired isoindoline ester 3. Saponification and

amide coupling with an appropriately substituted amine of formula **4** with a coupling agent such as HATU yields the desired isoindoline compound of general formula **I'** (scheme 1).

Generally speaking, the sequence of steps used to synthesize the compounds of formula **I'**, which is a compound of formula **I**, and further functionalization can also be modified in certain cases.

The corresponding pharmaceutically acceptable salts with acids can be obtained by standard methods known to the person skilled in the art, e.g. by dissolving the compound of formula **I** in a suitable solvent such as e.g. dioxane or tetrahydrofuran and adding an appropriate amount of the corresponding acid. The products can usually be isolated by filtration or by chromatography. The conversion of a compound of formula **I** into a pharmaceutically acceptable salt with a base can be carried out by treatment of such a compound with such a base. One possible method to form such a salt is e.g. by addition of 1/n equivalents of a basic salt such as e.g. $M(OH)_n$, wherein M = metal or ammonium cation and n = number of hydroxide anions, to a solution of the compound in a suitable solvent (e.g. ethanol, ethanol-water mixture, tetrahydrofuran-water mixture) and to remove the solvent by evaporation or lyophilisation. Particular salts are hydrochloride, formate and trifluoroacetate.

Insofar as their preparation is not described in the examples, the compounds of formula **I** as well as all intermediate products can be prepared according to analogous methods or according to the methods set forth herein. Starting materials are commercially available, known in the art or can be prepared by methods known in the art or in analogy thereto.

It will be appreciated that the compounds of general formula **I** in this invention may be derivatised at functional groups to provide derivatives which are capable of conversion back to the parent compound *in vivo*.

Pharmacological Tests

The compounds of formula **I** and their pharmaceutically acceptable salts possess valuable pharmacological properties. The compounds were investigated in accordance with the test given hereinafter.

HTRF Phospho EGFR TMLR assay (cellular)

Cell line and media

H1975 cell line (CRL-5908; Lot BA70803) was obtained from American Type Culture Collection (Manassas, VA, USA). Cells were maintained at 37°C, 5% CO₂ in complete Media RPMI 1640 without phenol red containing 0.3 mg/ml glutamine, 100 IU/ml penicillin, and 100 mg/ml streptomycin (Gibco, 15140-122) supplemented with 10% fetal bovine serum (FBS, Gibco, 10091-148). Compounds were diluted into starving medium RPMI 1640 Media (Gibco,

11835-030) without phenol red containing 0.3 mg/ml glutamine, 100 IU/ml penicillin, and 100 mg/ml streptomycin (Gibco).

Protocol

- 5 Cells were cultured for 24 h in a 384-well plate (Greiner Bio-One, Nr. 784-080; 5000 cells/well) using 8 µl of complete medium/well. Then 4 µl/well of the 3× compound solution, containing a factor 3 dilution series of the compound or DMSO in starving medium, were added to the cells (final DMSO 0.33%). After 16 hours at 37°C, 5% CO₂, 95% rel. humidity cells were lysed by adding to the compound mix 4 µl/well of the supplemented lysis buffer (Cis-bio, Phospho-EGFR
- 10 HTRF kit, 64EG1PEH), followed by incubation for 30 min at room temperature with shaking (400 rpm). Then 4 µl of a mixture of anti-Phospho-EGFR Cryptate and of anti-Phospho-EGFR-d2 antibody solutions prepared in the detection buffer was added. The plates were then incubated for 4 h at room temperature before reading the fluorescence emission at 620 and 665 nm using an Envision reader (Perkin Elmer).

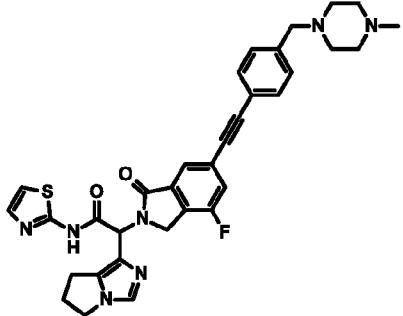
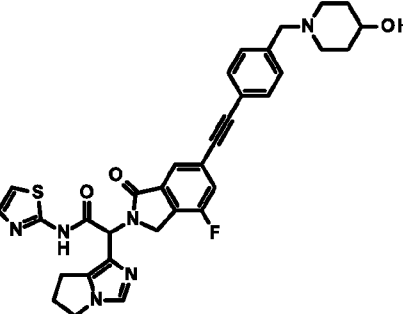
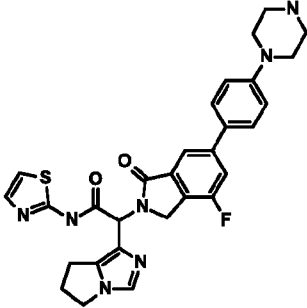
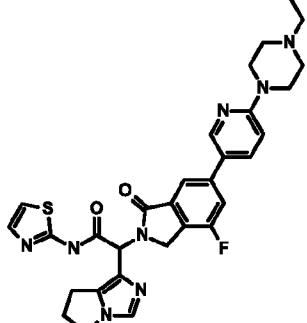
15 Cell line and media

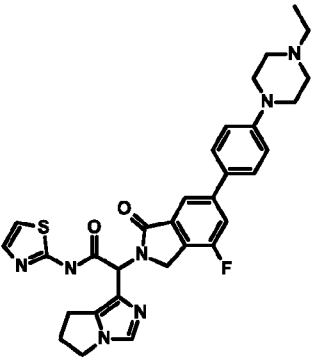
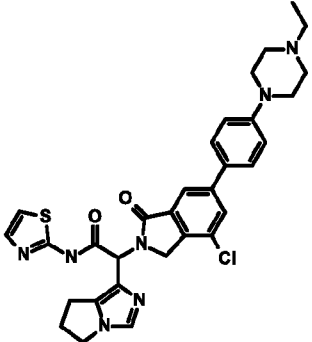
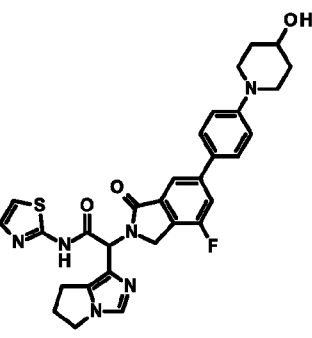
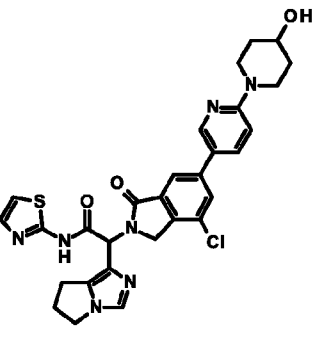
BaF3-TMLRCS cell line were obtained from Crownbio (San Diego, CA, USA). Cells were maintained at 37°C, 5% CO₂ in RPMI ATCC (Gibco 31870) + 2mM Glutamine + 0.5µg/ml Puromycin supplemented with 10% fetal bovine serum (FBS) (Gibco).

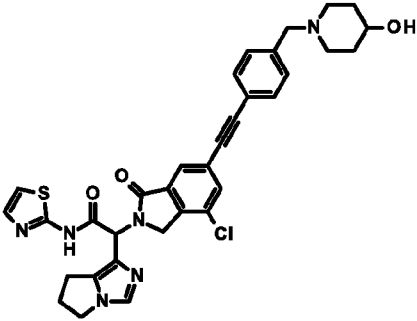
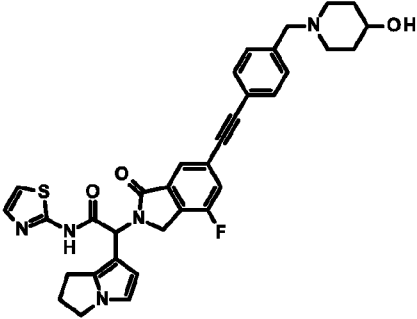
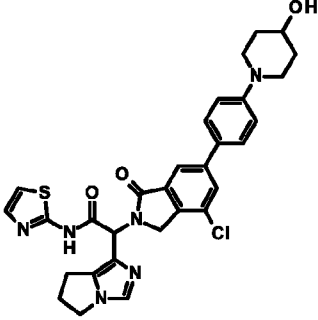
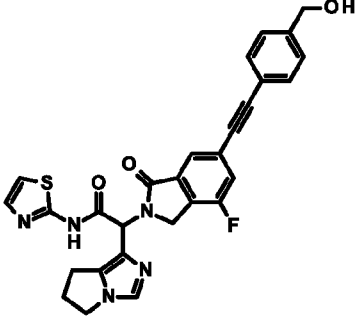
Protocol

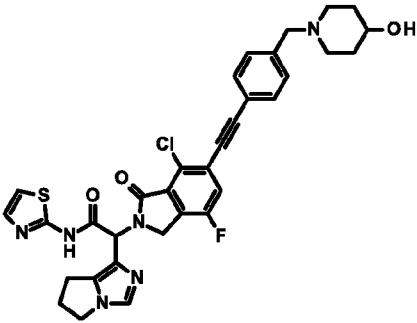
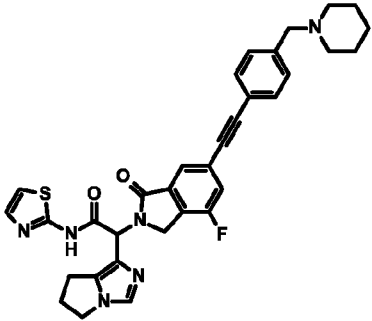
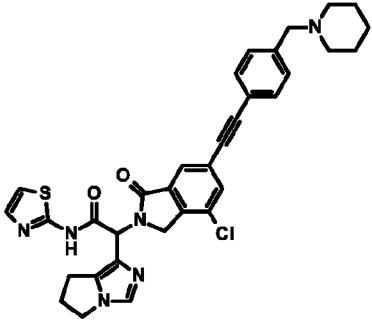
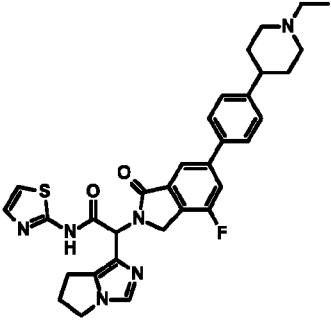
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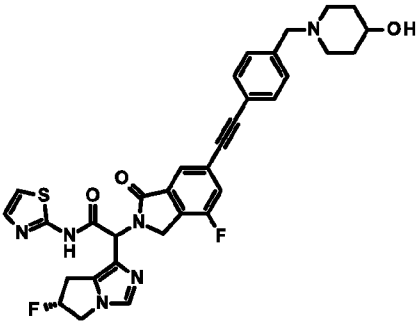
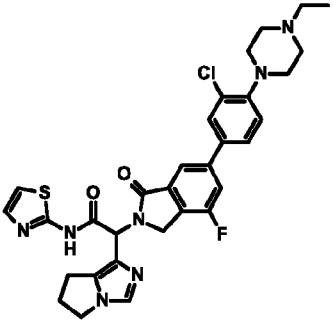
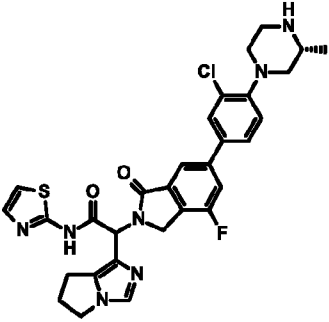
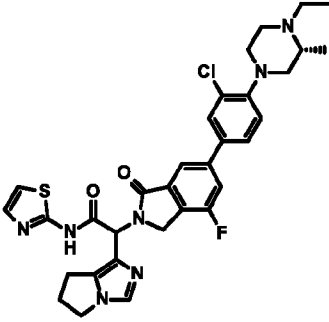
- Cells are transferred as above to Greiner Bio-One, Nr. 784-08 micro-titerplate at 20000 cells/well in 12.5 µl of growth medium/well after the plates had been pre-filled with 12.5 nl of DMSO solutions of the to be tested compounds (in dose response) or DMSO only. After spinning the plates at 300 x g for 30 seconds the cells were incubated for 4 hours at 37°C, 5% CO₂, 95%
- 25 humidity. The cells were lysed by adding to the compound mix 4 µl/well of the supplemented lysis buffer (Cis-bio, Phospho-EGFR HTRF kit, 64EG1PEH), followed by incubation for 30 min at room temperature with shaking (400 rpm). The plates were then frozen and stored overnight at -80°C. On the next day and after thawing the plates, 4 µl of a mixture of anti-Phospho-EGFR Cryptate and of anti-Phospho-EGFR-d2 antibody solutions prepared in the supplied detection
- 30 buffer was added to each well. The lidded plates were then incubated for 4 h at room temperature before reading the fluorescence emission at 616 and 665 nm using an Envision reader (Perkin Elmer). Data was analyzed in similar fashion as above using the normalized ratio of the 665 to 616 signals multiplied by 10000.

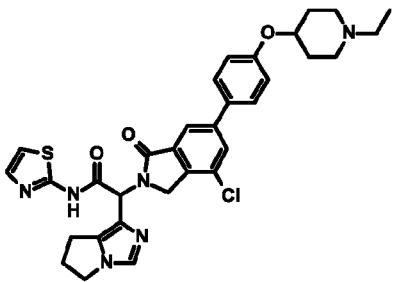
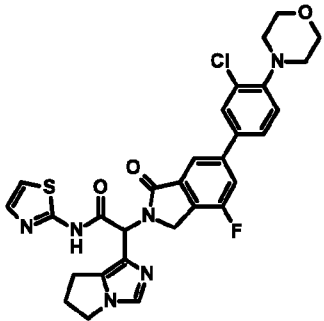
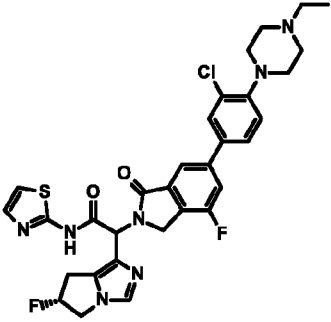
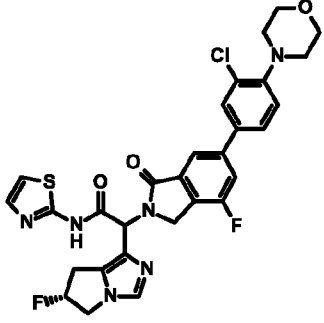
Exam.	Structure	IC ₅₀ (H1975)
1		3nM
2		1nM
3		2nM
4		4nM

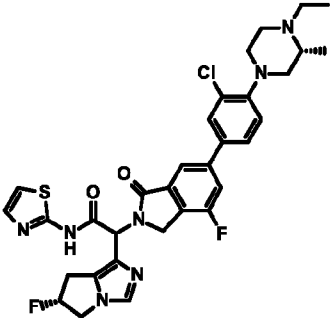
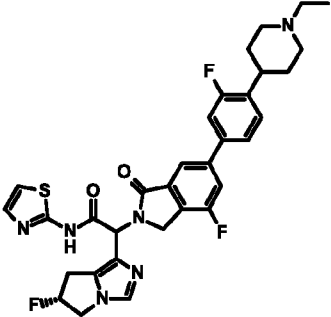
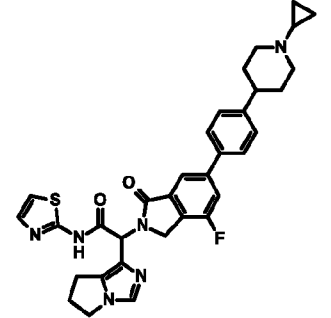
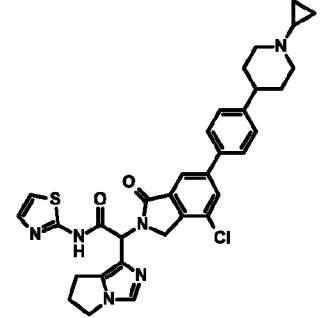
Exam.	Structure	IC ₅₀ (H1975)
5		3nM
6		4nM
7		1nM
8		2nM

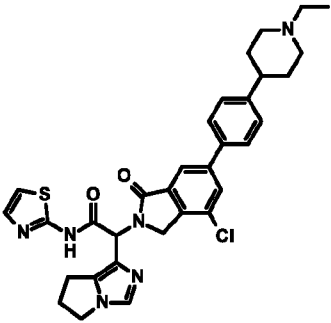
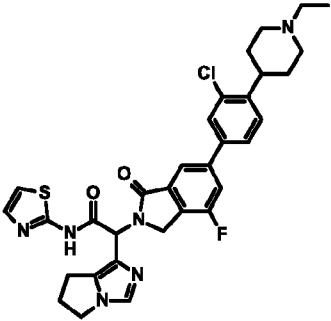
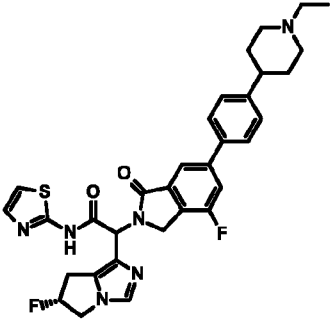
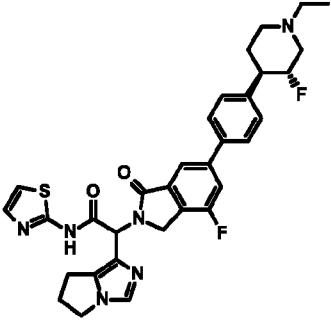
Exam.	Structure	IC ₅₀ (H1975)
9		4nM
10		8nM
11		2nM
12		2nM

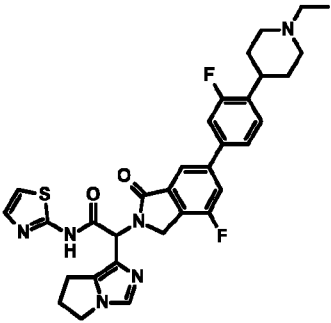
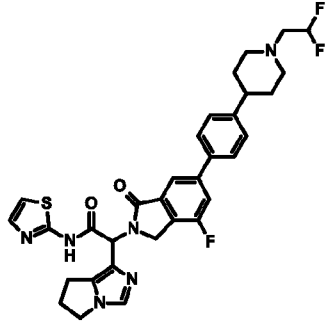
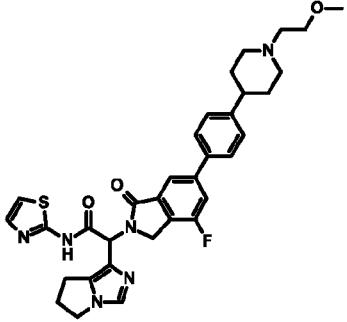
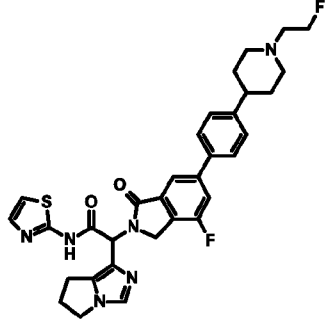
Exam.	Structure	IC ₅₀ (H1975)
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14		4nM
15		4nM
16		3nM

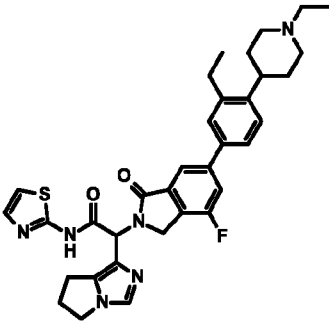
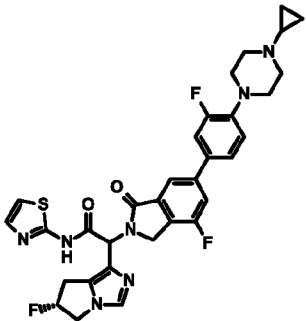
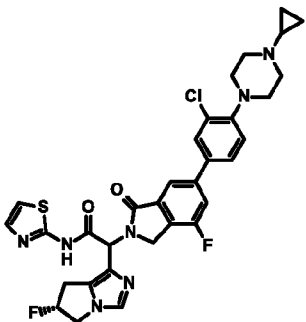
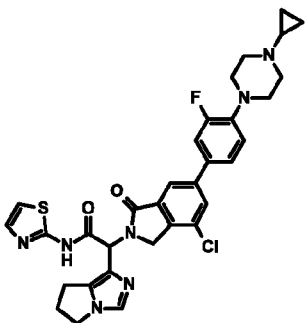
Exam.	Structure	IC ₅₀ (H1975)
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18		5nM
19		5nM
20		2nM

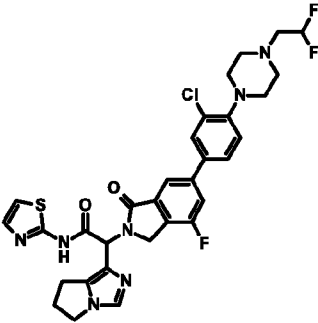
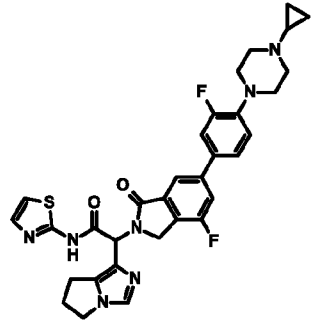
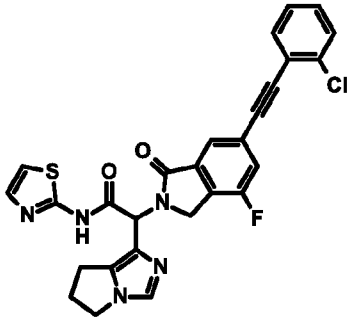
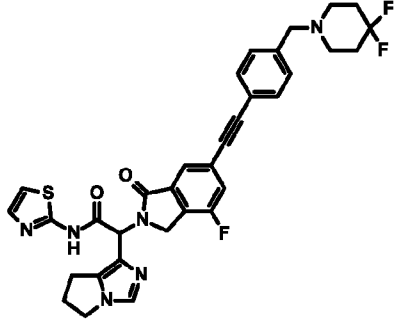
Exam.	Structure	IC ₅₀ (H1975)
21		5nM
22		3nM
23		4nM
24		3nM

Exam.	Structure	IC ₅₀ (H1975)
25		7nM
26		1nM
27		4nM
28		4nM

Exam.	Structure	IC ₅₀ (H1975)
29		1nM
30		1nM
31		1nM
32		3nM

Exam.	Structure	IC ₅₀ (H1975)
33		2nM
34		5nM
35		3nM
36		4nM

Exam.	Structure	IC ₅₀ (H1975)
37		3nM
38		6nM
39		11nM
40		7nM

Exam.	Structure	IC ₅₀ (H1975)
41		3nM
42		5nM
43		5nM
44		2nM

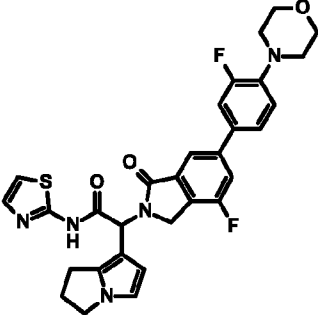
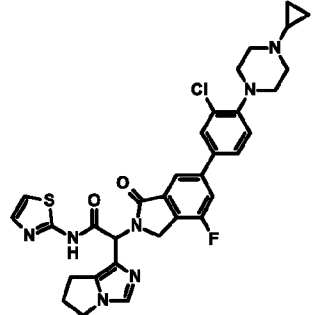
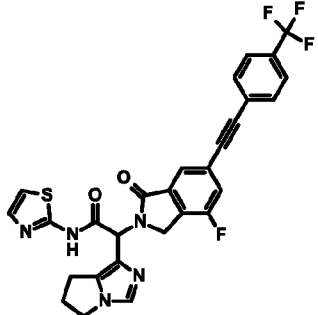
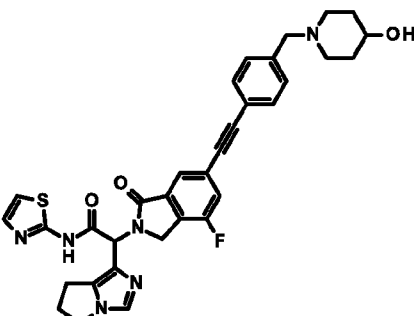
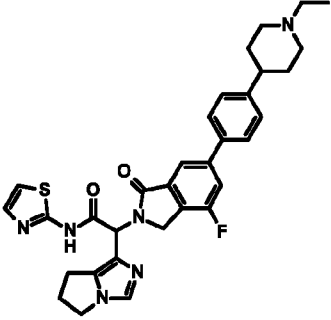
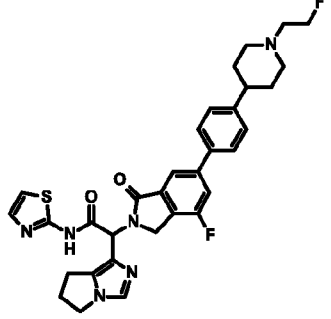
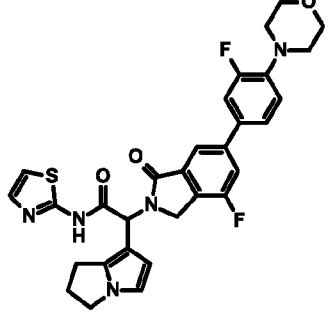
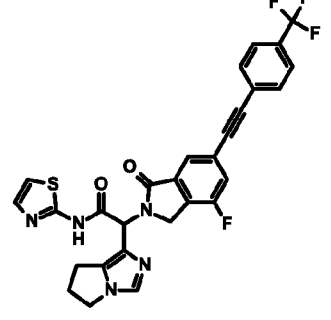
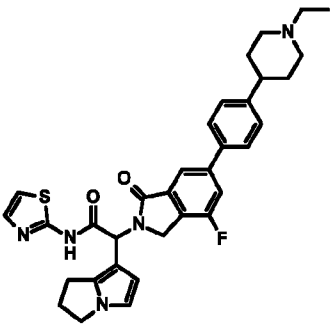
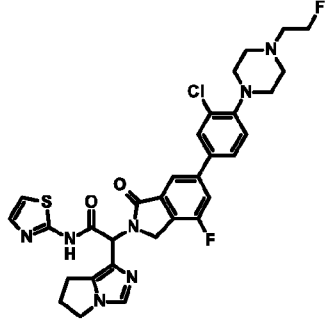
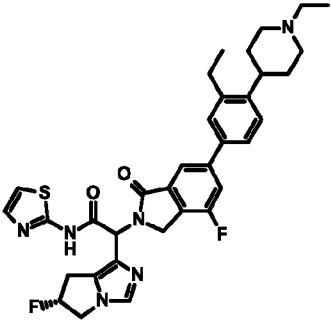
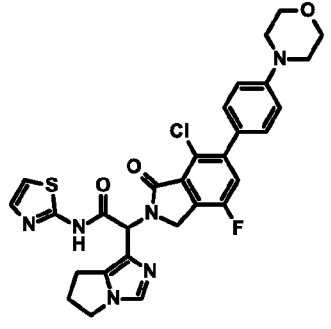
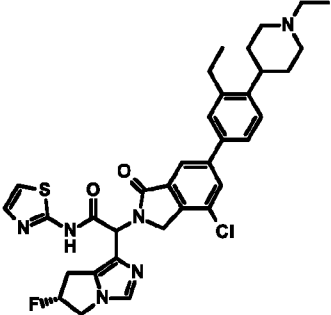
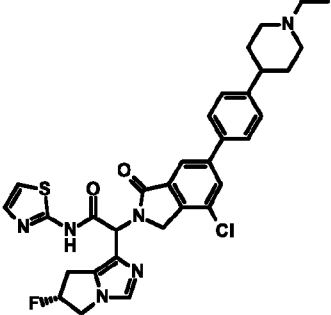
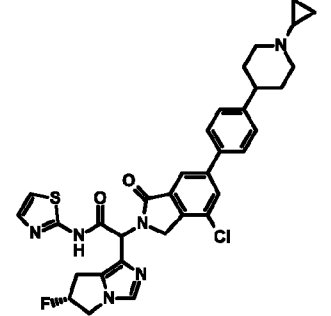
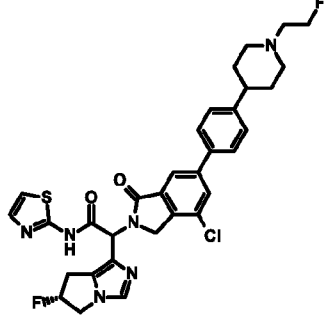
Exam.	Structure	IC ₅₀ (H1975)
45		2nM
46		9nM
47		9nM

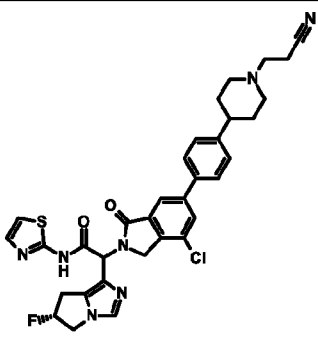
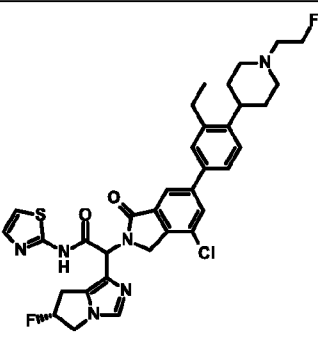
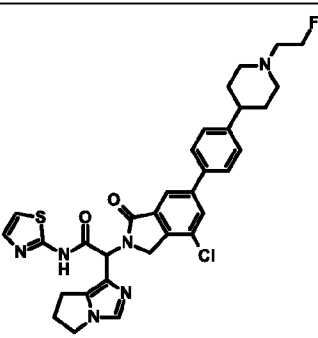
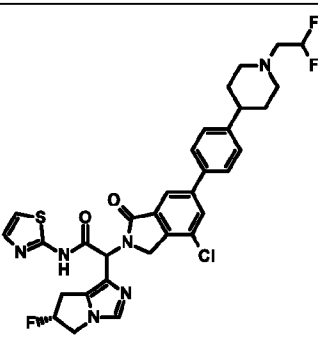
Table 1: H1975 cellular HTRF Phospho EGFR TMLR assay data

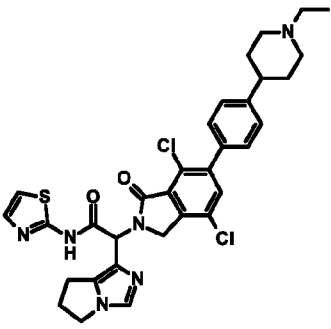
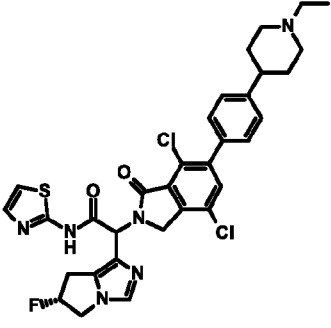
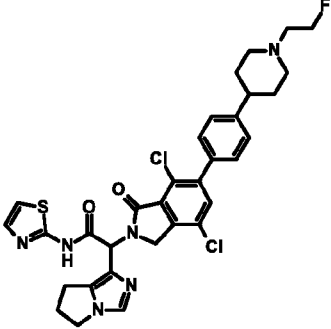
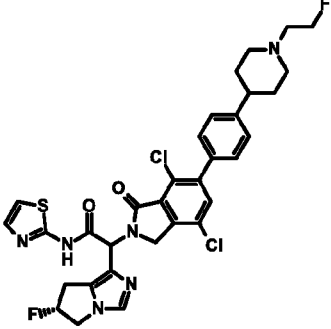
Exam.	Structure	IC ₅₀ (BaF3 TMLRCS)
2		5nM

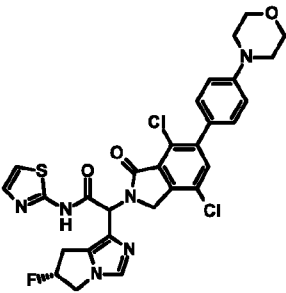
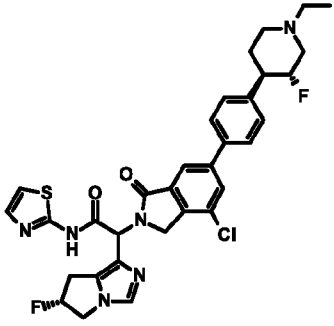
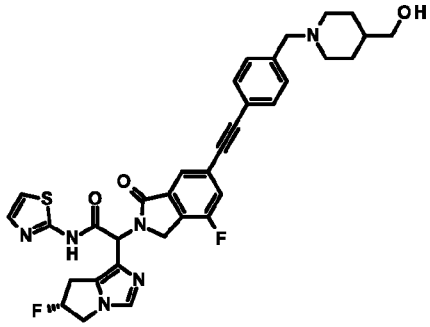
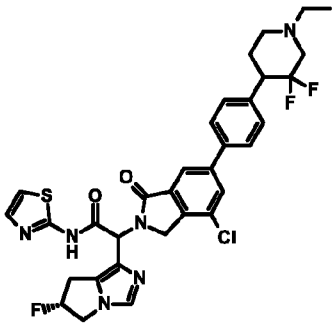
Exam.	Structure	IC ₅₀ (BaF3 TMLRCS)
16		4nM
36		5nM
45		30nM
47		29nM

Exam.	Structure	IC ₅₀ (BaF3 TMLRCS)
48		24nM
49		9nM
50		10nM
51		11nM

Exam.	Structure	IC ₅₀ (BaF3 TMLRCS)
52		10nM
53		4nM
54		12nM
55		4nM

Exam.	Structure	IC ₅₀ (BaF3 TMLRCS)
56		7nM
57		23nM
58		11nM
59		16nM

Exam.	Structure	IC ₅₀ (BaF3 TMLRCS)
60		11nM
61		10nM
62		14nM
63		11nM

Exam.	Structure	IC ₅₀ (BaF3 TMLRCS)
64		10nM
65		10nM
66		3nM
67		9nM

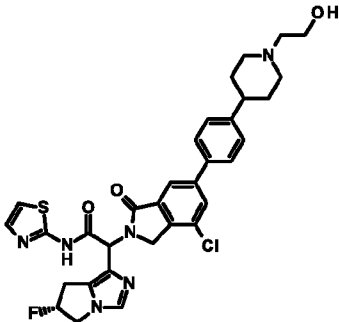
Exam.	Structure	IC ₅₀ (BaF3 TMLRCS)
68		8nM

Table 2: BaF3 cellular HTRF Phospho EGFR TMLRCS assay data

Pharmaceutical Compositions

The compounds of formula I and the pharmaceutically acceptable salts can be used as therapeutically active substances, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatin capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of formula I and the pharmaceutically acceptable salts thereof can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acids or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatin capsules. Suitable carriers for soft gelatin capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active substance no carriers are however usually required in the case of soft gelatin capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, glycerol, vegetable oil and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

The pharmaceutical preparations can, moreover, contain pharmaceutically acceptable auxiliary substances such as preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

Medicaments containing a compound of formula I or a pharmaceutically acceptable salt thereof and a therapeutically inert carrier are also provided by the present invention, as is a process for their production, which comprises bringing one or more compounds of formula I and/or pharmaceutically acceptable salts thereof and, if desired, one or more other therapeutically

valuable substances into a galenical administration form together with one or more therapeutically inert carriers.

The dosage can vary within wide limits and will, of course, have to be adjusted to the individual requirements in each particular case. In the case of oral administration the dosage for adults can vary from about 0.01 mg to about 1000 mg per day of a compound of general formula I or of the corresponding amount of a pharmaceutically acceptable salt thereof. The daily dosage may be administered as single dose or in divided doses and, in addition, the upper limit can also be exceeded when this is found to be indicated.

The following examples illustrate the present invention without limiting it, but serve merely as representative thereof. The pharmaceutical preparations conveniently contain about 1-500 mg, particularly 1-100 mg, of a compound of formula I. Examples of compositions according to the invention are:

Example A

Tablets of the following composition are manufactured in the usual manner:

ingredient	mg/tablet			
	5	25	100	500
Compound of formula I	5	25	100	500
Lactose Anhydrous DTG	125	105	30	150
Sta-Rx 1500	6	6	6	60
Microcrystalline Cellulose	30	30	30	450
Magnesium Stearate	1	1	1	1
Total	167	167	167	831

Table 2: possible tablet composition

Manufacturing Procedure

1. Mix ingredients 1, 2, 3 and 4 and granulate with purified water.
2. Dry the granules at 50°C.
3. Pass the granules through suitable milling equipment.
4. Add ingredient 5 and mix for three minutes; compress on a suitable press.

Example B-1

Capsules of the following composition are manufactured:

ingredient	mg/capsule			
	5	25	100	500
Compound of formula I	5	25	100	500
Hydrous Lactose	159	123	148	-
Corn Starch	25	35	40	70
Talc	10	15	10	25
Magnesium Stearate	1	2	2	5
Total	200	200	300	600

Table 3: possible capsule ingredient composition

Manufacturing Procedure

1. Mix ingredients 1, 2 and 3 in a suitable mixer for 30 minutes.
2. Add ingredients 4 and 5 and mix for 3 minutes.
- 5 3. Fill into a suitable capsule.

The compound of formula I, lactose and corn starch are firstly mixed in a mixer and then in a comminuting machine. The mixture is returned to the mixer; the talc is added thereto and mixed thoroughly. The mixture is filled by machine into suitable capsules, e.g. hard gelatin capsules.

Example B-2

- 10 Soft Gelatin Capsules of the following composition are manufactured:

ingredient	mg/capsule
Compound of formula I	5
Yellow wax	8
Hydrogenated Soya bean oil	8
Partially hydrogenated plant oils	34
Soya bean oil	110
Total	165

Table 4: possible soft gelatin capsule ingredient composition

ingredient	mg/capsule
Gelatin	75
Glycerol 85 %	32
Karion 83	8 (dry matter)
Titan dioxide	0.4
Iron oxide yellow	1.1
Total	116.5

Table 5: possible soft gelatin capsule composition

Manufacturing Procedure

- The compound of formula I is dissolved in a warm melting of the other ingredients and the mixture is filled into soft gelatin capsules of appropriate size. The filled soft gelatin capsules are treated according to the usual procedures.

Example C

Suppositories of the following composition are manufactured:

ingredient	mg/supp.
Compound of formula I	15
Suppository mass	1285
Total	1300

Table 6: possible suppository composition

Manufacturing Procedure

- The suppository mass is melted in a glass or steel vessel, mixed thoroughly and cooled to 45°C. Thereupon, the finely powdered compound of formula I is added thereto and stirred until it has dispersed completely. The mixture is poured into suppository moulds of suitable size, left to cool; the suppositories are then removed from the moulds and packed individually in wax paper or metal foil.

15 Example D

Injection solutions of the following composition are manufactured:

ingredient	mg/injection solution.
Compound of formula I	3
Polyethylene Glycol 400	150
acetic acid	q.s. ad pH 5.0
water for injection solutions	ad 1.0 ml

Table 7: possible injection solution composition

Manufacturing Procedure

- The compound of formula I is dissolved in a mixture of Polyethylene Glycol 400 and water for injection (part). The pH is adjusted to 5.0 by acetic acid. The volume is adjusted to 1.0 ml by addition of the residual amount of water. The solution is filtered, filled into vials using an appropriate overage and sterilized.

Example E

Sachets of the following composition are manufactured:

ingredient	mg/sachet
Compound of formula I	50
Lactose, fine powder	1015
Microcrystalline cellulose (AVICEL PH 102)	1400
Sodium carboxymethyl cellulose	14
Polyvinylpyrrolidone K 30	10
Magnesium stearate	10
Flavoring additives	1
Total	2500

Table 8: possible sachet composition

Manufacturing Procedure

- 5 The compound of formula I is mixed with lactose, microcrystalline cellulose and sodium carboxymethyl cellulose and granulated with a mixture of polyvinylpyrrolidone in water. The granulate is mixed with magnesium stearate and the flavoring additives and filled into sachets.

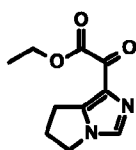
Experimental Part

- 10 The following examples are provided for illustration of the invention. They should not be considered as limiting the scope of the invention, but merely as being representative thereof.

Example 1

(2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-[4-fluoro-6-[2-[4-[(4-methylpiperazin-1-yl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide

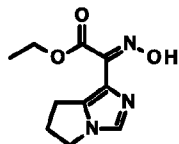
- 15 Step 1: Ethyl 2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-oxo-acetate



- 20 To a solution of ethyl 2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)acetate¹⁴ (20.0 g, 102.97 mmol) dissolved in 200 ml of 1,4-dioxane was added selenium dioxide (22.85 g, 205.94 mmol, 2 equiv.). The reaction mixture was stirred for 5 hours at 80°C. The reaction mixture was concentrated under vacuum to give a residue. The crude product was purified by flash chromatography on a silica gel column eluting with petroleum ether:ethyl acetate 2:1 to ethyl

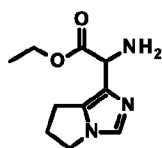
acetate:ethanol 10:1 gradient to obtain the desired ethyl 2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-oxo-acetate (quant. yield) as a light brown oil, MS: $m/e = 209.1$ ($M+H^+$).

Step 2: Ethyl 2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-hydroxyimino-acetate



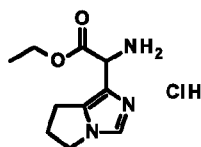
- 5 To a solution of ethyl 2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-oxo-acetate (*Example 1, step 1*) (17.5 g, 84.05 mmol) dissolved in 145 ml of ethanol was added hydroxylamine hydrochloride (6.42 g, 92.45 mmol, 1.1 equiv.) and sodium acetate (13.79 g, 168.1 mmol, 2 equiv.) at room temperature. The reaction mixture was stirred for 3.5 hours at 80°C. The reaction mixture was concentrated and extracted with water and five times with a mixture of ethanol/THF/ethyl
- 10 acetate 1:1:8. The organic layers were concentrated to dryness. The desired ethyl 2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-hydroxyimino-acetate (15 g, 80 % yield) was obtained as a yellow solid, MS: $m/e = 224.1$ ($M+H^+$) and used directly in the next step.

Step 3: Ethyl (2*RS*)-2-amino-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate



- 15 To a solution of ethyl 2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-hydroxyimino-acetate (*Example 1, step 2*) (15.0 g, 67.2 mmol) dissolved in 225 ml of ethanol and 120 ml of THF was added Pd/C (30.0g, 67.2 mmol, 1 eq, 10%) at room temperature. The mixture was hydrogenated with H_2 for 24 hours at 45°C. The reaction mixture was filtered and the filtrate was concentrated under vacuum. The desired ethyl (2*RS*)-2-amino-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-
- 20 yl)acetate (quant. yield) was obtained as a brown oil, MS: $m/e = 210.1$ ($M+H^+$) and used directly in the next step.

Step 4: Ethyl (2*RS*)-2-amino-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate hydrochloride

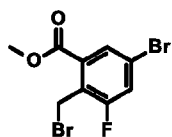


- 25 A solution of ethyl (2*RS*)-2-amino-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (*Example 1, step 3*) (15.0 g, 82.79 mmol) in HCl/EtOH (300 ml, 1200 mmol, 14.5 equiv., 2.5 mol/L) was stirred at 25 °C for 36 hours. The reaction mixture was concentrated under vacuum below 25°C to give a residue as brown oil. 150 ml of acetonitrile were added to the residue and

the precipitated yellow solid was collected and dried under vacuum below 25 °C to give the desired ethyl (2*RS*)-2-amino-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)acetate hydrochloride (quant. yield) as yellow solid, MS: $m/e = 210.1$ ($M+H^+$).

Step 5: Methyl 5-bromo-2-(bromomethyl)-3-fluoro-benzoate

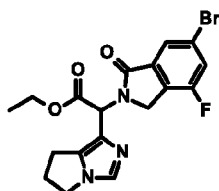
5



Methyl 5-bromo-3-fluoro-2-methylbenzoate¹⁵ (5.91 g, 23.9 mmol) was dissolved in 100 ml trifluorotoluene and N-bromosuccinimide (4.26 g, 23.9 mmol, 1 equiv.) and AIBN (393 mg, 2.39 mmol, 0.1 equiv.) were added at room temperature. The mixture was stirred at 110°C for 3 hours. The reaction mixture was cooled, extracted with water and two times with ethyl acetate. The organic layers were dried over sodium sulfate and concentrated to dryness. The crude product was purified by flash chromatography on a silica gel column eluting with an ethyl acetate:heptane 0:100 to 50:50 gradient to obtain the desired methyl 5-bromo-2-(bromomethyl)-3-fluoro-benzoate (7.29 g, 94 % yield) as a light yellow liquid, MS: $m/e = 326.8$ ($M+H^+$).

15

Step 6: Ethyl (2*RS*)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)acetate

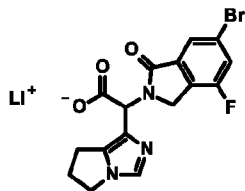


20

Ethyl (2*RS*)-2-amino-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)acetate hydrochloride (*Example 1, step 4*) (4.15 g, 16.9 mmol, 1 equiv.) was dissolved in 35 ml of DMF. Methyl 5-bromo-2-(bromomethyl)-3-fluoro-benzoate (*Example 1, step 5*) (5.0 g, 15.3mmol) and triethylamine (10.7 ml, 76.7 mmol, 5 equiv.) were added at room temperature. The mixture was stirred at 80°C for 16 hours. The reaction mixture was extracted with water and two times with ethyl acetate. The organic layers were extracted with brine, dried over sodium sulfate and concentrated to dryness. The crude product was purified by flash chromatography on a silica gel column eluting with a dichloromethane:methanol 100:0 to 90:10 gradient to obtain the desired ethyl (2*RS*)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)acetate (2.6 g, 40 % yield) as a yellow solid, MS: $m/e = 422.1/424.1$ ($M+H^+$).

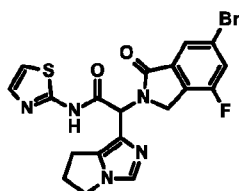
25

Step 7: Lithium ((2*RS*)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)acetate



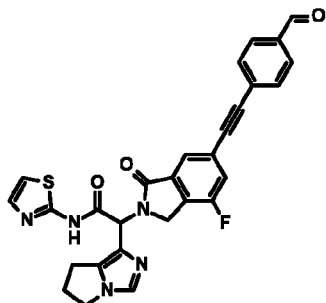
(*2RS*)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (*Example 1, step 6*) (1.96 g, 4.64 mmol) was dissolved in 16 ml of ethanol. LiOH (1M in water) (5.57 ml, 5.57 mmol, 1.2 equiv.) was added at room temperature. The mixture was stirred for 1 hour at room temperature. The reaction mixture was concentrated in vacuo to afford the desired crude lithium ((*2RS*)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (1.92 g, quant.) as a light brown solid, MS: $m/e = 394.1/396.1$ ($M+H^+$).

Step 8: (*2RS*)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide



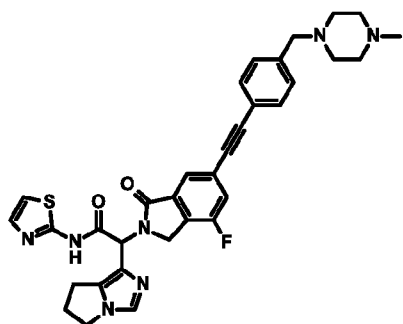
Lithium ((*2RS*)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (*Example 1, step 7*) (2.53 g, 6.32 mmol) was dissolved in 10 ml of DMF. Thiazol-2-amine (760 mg, 7.59 mmol, 1.2 equiv.), Hunig's base (5.5 ml, 31.6 mmol, 5 equiv.) and HATU (2.89 g, 7.59 mmol, 1.2 equiv.) were added at room temperature. The mixture was stirred at room temperature for 1 hour. The reaction mixture was extracted with water and two times with a 9:1 mixture of dichloromethane:methanol. The organic layers were extracted with water, dried over sodium sulfate and concentrated to dryness. The crude product was purified by flash chromatography on a silica gel column eluting with a dichloromethane:methanol 100:0 to 80:20 gradient to obtain the desired (*2RS*)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide (1.8 g, 60 % yield) as a light brown solid, MS: $m/e = 476.1/478.1$ ($M+H^+$).

Step 9: (*2RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-6-[2-(4-formylphenyl)ethynyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide



(2*RS*)-2-(6-Bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide (*Example 1, step 8*) (140 mg, 0.29 mmol) and 4-ethynylbenzaldehyde (49.7 mg, 0.382 mmol, 1.3 equiv.) were dissolved in 12 ml of DMF. triethylamine (89 mg, 0.123 ml, 0.882 mmol, 3 equiv.), bis-(triphenylphosphine)-palladium(II)dichloride (10 mg, 0.015 mmol, 0.05 equiv.), triphenylphosphine (8 mg, 0.03 mmol, 0.1 equiv.) and copper(I)iodide (3 mg, 0.015 mmol, 0.05 equiv.) were added and the mixture was stirred for 4 hours at 80°C. The reaction mixture was extracted with water and two times with ethyl acetate. The organic layers were extracted with brine, dried over sodium sulfate and concentrated to dryness. The crude product was purified by flash chromatography on a silica gel column eluting with a dichloromethane:methanol 100:0 to 90:10 gradient to obtain the desired (2*RS*)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-6-[2-(4-formylphenyl)ethynyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide (130 mg, 86 % yield) as a yellow solid, MS: $m/e = 526.1$ ($M+H^+$).

Step 10: (2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-6-[2-[4-(4-methylpiperazin-1-yl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide



(2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-6-[2-(4-formylphenyl)ethynyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide (*Example 1, step 9*) (40 mg, 0.076 mmol) was dissolved in 1 ml of dichloromethane. 1-Methylpiperazine (11 mg, 0.114 mmol, 1.5 equiv.) and sodium triacetoxyhydroborate (24 mg, 0.114 mmol, 1.5 equiv.) were added at room temperature. The mixture was stirred at room temperature for 16 hours. The reaction mixture was extracted with water and two times with dichloromethane. The organic layers were extracted with brine, dried over sodium sulfate and concentrated to dryness. The crude product was purified by flash chromatography on a silica gel column eluting with a dichloromethane:methanol 100:0 to 85:15 gradient to obtain the desired (2*RS*)-2-(6,7-dihydro-5H-

pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-6-[2-[4-[(4-methylpiperazin-1-yl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide (17 mg, 37 % yield) as a white solid, MS: $m/e = 610.4$ ($M+H^+$).

Example 2

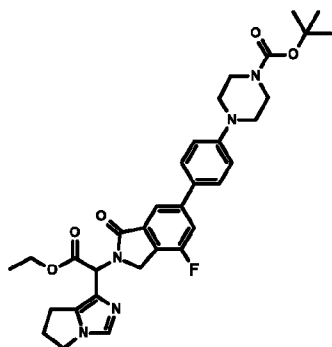
5 (2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-6-[2-[4-[(4-hydroxy-1-piperidyl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide

The title compound was obtained as a white solid, MS: $m/e = 611.3$ ($M+H^+$), using chemistry similar to that described in Example 1, step 10 starting from (2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-6-[2-(4-formylphenyl)ethynyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide (*Example 1, step 9*) and piperidin-4-ol.

Example 3

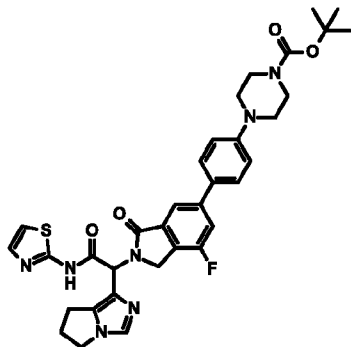
(2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-1-oxo-6-(4-piperazin-1-ylphenyl)isoindolin-2-yl]-N-thiazol-2-yl-acetamide

Step 1: tert-Butyl 4-[4-[7-fluoro-3-oxo-2-[(1*RS*)-1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-ethoxy-2-oxo-ethyl]isoindolin-5-yl]phenyl]piperazine-1-carboxylate



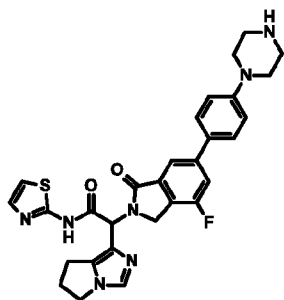
Ethyl (2*RS*)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (*Example 1, step 6*) (56 mg, 0.133 mmol) and (4-(4-(tert-butoxycarbonyl)piperazin-1-yl)phenyl)boronic acid¹⁶ (41 mg, 0.133 mmol, 1.0 equiv.) were dissolved in 1.0 ml of 1,2-dimethoxyethane and 2M aq. Na₂CO₃-solution (0.199 ml, 0.398 mmol, 3.0 equiv.). Tetrakis(triphenylphosphine)palladium (0) (15 mg, 0.0133 mmol, 0.1 equiv.) was added and the reaction mixture was stirred at 80°C for 4 hours. The reaction mixture was cooled to room temperature and then extracted with ethyl acetate and saturated NaHCO₃-solution. The aqueous layer was back-extracted with ethyl acetate. The organic layers were washed with water and brine. The organic layers were combined, dried over sodium sulfate, filtered and concentrated to dryness. The crude product was purified by flash chromatography on a silica gel column eluting with an ethyl acetate:heptane 5:95 to 100:0 gradient. The desired tert-butyl 4-[4-[7-fluoro-3-oxo-2-[(1*RS*)-1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-ethoxy-2-oxo-ethyl]isoindolin-5-yl]phenyl]piperazine-1-carboxylate (48 mg, 60 % yield) was obtained as a light brown oil, MS: $m/e = 604.4$ ($M+H^+$).

Step 2: tert-Butyl 4-[4-[7-fluoro-3-oxo-2-[(1*RS*)-1-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-oxo-2-(thiazol-2-ylamino)ethyl]isoindolin-5-yl]phenyl]piperazine-1-carboxylate



tert-Butyl 4-[4-[7-fluoro-3-oxo-2-[(1*RS*)-1-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-ethoxy-2-oxo-ethyl]isoindolin-5-yl]phenyl]piperazine-1-carboxylate (*Example 3, step 1*) (48 mg, 0.0795 mmol) was combined with 11 ml of ethanol to give a light yellow solution. LiOH (1M in water) (0.0954 ml, 0.0954 mmol, 1.2 equiv.) was added. The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated in vacuo. The residue was taken up in ethanol and concentrated in vacuo and then dissolved in 7 ml of DMF. Thiazol-2-amine (9.55 mg, 0.0954 mmol, 1.2 equiv.) and Hunig's base (0.0694 ml, 0.398 mmol, 5 equiv.) were added followed by HATU (36.3 mg, 0.0954 mmol, 1.2 equiv.). The mixture was stirred at room temperature for 1 hour. The reaction mixture was extracted with ethyl acetate and saturated NaHCO₃-solution. The aqueous layer was back-extracted with ethyl acetate. The organic layers were washed with water and brine. The organic layers were combined, dried over sodium sulfate, filtered and concentrated to dryness. The crude product was purified by flash chromatography on a silica gel column eluting with a dichloromethane:methanol 100:0 to 90:10 gradient to obtain the desired *tert*-butyl 4-[4-[7-fluoro-3-oxo-2-[(1*RS*)-1-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-oxo-2-(thiazol-2-ylamino)ethyl]isoindolin-5-yl]phenyl]piperazine-1-carboxylate (22 mg, 42 % yield) as a yellow oil, MS: *m/e* = 658.3 (*M*+*H*⁺).

Step 3: (2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-[4-fluoro-1-oxo-6-(4-piperazin-1-ylphenyl)isoindolin-2-yl]-N-thiazol-2-yl-acetamide



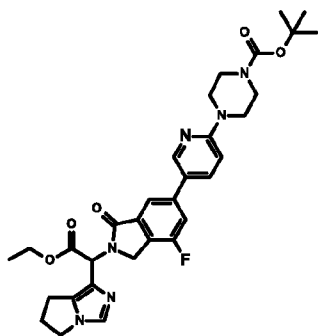
tert-Butyl 4-[4-[7-fluoro-3-oxo-2-[(1*RS*)-1-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-oxo-2-(thiazol-2-ylamino)ethyl]isoindolin-5-yl]phenyl]piperazine-1-carboxylate (*Example 3, step 2*) (26 mg, 0.0395 mmol) was [dissolved/suspended] in 0.5ml of dichloromethane and 0.25

ml of methanol. HCl (4 M in dioxane) (0.099 ml, 0.395 mmol, 10 equiv.) was added at room temperature and the reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was extracted with saturated NaHCO₃-solution and twice with dichloromethane. The organic layers were combined, dried over sodium sulfate, filtered and concentrated to dryness. The
 5 desired (2*RS*)-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-[4-fluoro-1-oxo-6-(4-piperazin-1-ylphenyl)isoindolin-2-yl]-N-thiazol-2-yl-acetamide (22 mg, 99.8 % yield) was obtained as a light yellow oil, MS: *m/e* = 558.2 (M+H⁺).

Example 4

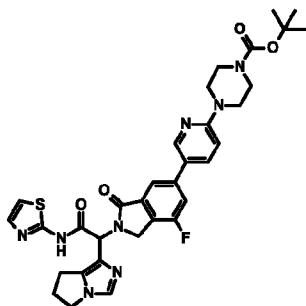
(2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-[6-[6-(4-ethylpiperazin-1-yl)-3-pyridyl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide

Step 1: tert-Butyl 4-[5-[7-fluoro-3-oxo-2-[(1*RS*)-1-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-ethoxy-2-oxo-ethyl]isoindolin-5-yl]-2-pyridyl]piperazine-1-carboxylate



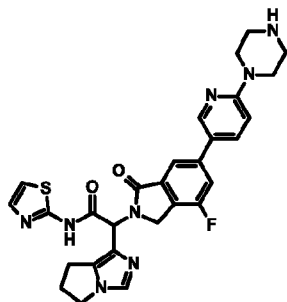
The title compound was obtained as a brown oil, MS: *m/e* = 605.3 (M+H⁺), using chemistry
 15 similar to that described in Example 3, step 1 starting from ethyl (2*RS*)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)acetate (*Example 1, step 6*) and (6-(4-(tert-butoxycarbonyl)piperazin-1-yl)pyridin-3-yl)boronic acid¹⁷.

Step 2: tert-Butyl 4-[5-[7-fluoro-3-oxo-2-[(1*RS*)-1-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-oxo-2-(thiazol-2-ylamino)ethyl]isoindolin-5-yl]-2-pyridyl]piperazine-1-carboxylate



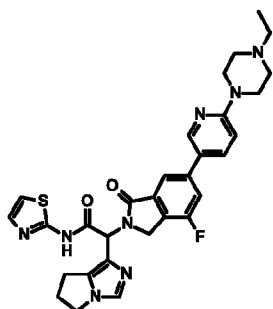
The title compound was obtained as a yellow oil, MS: *m/e* = 659.1 (M+H⁺), using chemistry
 20 similar to that described in Example 3, step 2 starting from tert-butyl 4-[5-[7-fluoro-3-oxo-2-[(1*RS*)-1-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-ethoxy-2-oxo-ethyl]isoindolin-5-yl]-2-pyridyl]piperazine-1-carboxylate (*Example 4, step 1*) and thiazol-2-amine.

Step 3: (2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-[4-fluoro-1-oxo-6-(6-piperazin-1-yl-3-pyridyl)isoindolin-2-yl]-N-thiazol-2-yl-acetamide



The title compound was obtained as a light brown solid, MS: $m/e = 559.1$ ($M+H^+$), using chemistry similar to that described in Example 3, step 3 starting from tert-butyl 4-[5-[7-fluoro-3-oxo-2-[(1*RS*)-1-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-oxo-2-(thiazol-2-ylamino)ethyl]isoindolin-5-yl]-2-pyridyl]piperazine-1-carboxylate (*Example 4, step 2*).

Step 4: (2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-[6-[6-(4-ethylpiperazin-1-yl)-3-pyridyl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide



(2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-[4-fluoro-1-oxo-6-(6-piperazin-1-yl-3-pyridyl)isoindolin-2-yl]-N-thiazol-2-yl-acetamide (*Example 4, step 3*) (45 mg, 0.0806 mmol) was dissolved in 1.0 ml of DMF. Ethyl iodide (13.8 mg, 7.16 μ l, 0.0886 mmol, 1.1 equiv.) and Hunig's base (41.6 mg, 56.3 μ l, 0.322 mmol, 4 equiv.) were added at room temperature. The reaction mixture was stirred at 60°C for 1 hour. The reaction mixture was cooled to room temperature and then extracted with ethyl acetate and water. The aqueous layer was back-extracted with ethyl acetate. The organic layers were washed with brine. The organic layers were combined, dried over sodium sulfate, filtered and concentrated to dryness. The crude product was purified by flash chromatography on a silica gel column eluting with a dichloromethane:methanol 100:0 to 85:15 gradient to obtain the desired (2*RS*)-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-[6-[6-(4-ethylpiperazin-1-yl)-3-pyridyl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide (24 mg, 51 % yield) as a light yellow solid, MS: $m/e = 587.3$ ($M+H^+$).

Example 5

(2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-[6-[4-(4-ethylpiperazin-1-yl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide

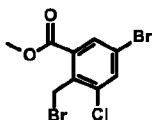
The title compound was obtained as a light yellow solid, MS: $m/e = 586.3$ ($M+H^+$), using chemistry similar to that described in Example 4, step 4 starting from (2*RS*)-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-[4-fluoro-1-oxo-6-(4-piperazin-1-ylphenyl)isoindolin-2-yl]-N-thiazol-2-yl-acetamide (*Example 3, step 3*) and ethyl iodide.

5

Example 6

(2*RS*)-2-[4-Chloro-6-[4-(4-ethylpiperazin-1-yl)phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide

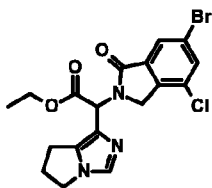
Step 1: Methyl 5-bromo-2-(bromomethyl)-3-chloro-benzoate



10

The title compound was obtained as a colorless solid, MS: $m/e = 343.4$ ($M+H^+$), using chemistry similar to that described in Example 1, step 5 starting from methyl 5-bromo-3-chloro-2-methyl-benzoate¹⁸.

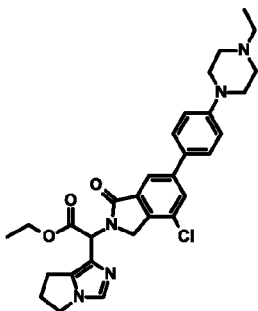
Step 2: Ethyl (2*RS*)-2-(6-bromo-4-chloro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)acetate



15

The title compound was obtained as a red amorphous, MS: $m/e = 438.0/440.0$ ($M+H^+$), using chemistry similar to that described in Example 1, step 6 starting from ethyl (2*RS*)-2-amino-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)acetate (*Example 1, step 3*) and methyl 5-bromo-2-(bromomethyl)-3-chloro-benzoate (*Example 6, step 1*).

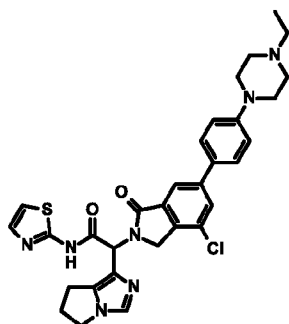
Step 3: Ethyl (2*RS*)-2-[4-chloro-6-[4-(4-ethylpiperazin-1-yl)phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)acetate



The title compound was obtained as an off-white amorphous, MS: $m/e = 548.3$ ($M+H^+$), using chemistry similar to that described in Example 3, step 1 starting from ethyl (2*RS*)-2-(6-

bromo-4-chloro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (*Example 6, step 2*) and 1-ethyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine¹⁹.

Step 4: (2*RS*)-2-[4-Chloro-6-[4-(4-ethylpiperazin-1-yl)phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-
 5 dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide

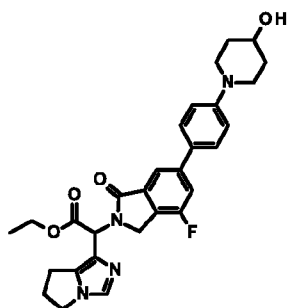


The title compound was obtained as a light yellow solid, MS: $m/e = 602.2$ ($M+H^+$), using chemistry similar to that described in Example 3, step 2 starting from ethyl (2*RS*)-2-[4-chloro-6-[4-(4-ethylpiperazin-1-yl)phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (*Example 6, step 3*) and thiazol-2-amine.

Example 7

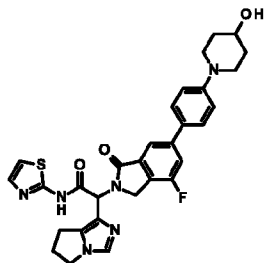
(2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-6-[4-(4-hydroxy-1-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide

Step 1: Ethyl (2*RS*)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-6-[4-(4-
 15 hydroxy-1-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]acetate



The title compound was obtained as a yellow solid, MS: $m/e = 519.2$ ($M+H^+$), using chemistry similar to that described in Example 3, step 1 starting from ethyl (2*RS*)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (*Example 1, step 6*) and 1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidin-4-ol²⁰.

Step 2: (2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-6-[4-(4-hydroxy-1-
piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide

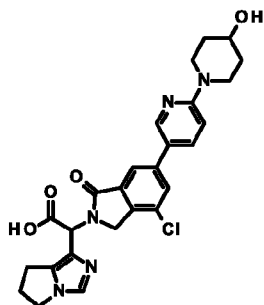


The title compound was obtained as a light brown solid, MS: $m/e = 573.1$ ($M+H^+$), using chemistry similar to that described in Example 3, step 2 starting from ethyl (2*RS*)-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-[4-fluoro-6-[4-(4-hydroxy-1-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]acetate (Example 7, step 1) and thiazol-2-amine.

Example 8

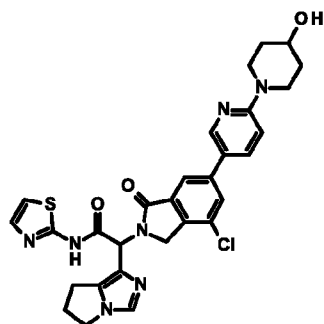
(2*RS*)-2-[4-Chloro-6-[6-(4-hydroxy-1-piperidyl)-3-pyridyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide

Step 1: (2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-[4-fluoro-6-[6-(4-hydroxy-1-piperidyl)-3-pyridyl]-1-oxo-isoindolin-2-yl]acetic acid



The title compound was obtained as a dark grey solid, MS: $m/e = 508.3/510.3$ ($M+H^+$), using chemistry similar to that described in Example 3, step 1 starting from ethyl (2*RS*)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)acetate (Example 1, step 6) and (6-(4-hydroxypiperidin-1-yl)pyridin-3-yl)boronic acid by isolating the formed corresponding acid.

Step 2: (2*RS*)-2-[4-Chloro-6-[6-(4-hydroxy-1-piperidyl)-3-pyridyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide



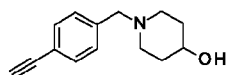
The title compound was obtained as a light brown solid, MS: $m/e = 590.1/592.1$ ($M+H^+$), using chemistry similar to that described in Example 1, step 8 starting from (2*RS*)-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-[4-fluoro-6-[6-(4-hydroxy-1-piperidyl)-3-pyridyl]-1-oxo-isoindolin-2-yl]acetic acid (*Example 8, step 1*) and thiazol-2-amine.

5

Example 9

(2*RS*)-2-[4-Chloro-6-[2-[4-[(4-hydroxy-1-piperidyl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide

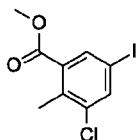
Step 1: 1-[4-Ethynylphenyl)methyl]piperidin-4-ol



10

The title compound was obtained as a yellow solid, MS: $m/e = 216.2$ ($M+H^+$), using chemistry similar to that described in Example 1, step 10 starting from 4-ethynylbenzaldehyde and piperidin-4-ol.

Step 2: Methyl 3-chloro-5-iodo-2-methyl-benzoate

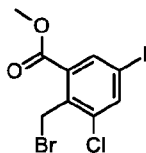


15

3-Chloro-5-iodo-2-methyl-benzoic acid²¹ (1 g, 3.37 mmol) was dissolved in 20 ml of methanol and sulfuric acid (33.1 mg, 0.018 ml, 0.337 mmol, 0.1 equiv.) was added at room temperature. The mixture was stirred at 70°C for 4 hours. Sulfuric acid (0.18 ml, 3.37 mmol, 1.0 equiv.) was added and the mixture was stirred at 80°C for 16 hours. The reaction mixture was concentrated to a volume of ~5 ml and then extracted with ethyl acetate and saturated NaHCO₃-solution. The aqueous layer was back-extracted with ethyl acetate. The organic layers were washed with water. The organic layers were combined, dried over sodium sulfate, filtered and concentrated on isolute® to dryness. The crude product was purified by flash chromatography on a silica gel column eluting with an ethyl acetate:heptane 0:100 to 50:50 gradient. The desired methyl 3-chloro-5-iodo-2-methyl-benzoate (941 mg, 90 % yield) was obtained as a white solid, MS: $m/e = 309.1$ ($M-H^-$).

25

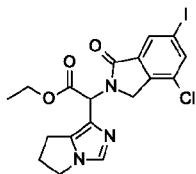
Step 3: Methyl 2-(bromomethyl)-3-chloro-5-iodo-benzoate



The title compound was obtained as a white solid, MS: $m/e = 388.4$ ($M-H^-$), using chemistry similar to that described in Example 1, step 5 starting from methyl 3-chloro-5-iodo-2-methyl-benzoate (*Example 9, step 2*).

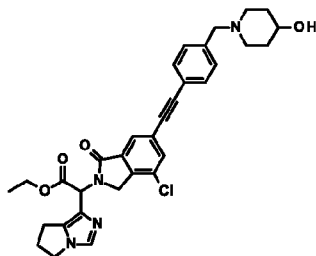
30

Step 4: Ethyl (2*RS*)-2-(4-chloro-6-iodo-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-
c]imidazol-1-yl)acetate



The title compound was obtained as a dark brown semisolid, MS: $m/e = 486.1/488.0$ ($M+H^+$),
5 using chemistry similar to that described in Example 1, step 6 starting from ethyl (2*RS*)-2-amino-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate hydrochloride (*Example 1, step 4*) and methyl 2-(bromomethyl)-3-chloro-5-iodo-benzoate (*Example 9, step 3*).

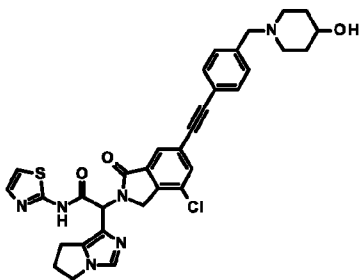
Step 5: Ethyl (2*RS*)-2-[4-chloro-6-[2-[4-[(4-hydroxy-1-piperidyl)methyl]phenyl]ethynyl]-1-oxo-
isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate



10

The title compound was obtained as a yellow solid, MS: $m/e = 573.2/575.2$ ($M+H^+$), using
chemistry similar to that described in Example 1, step 9 starting from ethyl (2*RS*)-2-(4-chloro-6-
iodo-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (*Example 9,*
step 4) and 1-[(4-ethynylphenyl)methyl]piperidin-4-ol (*Example 9, step 1*).

15 Step 6: (2*RS*)-2-[4-Chloro-6-[2-[4-[(4-hydroxy-1-piperidyl)methyl]phenyl]ethynyl]-1-oxo-
isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide

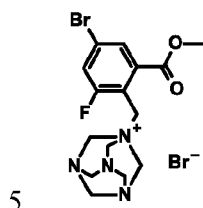


The title compound was obtained as a light yellow solid, MS: $m/e = 627.5/629.5$ ($M+H^+$),
using chemistry similar to that described in Example 3, step 2 starting from ethyl (2*RS*)-2-[4-
20 chloro-6-[2-[4-[(4-hydroxy-1-piperidyl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-2-(6,7-
dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (*Example 9, step 5*) and thiazol-2-amine.

Example 10

(2*RS*)-2-(6,7-Dihydro-5H-pyrrolizin-1-yl)-2-[4-fluoro-6-[2-[4-[(4-hydroxy-1-piperidyl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide

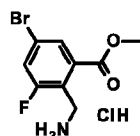
Step 1: Methyl 5-bromo-3-fluoro-2-(3,5,7-triaza-1-azoniatricyclo[3.3.1.1^{3,7}]decan-1-ylmethyl)benzoate bromide



Methyl 5-bromo-2-(bromomethyl)-3-fluoro-benzoate (*Example 1, step 4*) (300 mg, 0.920 mmol) was dissolved in 5 ml of chloroform and 1,3,5,7-tetrazatricyclo[3.3.1.1^{3,7}]decane (135 mg, 0.966 mmol, 1.05 equiv.) was added at room temperature. The reaction mixture was stirred at 70°C for 2 hours. The resulting suspension was filtered and washed two times with dichloromethane.

10 The filter cake was dried to afford the desired methyl 5-bromo-3-fluoro-2-(3,5,7-triaza-1-azoniatricyclo[3.3.1.1^{3,7}]decan-1-ylmethyl)benzoate bromide (369 mg, 86 % yield) as a white solid, MS: $m/e = 385.2/387.2$ ($M+H^+$).

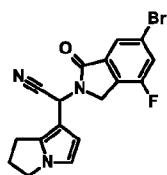
Step 2: Methyl 2-(aminomethyl)-5-bromo-3-fluoro-benzoate hydrochloride



15 Methyl 5-bromo-3-fluoro-2-(3,5,7-triaza-1-azoniatricyclo[3.3.1.1^{3,7}]decan-1-ylmethyl)benzoate bromide (*Example 10, step 1*) (369 mg, 0.792 mmol) was suspended in 5 ml of methanol and HCl (25% in water) (0.618 ml, 4.75 mmol, 6 equiv.) was added at room temperature. The reaction mixture was stirred at 75°C for 2 hours. The reaction mixture was concentrated to dryness and used without further purification. The desired methyl 2-(aminomethyl)-5-bromo-3-

20 fluoro-benzoate hydrochloride (393 mg, quantitative, 60% purity) was obtained as a white solid, MS: $m/e = 262.1$ ($M-H$).

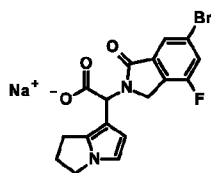
Step 3: (2*RS*)-2-(6-Bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolizin-1-yl)acetonitrile



25 A mixture of 6,7-dihydro-5H-pyrrolizine-1-carbaldehyde²² (100 mg, 0.740 mmol), methyl 2-(aminomethyl)-5-bromo-3-fluoro-benzoate hydrochloride (*Example 10, step 2*) (379 mg, 0.888 mmol, purity=70%, 1.2 equiv.) in 3.0 ml of acetonitrile was stirred at 70°C for 16 hours. Trimethylsilyl cyanide (89.9 mg, 0.113 ml, 0.888 mmol, 1.2 equiv.) was added at room

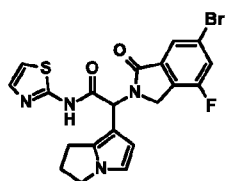
temperature and the reaction mixture was stirred at 70°C for 2 hours. Hunig's base (191 mg, 0.258 ml, 1.48 mmol, 2.0 equiv.) was added at room temperature and the reaction mixture was stirred at 70°C for 4 hours. The reaction mixture was extracted with saturated NaHCO₃-solution and two times with ethyl acetate. The organic layers were washed with water and brine, dried over sodium sulfate and concentrated to dryness. The crude product was purified by flash chromatography on a silica gel column eluting with an ethyl acetate:heptane 0:100 to 100:0 gradient to obtain the desired (2*RS*)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolizin-1-yl)acetonitrile (70 mg, 25 % yield) as a yellow solid, MS: m/e = 374.0/375.9 (M+H⁺).

Step 4: Sodium (2*RS*)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolizin-1-yl)acetate



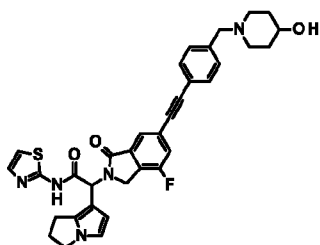
(2*RS*)-2-(6-Bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolizin-1-yl)acetonitrile (*Example 10, step 3*) (110 mg, 0.294 mmol) was dissolved in 1.0 ml of ethanol. NaOH (2M in water) (0.294 ml, 0.588 mmol, 2 equiv.) was added at room temperature. The mixture was stirred at 85°C for 16 hours. The reaction mixture was cooled to room temperature and then concentrated to dryness. The desired sodium (2*RS*)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolizin-1-yl)acetate (165 mg, 95 % yield, 70% purity) was obtained as a yellow solid, MS: m/e = 393.0/395.0 (M+H⁺) and used in the next step without further purification.

Step 5: (2*RS*)-2-(6-Bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolizin-1-yl)-N-thiazol-2-yl-acetamide



The title compound was obtained as a light brown solid, MS: m/e = 474.9/476.9 (M+H⁺), using chemistry similar to that described in *Example 1, step 7* starting from sodium (2*RS*)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolizin-1-yl)acetate (*Example 10, step 4*) and thiazol-2-amine.

Step 6: (2*RS*)-2-(6,7-Dihydro-5H-pyrrolizin-1-yl)-2-[4-fluoro-6-[2-[4-[(4-hydroxy-1-piperidyl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide

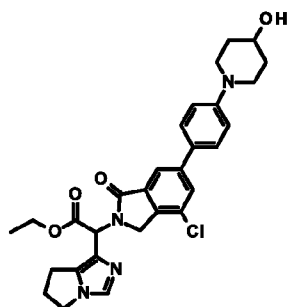


The title compound was obtained as a yellow solid, MS: $m/e = 610.4$ ($M+H^+$), using chemistry similar to that described in Example 1, step 9 starting from (2*RS*)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolizin-1-yl)-N-thiazol-2-yl-acetamide (Example 10, step 5) and 1-[(4-ethynylphenyl)methyl]piperidin-4-ol (Example 9, step 1).

Example 11

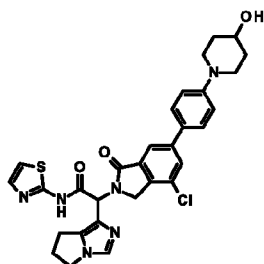
(2*RS*)-2-[4-Chloro-6-[4-(4-hydroxy-1-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide

Step 1: Ethyl (2*RS*)-2-[4-Chloro-6-[4-(4-hydroxy-1-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate



The title compound was obtained as a brown solid, MS: $m/e = 535.2/537.2$ ($M+H^+$), using chemistry similar to that described in Example 3, step 1 starting from ethyl (2*RS*)-2-(4-chloro-6-iodo-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (Example 9, step 4) and 1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidin-4-ol²⁰.

Step 2: (2*RS*)-2-[4-Chloro-6-[4-(4-hydroxy-1-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide



The title compound was obtained as a white solid, MS: $m/e = 589.2/591.2$ ($M+H^+$), using chemistry similar to that described in Example 3, step 2 starting from ethyl (2*RS*)-2-[4-chloro-6-

[4-(4-hydroxy-1-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (*Example 11, step 1*) and thiazol-2-amine.

Example 12

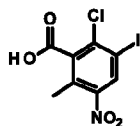
(2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-6-[2-[4-(hydroxymethyl)phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide

The title compound was obtained as a light yellow solid, MS: $m/e = 526.1$ ($M+H^+$), using chemistry similar to that described in Example 1, step 9 starting from (2*RS*)-2-(6-Bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide (*Example 1, step 8*) and (4-ethynylphenyl)methanol.

Example 13

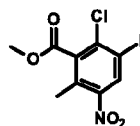
(2*RS*)-2-[7-chloro-4-fluoro-6-[2-[4-[(4-hydroxy-1-piperidyl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide

Step 1: 2-Chloro-3-iodo-6-methyl-5-nitrobenzoic acid



6-Chloro-2-methyl-3-nitrobenzoic acid²³ (3.8 g, 15.9 mmol) was dissolved in 18 ml of sulfuric acid. 1,3-Diiodo-5,5-dimethylimidazolidine-2,4-dione (6.9 g, 18.2 mmol, 1.15 equiv.) was added at room temperature. The mixture was stirred at room temperature for 16 hours. The reaction mixture was poured onto water and the resulting precipitate filtered off. The solid was dried to obtain the desired 2-chloro-3-iodo-6-methyl-5-nitrobenzoic acid (5.37 g, quant. yield) as a brown foam, MS: $m/e = 339.8/341.7$ ($M+H^+$).

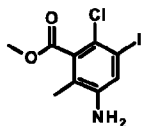
Step 2: Methyl 2-chloro-3-iodo-6-methyl-5-nitrobenzoate



2-Chloro-3-iodo-6-methyl-5-nitrobenzoic acid (*Example 13, step 1*) (5.37 g, 14.2 mmol) was dissolved in 25 ml of DMF. Potassium carbonate (3.9 g, 28.3 mmol, 2 equiv.) and iodomethane (2.1 g, 14.9 mmol, 1.05 equiv.) were added at room temperature. The mixture was stirred at room temperature for 2 hours. The reaction mixture was extracted with saturated sodium bicarbonate solution and two times with ethyl acetate. The organic layers were extracted with water and 10% lithium chloride solution. The organic layers were combined, dried over sodium sulfate and concentrated to dryness. The crude product was purified by flash chromatography on a silica gel column eluting with a heptane:ethyl acetate 100:0 to 60:40 gradient to obtain the desired methyl

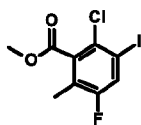
2-chloro-3-iodo-6-methyl-5-nitrobenzoate (2.89 g, 57 % yield) as a light yellow solid, MS: $m/e = 353.9/355.9$ ($M+H^+$).

Step 3: Methyl 3-amino-6-chloro-5-iodo-2-methylbenzoate



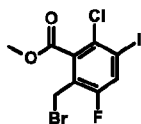
- 5 Methyl 2-chloro-3-iodo-6-methyl-5-nitrobenzoate (*Example 13, step 2*) (2.89 g, 8.13 mmol) was dissolved in 30 ml of methanol and 15 ml of water. Ammonium chloride (4.35 g, 81.3 mmol, 10 equiv.) and iron (2.72 g, 48.8 mmol, 6 equiv.) were added at room temperature. The mixture was stirred at 70°C for 16 hours. The reaction mixture was filtered and evaporated to dryness. The residue was extracted with saturated sodiumbicarbonate solution and two times with ethyl acetate.
- 10 The organic layers were extracted with water and brine. The organic layers were combined, dried over sodium sulfate and concentrated to dryness. The crude product was purified by flash chromatography on a silica gel column eluting with a heptane:ethyl acetate 100:0 to 30:70 gradient to obtain the desired methyl 3-amino-6-chloro-5-iodo-2-methylbenzoate (1.9 g, 72 % yield) as an orange oil, MS: $m/e = 324.9/326.9$ ($M+H^+$).

- 15 Step 4: Methyl 2-chloro-5-fluoro-3-iodo-6-methylbenzoate (696 mg, 2.12 mmol, 49.1 % yield)



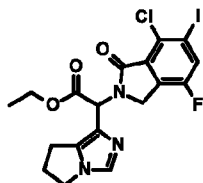
- Methyl 3-amino-6-chloro-5-iodo-2-methylbenzoate (*Example 13, step 3*) (1.4 g, 4.3 mmol) was dissolved in 10 ml of dioxane. Nitrosonium tetrafluoroborate (0.55 g, 4.74 mmol, 1.1 equiv.) was added in portion and under ice cooling at room temperature. The mixture was stirred at room
- 20 temperature for 30 minutes and at 110°C for 90 minutes. The reaction mixture was poured onto water and extracted twice with ethyl acetate. The organic layers were extracted with brine, dried over sodium sulfate and concentrated to dryness. The crude product was purified by flash chromatography on a silica gel column eluting with a heptane:ethyl acetate 100:0 to 75:25 gradient to obtain the desired methyl 2-chloro-5-fluoro-3-iodo-6-methylbenzoate (696 mg, 49 % yield) as
- 25 a colorless oil, MS: $m/e = 327.1/329.1$ ($M-H^+$).

Step 5: Methyl 2-(bromomethyl)-6-chloro-3-fluoro-5-iodobenzoate



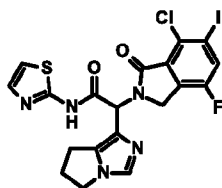
The title compound was obtained as a colorless solid, MS: $m/e = 409.0$ ($M+H^+$), using chemistry similar to that described in Example 1, step 5 starting from methyl 2-chloro-5-fluoro-3-iodo-6-methylbenzoate (*Example 13, step 4*).

Step 6: Ethyl (2*RS*)-2-(7-chloro-4-fluoro-6-iodo-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)acetate



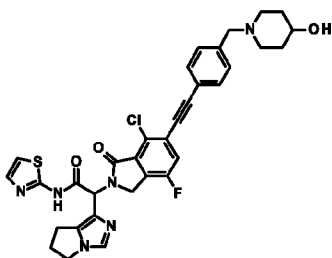
The title compound was obtained as a brown solid, MS: $m/e = 504.1/506.1$ ($M+H^+$), using chemistry similar to that described in Example 1, step 6 starting from ethyl (2*RS*)-2-amino-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)acetate hydrochloride (*Example 1, step 4*) and methyl 2-(bromomethyl)-6-chloro-3-fluoro-5-iodobenzoate (*Example 13, step 5*).

Step 7: (2*RS*)-2-(7-Chloro-4-fluoro-6-iodo-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide



The title compound was obtained as a light yellow solid, MS: $m/e = 558.1/560.1$ ($M+H^+$), using chemistry similar to that described in Example 3, step 2 starting from ethyl (2*RS*)-2-(7-chloro-4-fluoro-6-iodo-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)acetate (*Example 13, step 6*) and thiazol-2-amine.

Step 8: (2*RS*)-2-[7-Chloro-4-fluoro-6-[2-[4-[(4-hydroxy-1-piperidyl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide



The title compound was obtained as a light brown solid, MS: $m/e = 645.3/647.3$ ($M+H^+$), using chemistry similar to that described in Example 1, step 9 starting from (2*RS*)-2-(7-chloro-4-fluoro-6-iodo-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-

2-yl-acetamide (*Example 13, step 7*) and 1-[(4-ethynylphenyl)methyl]piperidin-4-ol (*Example 9, step 1*).

Example 14

5 **(2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-1-oxo-6-[2-[4-(1-piperidylmethyl)phenyl]ethynyl]isoindolin-2-yl]-N-thiazol-2-yl-acetamide**

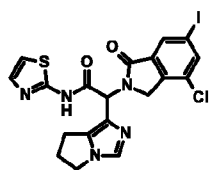
The title compound was obtained as a light yellow semisolid, MS: $m/e = 595.4$ ($M+H^+$), using chemistry similar to that described in Example 1, step 10 starting from (2*RS*)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-6-[2-(4-formylphenyl)ethynyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide (*Example 1, step 9*) and piperidine.

10

Example 15

(2*RS*)-2-[4-Chloro-1-oxo-6-[2-[4-(1-piperidylmethyl)phenyl]ethynyl]isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide

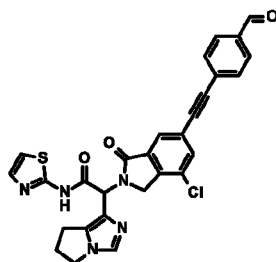
Step 1: (2*RS*)-2-(4-Chloro-6-iodo-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide



15

The title compound was obtained as a yellow foam, MS: $m/e = 540.1/542.1$ ($M+H^+$), using chemistry similar to that described in Example 3, step 2 starting from ethyl (2*RS*)-2-(4-chloro-6-iodo-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (*Example 9, step 4*) and thiazol-2-amine.

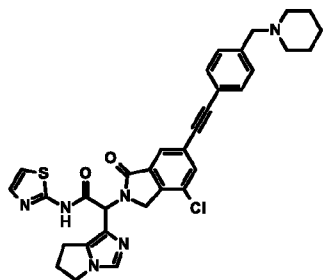
20 Step 2: (2*RS*)-2-[4-Chloro-6-[2-(4-formylphenyl)ethynyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide



The title compound was obtained as a yellow foam, MS: $m/e = 542.3/544.3$ ($M+H^+$), using chemistry similar to that described in Example 1, step 9 starting from (2*RS*)-2-(4-chloro-6-iodo-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide (*Example 15, step 1*) and 4-ethynylbenzaldehyde.

25

Step 3: (2RS)-2-[4-Chloro-1-oxo-6-[2-[4-(1-piperidylmethyl)phenyl]ethynyl]isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide

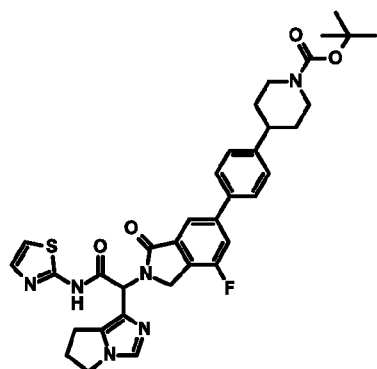


The title compound was obtained as a light yellow solid, MS: $m/e = 611.5/613.5$ ($M+H^+$), using chemistry similar to that described in Example 1, step 10 starting from (2RS)-2-[4-chloro-6-[2-(4-formylphenyl)ethynyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide (*Example 15, step 2*) and piperidine.

Example 16

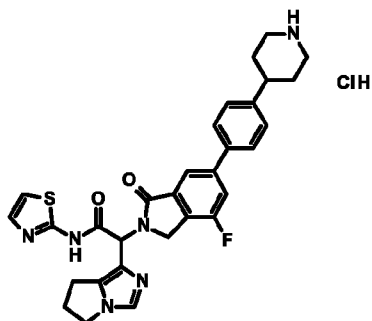
(2RS)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[6-[4-(1-ethyl-4-piperidyl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide

Step 1: tert-Butyl 4-[4-[2-[(1RS)-1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-oxo-2-(thiazol-2-ylamino)ethyl]-7-fluoro-3-oxo-isoindolin-5-yl]phenyl]piperidine-1-carboxylate



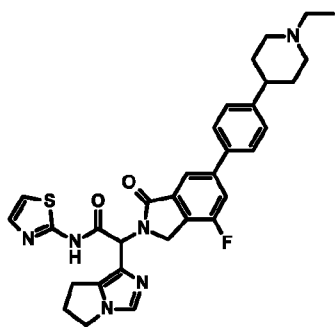
The title compound was obtained as a brown solid, MS: $m/e = 657.5$ ($M+H^+$), using chemistry similar to that described in Example 3, step 1 starting from (2RS)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide (*Example 10, step 5*) and (4-(1-(tert-butoxycarbonyl)piperidin-4-yl)phenyl)boronic acid.

Step 2: (2RS)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-1-oxo-6-[4-(4-piperidyl)phenyl]isoindolin-2-yl]-N-thiazol-2-yl-acetamide hydrochloride



The title compound was obtained as a yellow solid, MS: $m/e = 557.4$ ($M+H^+$), using chemistry similar to that described in Example 3, step 3 starting from tert-butyl 4-[4-[2-[(1RS)-1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-oxo-2-(thiazol-2-ylamino)ethyl]-7-fluoro-3-oxo-isoindolin-5-yl]phenyl]piperidine-1-carboxylate (*Example 16, step 1*).

Step 3: (2RS)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[6-[4-(1-ethyl-4-piperidyl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide

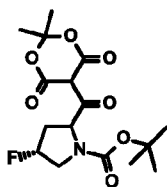


The title compound was obtained as a white solid, MS: $m/e = 585.4$ ($M+H^+$), using chemistry similar to that described in Example 4, step 4 starting from (2RS)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-1-oxo-6-[4-(4-piperidyl)phenyl]isoindolin-2-yl]-N-thiazol-2-yl-acetamide hydrochloride (*Example 16, step 2*) and ethyliodide.

Example 17

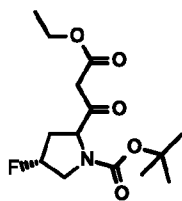
(2RS)-2-[(6R)-6-Fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-[4-fluoro-6-[2-[4-[(4-hydroxy-1-piperidyl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide

Step 1: tert-Butyl (2RS,4R)-2-(2,2-dimethyl-4,6-dioxo-1,3-dioxane-5-carbonyl)-4-fluoro-pyrrolidine-1-carboxylate



To a solution of (2S,4R)-1-tert-butoxycarbonyl-4-fluoro-pyrrolidine-2-carboxylic acid (450.0 g, 1.93 mol, 1.00 eq.) and 2,2-dimethyl-1,3-dioxane-4,6-dione (278.0 g, 1.93 mol, 1.00eq.) in dichloromethane (3.00 L) was added DMAP (471.4 g, 3.86 mol, 2.00 eq.) and the mixture was cooled down to 0 °C. DCC (398.0 g, 1.93 mol, 390.3 mL, 1.00 eq.) was added in several portions and the reaction mixture was stirred at 25 °C for 12 hours. The reaction mixture was filtered and then the filtrate was washed with 1M HCl (2.00 L) and then organic layer were concentrated in vacuum to give the desired product (1.20 kg, 3.34 mol, 86.5% yield) as a yellow solid used directly for next step.

Step 2: tert-Butyl (2RS,4R)-2-(3-ethoxy-3-oxo-propanoyl)-4-fluoro-pyrrolidine-1-carboxylate

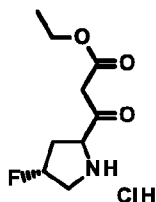


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A mixture of tert-butyl (2RS,4R)-2-(2,2-dimethyl-4,6-dioxo-1,3-dioxane-5-carbonyl)-4-fluoro-pyrrolidine-1-carboxylate (*Example 17, step 1*) (650.0 g, 1.81 mol, 1.00 eq.) in EtOH (2.00 L) was stirred at 95 °C for 12 hours. The reaction mixture was concentrated under reduced pressure to yield the desired product as a light yellow oil (1.00 kg, 3.30 mol, 91.1% yield) which was used for next step directly.

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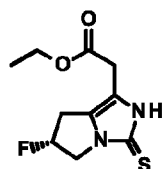
Step 3: Ethyl 3-[(2RS,4R)-4-fluoropyrrolidin-2-yl]-3-oxo-propanoate hydrochloride



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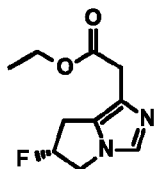
A mixture of tert-butyl (2RS,4R)-2-(3-ethoxy-3-oxo-propanoyl)-4-fluoro-pyrrolidine-1-carboxylate (320.0 g, 1.05 mol, 1.00 eq.) and HCl/EtOAc (4.00 M, 800.0 mL, 3.03 eq.) was stirred at 25 °C for 2 hours. The reaction mixture was concentrated under reduced pressure to give the desired product (603.0 g, 2.97 mol, 93.8% yield) as a red oil that was used directly for next reaction without further purification.

Step 4: Ethyl 2-[(6R)-6-fluoro-3-thioxo-2,5,6,7-tetrahydropyrrolo[1,2-c]imidazol-1-yl]acetate



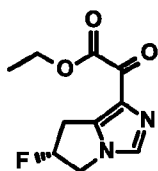
To a solution of ethyl 3-[(2RS,4R)-4-fluoropyrrolidin-2-yl]-3-oxo-propanoate hydrochloride (200.0 g, 834.5 mmol, 1.00 eq., HCl) in EtOH (1.20 L), KSCN (89.20 g, 917.9 mmol, 89.2 mL, 1.10 eq.) was added and the mixture was heated to 90 °C and stirred for 12 hours. The mixture was concentrated in vacuum to give a crude solid. The crude solid was washed with EtOAc (5.00 L) and H₂O (3.00 L) and concentrated in vacuum to give compound 5 (555.0 g, 2.27 mol, 90.7% yield) as a white solid.

Step 5: Ethyl 2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate



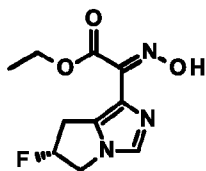
A mixture of ethyl 2-[(6R)-6-fluoro-3-thioxo-2,5,6,7-tetrahydropyrrolo[1,2-c]imidazol-1-yl]acetate (285.0 g, 1.17 mol, 1.00 eq.) in AcOH (1.14 L) was added H₂O₂ (529.1 g, 4.67 mol, 448.4 mL, 30% purity, 4.00 eq.) dropwise at 0-25 °C. The reaction mixture was stirred at 25 °C for 30 minutes. The reaction mixture was diluted with water (4.00 L) and then adjusted to pH = 9 by addition of solid NaHCO₃ at 0 °C. The mixture was extracted six times with DCM (1.00 L each). The combined organic layers were washed with saturated NaCl solution (3.00 L) and the combined organic layers washed three times with saturated Na₂S₂O₃ solution (2.00 L each). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the desired product (156.0 g, crude) as a brown oil.

Step 6: Ethyl 2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-oxo-acetate



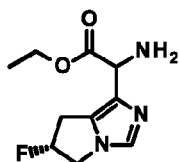
To a solution of ethyl 2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate (42.3 g, 199.3 mmol, 1.00 eq.) in dioxane (450.0 mL), SeO₂ (44.2 g, 398.6 mmol, 43.3 mL, 2.00 eq.) was added and the mixture was heated to 80 °C and stirred for 2 hours. The mixture was added silica gel and concentrated to give a residue which was purified with silica gel chromatography pure EtOAc to give the desired product (54.0 g, 238.7 mmol, 59.8% yield) as a black brown oil.

Step 7: Ethyl 2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-hydroxyimino-acetate



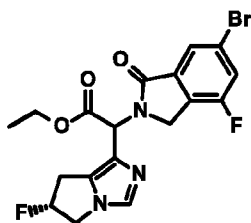
To a solution of ethyl 2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-oxoacetate (18.6 g, 82.2 mmol, 1.00 eq.) in EtOH (90.0 mL) was added NaOAc (13.5 g, 164.5 mmol, 2.00 eq.) and NH₂OH·HCl (6.30 g, 90.5 mmol, 1.10 eq.) The reaction mixture was stirred at 80 °C for 2 hours. The mixture was cooled to 25 °C and filtered then concentrated to give a residue which was diluted with EtOAc: EtOH (20:1)(300.0 mL) and washed with water (200.0 mL) and saturated NaCl solution (200.0 mL), dried with anhydrous Na₂SO₄ to give the desired product (18.0 g, 74.6 mmol, 90.8% yield) as a black brown oil which was used directly without further purification.

Step 8: Ethyl (2RS)-2-amino-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate



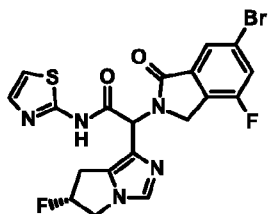
A solution of ethyl 2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-hydroxyiminoacetate (18.0 g, 70.9 mmol, 1.00 eq.) and Pd/C (36.0 g, 10% purity) in THF (90.0 mL) and EtOH (180.0 mL) was stirred at 50 °C for 16 h under H₂ (15.0 Psi). The mixture was filtered and the filter cake was washed with EtOAc. The filtrate was concentrated to give the desired product (11.0 g, 43.3 mmol, 61.1% yield, 89.5% purity) as a green oil.

Step 9: Ethyl (2RS)-2-(6-bromo-4-fluoro-1-oxo-isindolin-2-yl)-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate



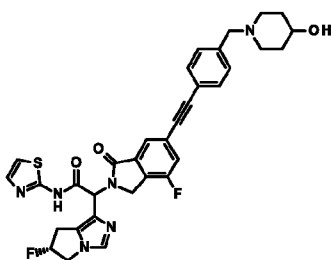
The title compound was obtained as a dark brown oil, MS: m/e = 442.0 (M+H⁺), using chemistry similar to that described in Example 1, step 6 starting from ethyl (2RS)-2-amino-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate (*Example 17, step 8*) and methyl 5-bromo-2-(bromomethyl)-3-fluorobenzoate (*Example 1, step 5*).

Step 10: (2RS)-2-(6-Bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide



The title compound was obtained as a dark brown solid, MS: $m/e = 494.2/496.2$ ($M+H^+$), using chemistry similar to that described in Example 3, step 2 starting from ethyl (2RS)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate (Example 17, step 9) and thiazol-2-amine.

Step 11: (2RS)-2-[(6R)-6-Fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-[4-fluoro-6-[2-[4-[(4-hydroxy-1-piperidyl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide

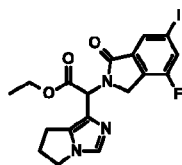


The title compound was obtained as a white solid, MS: $m/e = 627.5$ ($M+H^+$), using chemistry similar to that described in Example 1, step 9 starting from (2RS)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide (Example 17, step 10) and 1-[(4-ethynylphenyl)methyl]piperidin-4-ol (Example 9, step 1).

Example 18

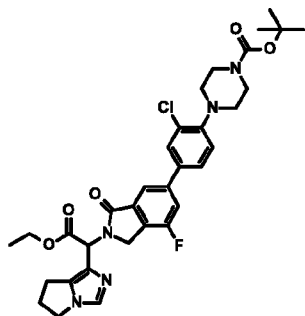
(2RS)-2-[6-[3-Chloro-4-(4-ethylpiperazin-1-yl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide

Step 1: Ethyl (2RS)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-(4-fluoro-6-iodo-1-oxo-isoindolin-2-yl)acetate



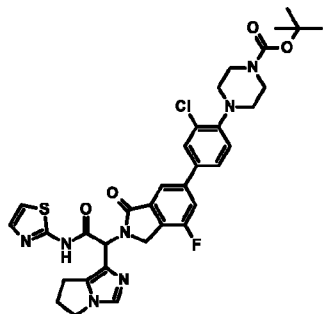
The title compound was obtained as a white solid using chemistry similar to that described in Example 1, step 5 and 6 starting from ethyl (2*RS*)-2-amino-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)acetate hydrochloride (*Example 1, step 4*) and methyl 5-iodo-3-fluoro-2-methylbenzoate instead of methyl 5-bromo-3-fluoro-2-methylbenzoate.

5 Step 2: tert-Butyl 4-[2-chloro-4-[2-[(1*RS*)-1-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-ethoxy-2-oxo-ethyl]-7-fluoro-3-oxo-isoindolin-5-yl]phenyl]piperazine-1-carboxylate



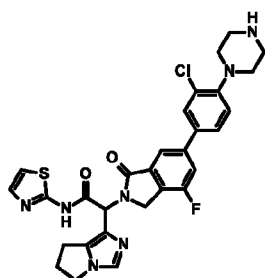
Ethyl (2*RS*)-2-(6-iodo-4-fluoro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)acetate (*Example 18, step 1*) (400 mg, 0.85 mmol) and (4-(4-(tert-
10 butoxycarbonyl)piperazin-1-yl)-3-chlorophenyl)boronic acid (348 mg, 1.02 mmol, 1.2 equiv.) were dissolved in toluene. Cesium carbonate (830 mg, 2.56 mmol, 3.0 equiv.) and PdCl₂(DPPF)-CH₂Cl₂ adduct (62 mg, 0.085 mmol, 0.1 equiv.) were added and the reaction mixture was stirred at 100°C for 1 hour. The reaction mixture was cooled to room temperature and then extracted with ethyl acetate and saturated NaHCO₃-solution. The aqueous layer was back-extracted with ethyl
15 acetate. The organic layers were washed with water and brine. The organic layers were combined, dried over sodium sulfate, filtered and concentrated to dryness. The crude product was purified by flash chromatography on a silica gel column eluting with a dichloromethane:methanol 100:0 to 90:10 gradient. The desired tert-Butyl 4-[2-chloro-4-[2-[(1*RS*)-1-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-ethoxy-2-oxo-ethyl]-7-fluoro-3-oxo-isoindolin-5-yl]phenyl]piperazine-1-
20 carboxylate (580 mg, 96 % yield) was obtained as a light brown oil, MS: *m/e* = 638.3/640.3 (M+H⁺).

Step 3: tert-Butyl 4-[2-chloro-4-[2-[(1*RS*)-1-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-oxo-2-(thiazol-2-ylamino)ethyl]-7-fluoro-3-oxo-isoindolin-5-yl]phenyl]piperazine-1-carboxylate



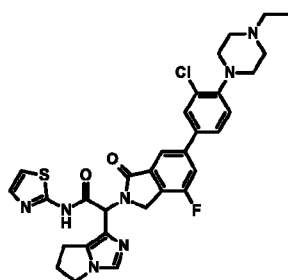
The title compound was obtained as a light brown oil, MS: $m/e = 692.3/694.3$ ($M+H^+$), using chemistry similar to that described in Example 3, step 2 starting from tert-butyl 4-[2-chloro-4-[2-[(1S)-1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-ethoxy-2-oxo-ethyl]-7-fluoro-3-oxo-isoindolin-5-yl]phenyl]piperazine-1-carboxylate (*Example 18, step 2*) and thiazol-2-amine.

Step 4: (2RS)-2-[6-(3-Chloro-4-piperazin-1-yl-phenyl)-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide



The title compound was obtained as a white solid, MS: $m/e = 592.4/594.3$ ($M+H^+$), using chemistry similar to that described in Example 4, step 3 starting from tert-butyl 4-[2-chloro-4-[2-[(1RS)-1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-oxo-2-(thiazol-2-ylamino)ethyl]-7-fluoro-3-oxo-isoindolin-5-yl]phenyl]piperazine-1-carboxylate (*Example 18, step 3*).

Step 5: (2RS)-2-[6-[3-Chloro-4-(4-ethylpiperazin-1-yl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide



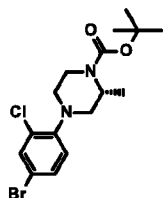
The title compound was obtained as a light yellow solid, MS: $m/e = 620.4/622.4$ ($M+H^+$), using chemistry similar to that described in Example 4, step 4 starting from (2RS)-2-[6-(3-chloro-

4-piperazin-1-yl-phenyl)-4-fluoro-1-oxo-isindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide (*Example 18, step 4*) and iodoethane.

Example 19

(2RS)-2-[6-[3-Chloro-4-[(3R)-3-methylpiperazin-1-yl]phenyl]-4-fluoro-1-oxo-isindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide

Step 1: tert-Butyl (2R)-4-(4-bromo-2-chloro-phenyl)-2-methyl-piperazine-1-carboxylate



4-Bromo-2-chloro-1-iodobenzene (3.1 g, 10 mmol) and tert-butyl (R)-2-methylpiperazine-1-carboxylate (2.0 g, 10 mmol, 1.0 equiv.) were dissolved in toluene. Sodium tert-butoxide (1.9 g,

20 mmol, 2.0 equiv.), XantPhos (578 mg, 1 mmol, 0.1 equiv.) and tris(dibenzylideneacetone)dipalladium (0) (457 mg, 0.5 mmol, 0.05 equiv.) were added and the

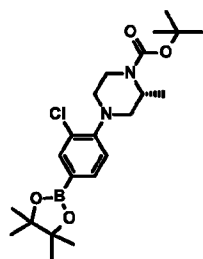
reaction mixture was stirred at 85°C for 16 hours. The reaction mixture was cooled to room temperature and then extracted with ethyl acetate and water. The aqueous layer was back-

extracted with ethyl acetate. The organic layers were washed with water and brine. The organic

layers were combined, dried over sodium sulfate, filtered and concentrated to dryness. The crude product was purified by flash chromatography on a silica gel column eluting with a hexane:ethyl acetate 100:0 to 90:10 gradient. The desired product (1.9 g, 39 % yield) was obtained as a yellow oil, MS: m/e = 389.1/391.1 (M+H⁺).

Step 2: tert-Butyl (2R)-4-[2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-

methyl-piperazine-1-carboxylate



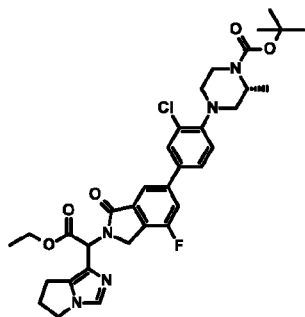
tert-Butyl (2R)-4-(4-bromo-2-chloro-phenyl)-2-methyl-piperazine-1-carboxylate (*Example 19, step 1*) (1.7 g, 3.85 mmol, 1.0 equiv.) and bis(pinacolato)diboron (1.17 g, 4.6 mmol, 1.2 equiv.)

were dissolved in dioxane. Potassium acetate (1.1 g, 11.6 mmol, 3.0 equiv.) and dichloro 1,1'-

bis(diphenylphosphino)ferrocene palladium(II) dichloromethane adduct (315 mg, 0.39 mmol, 0.1 equiv.) were added and the reaction mixture was stirred at 90°C for 16 hours. The reaction

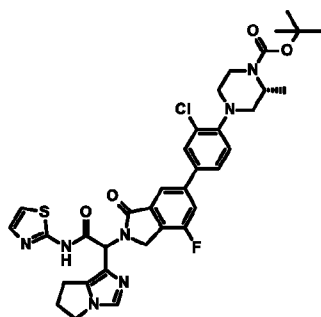
mixture was cooled to room temperature and concentrated to dryness. The crude product was purified by flash chromatography on a silica gel column eluting with a hexane:ethyl acetate 100:0 to 90:10 gradient. The desired product (930 mg, 53 % yield) was obtained as a light yellow foam, MS: $m/e = 437.4/439.4$ ($M+H^+$).

- 5 Step 3: tert-Butyl (2RS)-4-[2-chloro-4-[2-[(1S)-1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-ethoxy-2-oxo-ethyl]-7-fluoro-3-oxo-isoindolin-5-yl]phenyl]-2-methyl-piperazine-1-carboxylate



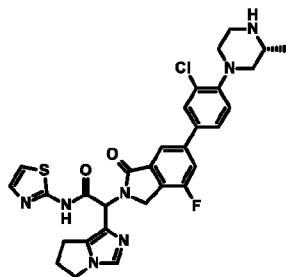
- The title compound was obtained as a light brown foam, MS: $m/e = 652.5/654.5$ ($M+H^+$),
 10 using chemistry similar to that described in Example 18, step 2 starting from Ethyl (2RS)-2-(6-iodo-4-fluoro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (Example 18, step 1) and tert-butyl (2R)-4-[2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-methyl-piperazine-1-carboxylate (Example 19, step 2).

- Step 4: tert-Butyl (2RS)-4-[2-chloro-4-[2-[(1S)-1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-oxo-2-(thiazol-2-ylamino)ethyl]-7-fluoro-3-oxo-isoindolin-5-yl]phenyl]-2-methyl-piperazine-1-carboxylate



- The title compound was obtained as a brown solid, MS: $m/e = 706.4/708.3$ ($M+H^+$), using
 chemistry similar to that described in Example 3, step 2 starting from tert-butyl (2RS)-4-[2-chloro-
 20 4-[2-[(1S)-1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-ethoxy-2-oxo-ethyl]-7-fluoro-3-oxo-isoindolin-5-yl]phenyl]-2-methyl-piperazine-1-carboxylate (Example 19, step 3) and thiazol-2-amine.

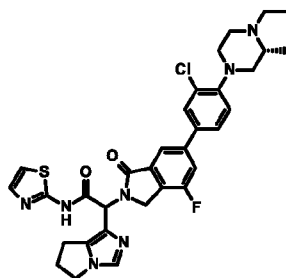
Step 5: (2RS)-2-[6-[3-Chloro-4-[(3R)-3-methylpiperazin-1-yl]phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide



The title compound was obtained as a light yellow solid, MS: $m/e = 606.3/608.3$ ($M+H^+$), using chemistry similar to that described in Example 4, step 3 starting from tert-butyl (2RS)-4-[2-chloro-4-[2-[(1S)-1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-oxo-2-(thiazol-2-ylamino)ethyl]-7-fluoro-3-oxo-isoindolin-5-yl]phenyl]-2-methyl-piperazine-1-carboxylate (Example 19, step 4).

Example 20

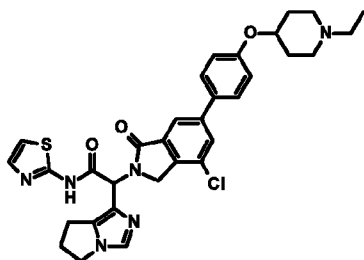
(2RS)-2-[6-[3-Chloro-4-[(3R)-4-ethyl-3-methyl-piperazin-1-yl]phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide



The title compound was obtained as a white foam, MS: $m/e = 634.5/536.5$ ($M+H^+$), using chemistry similar to that described in Example 4, step 4 starting from (2RS)-2-[6-[3-chloro-4-[(3R)-3-methylpiperazin-1-yl]phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide (Example 19, step 5) and iodoethane.

Example 21

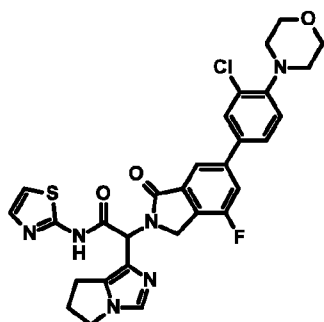
(2RS)-2-[4-Chloro-6-[4-[(1-ethyl-4-piperidyl)oxy]phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide



The title compound was obtained as a white solid, MS: $m/e = 617.4/619.4$ ($M+H^+$), using chemistry similar to that described in Example 18, step 2, Example 3, step 2, Example 4, step 3 and step 4 starting from ethyl (2RS)-2-(4-chloro-6-iodo-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (Example 9, step 4) and tert-butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine-1-carboxylate.

Example 22

(2RS)-2-[6-(3-Chloro-4-morpholino-phenyl)-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide



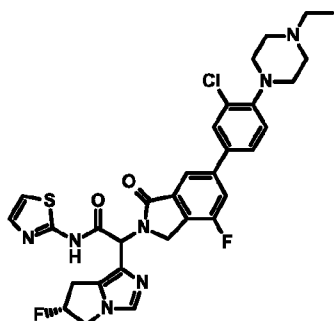
10

The title compound was obtained as a white solid, MS: $m/e = 593.3/595.3$ ($M+H^+$), using chemistry similar to that described in Example 18, step 2 and Example 3, step 2 starting from ethyl (2RS)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (Example 1, step 6) and (3-chloro-4-morpholinophenyl)boronic acid.

15

Example 23

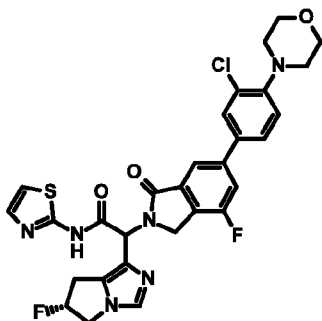
(2RS)-2-[6-[3-Chloro-4-(4-ethylpiperazin-1-yl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide



The title compound was obtained as a light yellow solid, MS: $m/e = 638.5/640.3$ ($M+H^+$), using chemistry similar to that described in Example 18, step 2, Example 3, step 2, Example 4, step 3 and step 4 starting from ethyl (2RS)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate (*Example 17, step 9*) and 4-(4-(tert-butoxycarbonyl)piperazin-1-yl)-3-chlorophenyl)boronic acid.

Example 24

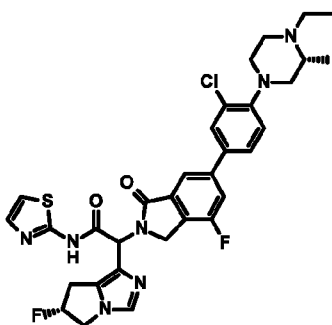
(2RS)-2-[6-(3-Chloro-4-morpholino-phenyl)-4-fluoro-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide



10 The title compound was obtained as a yellow foam, MS: $m/e = 611.3/613.3$ ($M+H^+$), using chemistry similar to that described in Example 18, step 2 and Example 3, step 2 starting from ethyl (2RS)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate (*Example 17, step 9*) and (3-chloro-4-morpholinophenyl)boronic acid.

Example 25

15 **(2RS)-2-[6-[3-Chloro-4-[(3R)-4-ethyl-3-methyl-piperazin-1-yl]phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide**



20 The title compound was obtained as a yellow foam, MS: $m/e = 652.4/654.2$ ($M+H^+$), using chemistry similar to that described in Example 18, step 2, Example 3, step 2, Example 4, step 3 and step 4 starting from ethyl (2RS)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate (*Example 17, step 9*) and tert-butyl

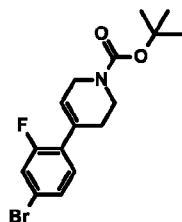
(2R)-4-[2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-methyl-piperazine-1-carboxylate (*Example 19, step 2*).

Example 26

(2RS)-2-[6-[4-(1-Ethyl-4-piperidyl)-3-fluoro-phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-

5 [(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide

Step 1: tert-Butyl 4-(4-bromo-2-fluoro-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylate



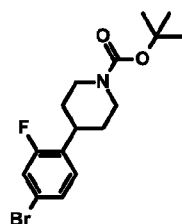
4-Bromo-2-fluoro-1-iodo-benzene (*CAS 105931-73-5*) (2.19 g, 7.28 mmol, 1.5 equiv.)

and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-

10 carboxylate (*CAS 286961-14-6*) (1.50 g, 4.85 mmol) were dissolved in 20 ml of dioxane. Sodium carbonate (2M in water) (7.28 ml, 14.6 mmol, 3.0 equiv.) and PdCl₂(dppf)-CH₂Cl₂ adduct (355 mg, 0.485 mmol, 0.1 equiv.) were added and the reaction mixture was stirred at 110 °C for 2 hours. The reaction mixture was cooled to room temperature and then extracted with ethyl acetate and saturated NaHCO₃-solution. The aqueous layer was backextracted with ethyl acetate.

15 The organic layers were washed with water. The organic layers were combined, dried over sodium sulfate, filtered and concentrated to dryness. The crude product was purified by flash chromatography on a silica gel column eluting with an ethyl acetate:heptane 0:100 to 70:30 gradient. The desired tert-butyl 4-(4-bromo-2-fluoro-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylate (1.35 g, 78 % yield) was obtained as a colorless oil, MS: m/e = 300.0/302.0 (M-tBu+H⁺).

Step 2: tert-Butyl 4-(4-bromo-2-fluoro-phenyl)piperidine-1-carboxylate



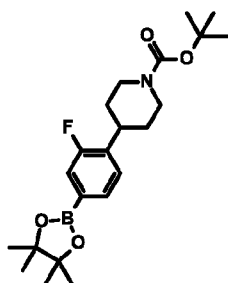
tert-Butyl 4-(4-bromo-2-fluoro-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylate

(*Example 26, step 1*) (820 mg, 2.3 mmol) was dissolved in 5 ml of ethyl acetate and put under

25 an argon atmosphere. Platinum (IV) oxide (35mg, 0.154 mmol, 0.07 equiv., purity = 80 %) was added at room temperature. The mixture was stirred at room temperature for 16 hours under an

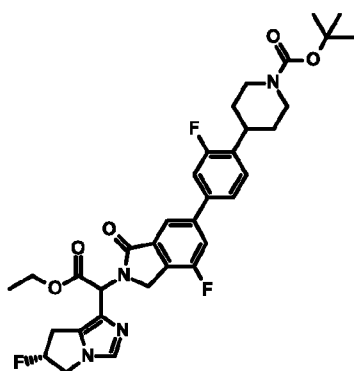
hydrogen atmosphere. Platinum (IV) oxide (35mg, 0.154 mmol, 0.07 equiv., purity = 80 %) was added and the hydrogenation continued for 4 hours. The reaction mixture was put under an argon atmosphere filtered and concentrated to dryness. The desired tert-butyl 4-(4-bromo-2-fluorophenyl)piperidine-1-carboxylate (820 mg, 85 % yield, purity = 85 %) was obtained as a colorless oil, MS: m/e = 302.0/304.0 (M-tBu+H⁺).

Step 3: tert-Butyl 4-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine-1-carboxylate



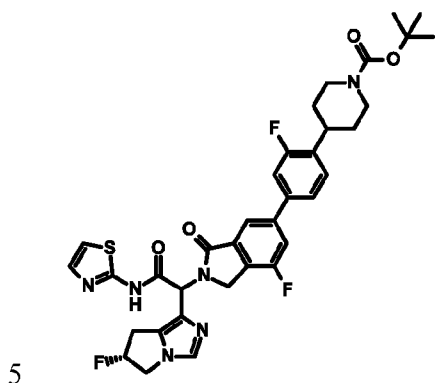
The title compound was obtained as a colorless oil, MS: m/e = 350.0 (M-tBu+H⁺), using chemistry similar to that described in Example 19, step 2 starting from tert-butyl 4-(4-bromo-2-fluorophenyl)piperidine-1-carboxylate (*Example 26, step 2*).

Step 4: tert-Butyl 4-[4-[2-[(1RS)-2-ethoxy-1-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-oxo-ethyl]-7-fluoro-3-oxo-isoindolin-5-yl]-2-fluoro-phenyl]piperidine-1-carboxylate



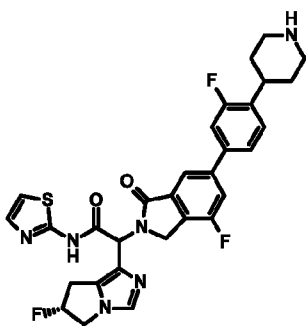
The title compound was obtained as a yellow oil, MS: m/e = 639.7 (M+H⁺), using chemistry similar to that described in Example 18, step 2 starting from ethyl (2RS)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate (*Example 17, step 9*) and tert-butyl 4-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine-1-carboxylate (*Example 26, step 3*).

Step 5: tert-Butyl 4-[2-fluoro-4-[7-fluoro-2-[(1RS)-1-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-oxo-2-(thiazol-2-ylamino)ethyl]-3-oxo-isoindolin-5-yl]phenyl]piperidine-1-carboxylate



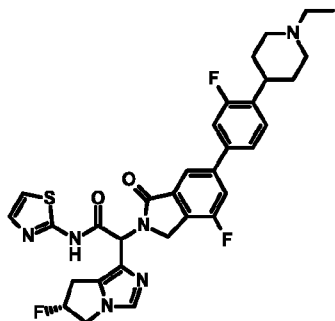
The title compound was obtained as a light brown solid, MS: $m/e = 693.5$ ($M+H^+$), using chemistry similar to that described in Example 3, step 2 starting from tert-butyl 4-[4-[2-[(1RS)-2-ethoxy-1-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-oxo-ethyl]-7-fluoro-3-oxo-isoindolin-5-yl]-2-fluoro-phenyl]piperidine-1-carboxylate (*Example 26, step 4*) and thiazol-2-amine.

Step 6: (2RS)-2-[(6R)-6-Fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-[4-fluoro-6-[3-fluoro-4-(4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide



The title compound was obtained as a yellow solid, MS: $m/e = 593.3$ ($M+H^+$), using chemistry similar to that described in Example 3, step 3 starting from tert-butyl 4-[2-fluoro-4-[7-fluoro-2-[(1RS)-1-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-oxo-2-(thiazol-2-ylamino)ethyl]-3-oxo-isoindolin-5-yl]phenyl]piperidine-1-carboxylate (*Example 26, step 5*).

Step 7: (2RS)-2-[6-[4-(1-Ethyl-4-piperidyl)-3-fluoro-phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide

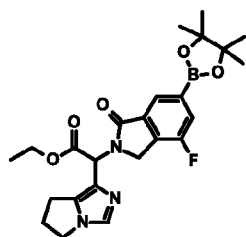


The title compound was obtained as an off-white solid, MS: $m/e = 621.3$ ($M+H^+$), using chemistry similar to that described in Example 4, step 4 starting from (2RS)-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-[4-fluoro-6-[3-fluoro-4-(4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide (*Example 26, step 6*) and ethyl iodide.

Example 27

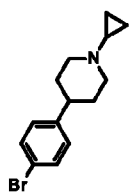
(2RS)-2-[6-[4-(1-Cyclopropyl-4-piperidyl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide

Step 1: Ethyl (2RS)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-1-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-2-yl]acetate



The title compound was obtained as a brown oil, MS: $m/e = 470.3$ ($M+H^+$), using chemistry similar to that described in Example 19, step 2 starting from ethyl (2RS)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (*Example 1, step 6*).

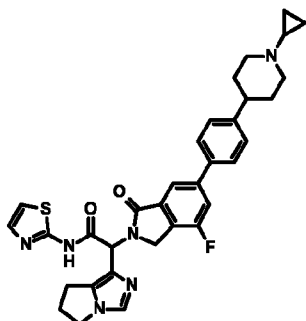
Step 2: 4-(4-Bromophenyl)-1-cyclopropyl-piperidine



4-(4-Bromophenyl)piperidine (0.6 g, 2.5 mmol) was dissolved in 5.6 ml of THF and 5.6 ml of methanol. (1-Ethoxycyclopropoxy)trimethylsilane (1.0 ml, 867 mg, 5.0 mmol, 2 equiv.), sodium cyanoborohydride (239 mg, 3.8 mmol, 1.5 equiv.) and acetic acid (0.24 ml, 4.2 mmol, 1.7 equiv.) were added and the reaction mixture was stirred at 50°C for 16 hours. The reaction mixture was cooled to room temperature and then extracted with dichloromethane and 2N

sodium hydroxide. The aqueous layer was back-extracted with dichloromethane. The organic layers were washed with water and brine. The organic layers were combined, dried over sodium sulfate, filtered and concentrated to dryness. The crude product was purified by flash chromatography on a silica gel column eluting with a hexane:ethyl acetate 100:0 to 70:30 gradient. The desired product (609 mg, 83 % yield) was obtained as a yellow solid, MS: $m/e = 280.1/281.8$ ($M+H^+$).

Step 3: (2RS)-2-[6-[4-(1-Cyclopropyl-4-piperidyl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide



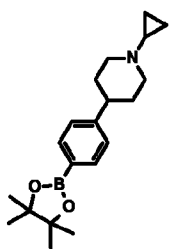
The title compound was obtained as a brown foam, MS: $m/e = 597.5$ ($M+H^+$), using chemistry similar to that described in Example 18, step 2 and Example 3, step 2 starting from ethyl (2RS)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-1-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-2-yl]acetate (*Example 27, step 1*) and 4-(4-bromophenyl)-1-cyclopropylpiperidine (*Example 27, step 2*).

15

Example 28

(2RS)-2-[4-Chloro-6-[4-(1-cyclopropyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide

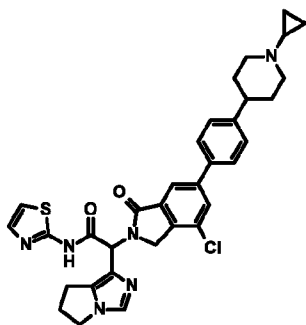
Step 1: 1-Cyclopropyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine



20

The title compound was obtained as a light brown solid, MS: $m/e = 328.2$ ($M+H^+$), using chemistry similar to that described in Example 19, step 2 starting from 4-(4-bromophenyl)-1-cyclopropylpiperidine (*Example 27, step 2*).

Step 2: (2RS)-2-[4-Chloro-6-[4-(1-cyclopropyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide

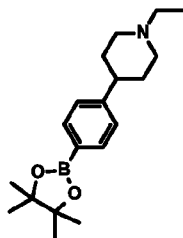


The title compound was obtained as a yellow solid, MS: $m/e = 613.3/615.3$ ($M+H^+$), using chemistry similar to that described in Example 18, step 2 and Example 3, step 2 starting from ethyl (2RS)-2-(4-chloro-6-iodo-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (*Example 9, step 4*) and 1-cyclopropyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine (*Example 28, step 1*).

Example 29

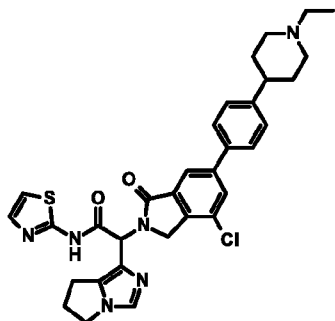
10 **(2RS)-2-[4-Chloro-6-[4-(1-ethyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide**

Step 1: 1-Ethyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine



The title compound was obtained as a brown solid, MS: $m/e = 316.2$ ($M+H^+$), using chemistry similar to that described in Example 4, step 4 and Example 19, step 2 starting from 4-(4-bromophenyl)piperidine and iodoethane.

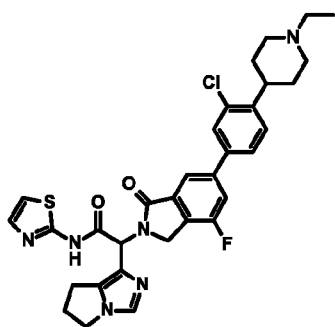
Step 2: (2RS)-2-[4-Chloro-6-[4-(1-ethyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide



The title compound was obtained as a white solid, MS: $m/e = 601.3/603.1$ ($M+H^+$), using chemistry similar to that described in Example 18, step 2 and Example 3, step 2 starting from ethyl (2RS)-2-(4-chloro-6-iodo-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (Example 9, step 4) and 1-ethyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine (Example 29, step 1).

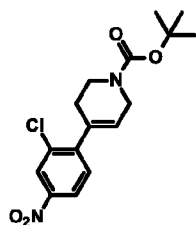
Example 30

(2RS)-2-[6-[3-Chloro-4-(1-ethyl-4-piperidyl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide



10

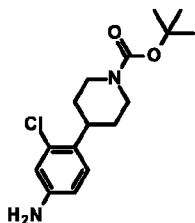
Step 1: tert-Butyl 4-(2-chloro-4-nitro-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylate



15

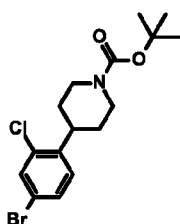
The title compound was obtained as a yellow oil using chemistry similar to that described in Example 18, step 2 starting from 1-bromo-2-chloro-4-nitro-benzene (CAS 29682-39-1) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (CAS 286961-14-6).

Step 2: tert-Butyl 4-(4-amino-2-chloro-phenyl)piperidine-1-carboxylate



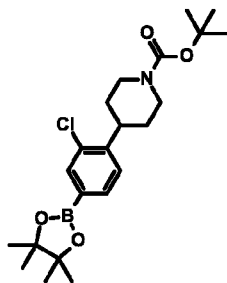
tert-Butyl 4-(2-chloro-4-nitro-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylate (*Example 30, step 1*) (1.56 g, 4.6 mmol) was dissolved in 25 ml of ethyl acetate and Pd-C (0.160 g, 1.5 mmol, 0.327 equiv.) was added at room temperature. The reaction mixture was stirred at room temperature for 16 hours under an hydrogen atmosphere. The reaction mixture was put under an argon atmosphere, filtered and concentrated to dryness. The reaction was put on again with platinum (IV) oxide (160 mg) as catalysator. The mixture was stirred at room temperature for 16 hours under an hydrogen atmosphere. The reaction mixture was put under an argon atmosphere, filtered and concentrated to dryness. The desired tert-butyl 4-(4-amino-2-chloro-phenyl)piperidine-1-carboxylate (1.20 g, 84 % yield) was obtained as a colorless oil, MS: m/e = 255.1 (M-tBu+H⁺).

Step 3: tert-Butyl 4-(4-bromo-2-chloro-phenyl)piperidine-1-carboxylate



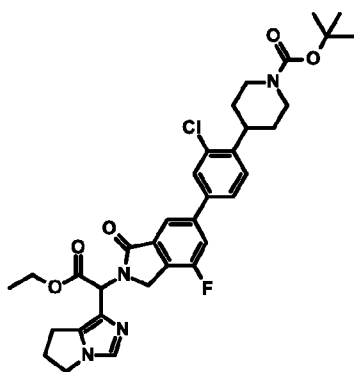
tert-Butyl nitrite (CAS 540-80-7) (558 mg, 0.644 ml, 4.87 mmol, 1.5 equiv.) and copper (II) bromide (CAS 7789-45-9) (871 mg, 3.9 mmol, 1.2 equiv.) were suspended in 15 ml of acetonitrile. tert-Butyl 4-(4-amino-2-chloro-phenyl)piperidine-1-carboxylate (*Example 30, step 2*) (1.01g, 3.25 mmol) dissolved in 2 ml of acetonitrile was added at 65 °C and the mixture was stirred at 65 °C for 2 hours. The reaction mixture was cooled to room temperature and then extracted with ethyl acetate and saturated NaHCO₃-solution. The aqueous layer was backextracted with ethyl acetate. The organic layers were washed with water and brine. The organic layers were combined, dried over sodium sulfate, filtered and concentrated to dryness. The crude product was purified by flash chromatography on a silica gel column eluting with a heptane:ethyl acetate 100:0 to 50:50 gradient to obtain the desired tert-butyl 4-(4-bromo-2-chloro-phenyl)piperidine-1-carboxylate (430 mg, 35 % yield) as a colorless oil, MS: m/e = 318.0/320.0 (M-tBu+H⁺).

Step 4: tert-Butyl 4-[2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine-1-carboxylate



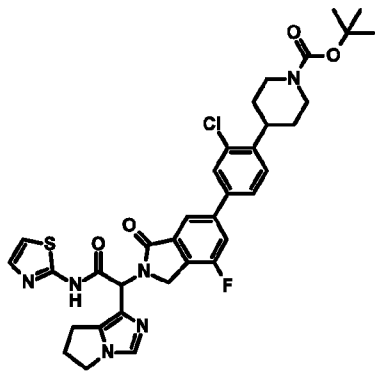
The title compound was obtained as a colorless oil, MS: $m/e = 366.1$ ($M-tBu+H^+$), using chemistry similar to that described in Example 19, step 2 starting from tert-butyl 4-(4-bromo-2-chloro-phenyl)piperidine-1-carboxylate (*Example 30, step 3*).

5 Step 5: tert-Butyl 4-[2-chloro-4-[2-[(1RS)-1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-ethoxy-2-oxo-ethyl]-7-fluoro-3-oxo-isoindolin-5-yl]phenyl]piperidine-1-carboxylate



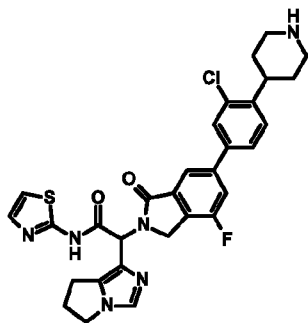
The title compound was obtained as a light brown solid, MS: $m/e = 637.4$ ($M+H^+$), using chemistry similar to that described in Example 18, step 2 starting from ethyl (2RS)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-(4-fluoro-6-iodo-1-oxo-isoindolin-2-yl)acetate (*Example 18, step 1*) and tert-butyl 4-[2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine-1-carboxylate (*Example 30, step 4*).

Step 6: tert-Butyl 4-[2-chloro-4-[2-[(1RS)-1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-oxo-2-(thiazol-2-ylamino)ethyl]-7-fluoro-3-oxo-isoindolin-5-yl]phenyl]piperidine-1-carboxylate



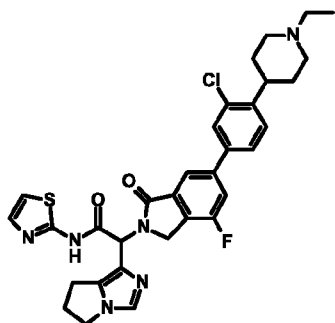
The title compound was obtained as a yellow solid, MS: $m/e = 691.5$ ($M+H^+$), using chemistry similar to that described in Example 3, step 2 starting from tert-butyl 4-[2-chloro-4-[2-[(1RS)-1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-ethoxy-2-oxo-ethyl]-7-fluoro-3-oxo-isoindolin-5-yl]phenyl]piperidine-1-carboxylate (*Example 30, step 5*) and thiazol-2-amine.

- 5 Step 7: (2RS)-2-[6-[3-Chloro-4-(4-piperidyl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide



- 10 The title compound was obtained as a yellow solid, MS: $m/e = 591.2$ ($M+H^+$), using chemistry similar to that described in Example 3, step 3 starting from tert-butyl 4-[2-chloro-4-[2-[(1RS)-1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-oxo-2-(thiazol-2-ylamino)ethyl]-7-fluoro-3-oxo-isoindolin-5-yl]phenyl]piperidine-1-carboxylate (*Example 30, step 6*).

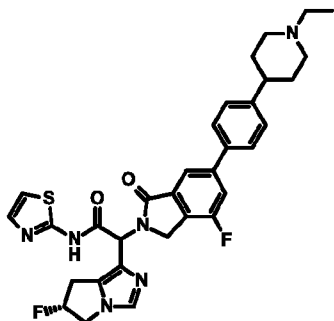
- Step 8: (2RS)-2-[6-[3-Chloro-4-(1-ethyl-4-piperidyl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide



- 15 The title compound was obtained as a light yellow solid, MS: $m/e = 619.3$ ($M+H^+$), using chemistry similar to that described in Example 4, step 4 starting from (2RS)-2-[6-[3-chloro-4-(4-piperidyl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide (*Example 30, step 7*) and ethyl iodide.

Example 31

- 20 **(2RS)-2-[6-[4-(1-Ethyl-4-piperidyl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide**

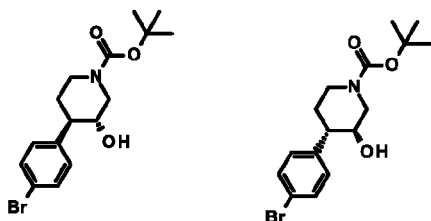


The title compound was obtained as a light brown oil, MS: $m/e = 603.4$ ($M+H^+$), using chemistry similar to that described in Example 18, step 2 and Example 3, step 2 starting from ethyl (2RS)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate (Example 17, step 9) and 1-ethyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine (Example 29, step 1).

Example 32

(2RS)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[6-[4-[(3R,4R)-1-ethyl-3-fluoro-4-piperidyl]phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide and (2RS)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[6-[4-[(3S,4S)-1-ethyl-3-fluoro-4-piperidyl]phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide

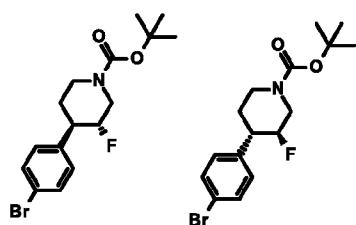
Step 1: tert-Butyl (3R,4R)-4-(4-bromophenyl)-3-hydroxy-piperidine-1-carboxylate and tert-butyl (3S,4S)-4-(4-bromophenyl)-3-hydroxy-piperidine-1-carboxylate



tert-Butyl 4-(4-bromophenyl)-3,6-dihydro-2H-pyridine-1-carboxylate (CAS 273727-44-9) (1.060 g, 3.13 mmol) was dissolved in 24 ml of THF and cooled to 0 °C. Borane tetrahydrofuran complex, 1.0 M solution in THF (CAS 14044-65-6) (6.6 ml, 6.6 mmol, 2.11 equiv.) was added dropwise at 0 °C. After the addition was complete, the ice bath was removed and the reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was cooled to 0 °C. Sodium hydroxide (6 M in water) (1.7 ml, 10.2 mmol, 3.25 equiv.) was added and the reaction mixture was stirred at 0 °C for 10 minutes. Hydrogen peroxide, 35 wt.% solution in water (977 mg, 0.88 ml, 10.1 mmol, 3.21 equiv.) was added and the reaction mixture was stirred at 50 °C for 2 hours. The reaction mixture was cooled to room temperature and the

excess of peroxide was quenched by addition of $\text{Na}_2\text{S}_2\text{O}_3$ -solution (10 % in water). The mixture was extracted with ethyl acetate and saturated NaHCO_3 -solution. The aqueous layer was backextracted twice with ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered and concentrated on isolute® to dryness. The crude product was purified by flash chromatography on a silica gel column eluting with an ethyl acetate:heptane 0:100 to 30:70 gradient. The desired products (894 mg, 76 % yield, purity = 95 %) were obtained as an off-white solid, MS: $m/e = 300.0/302.0$ ($\text{M-tBu}+\text{H}^+$).

Step 2: tert-Butyl (3R,4R)-4-(4-bromophenyl)-3-fluoro-piperidine-1-carboxylate and tert-butyl (3S,4S)-4-(4-bromophenyl)-3-fluoro-piperidine-1-carboxylate



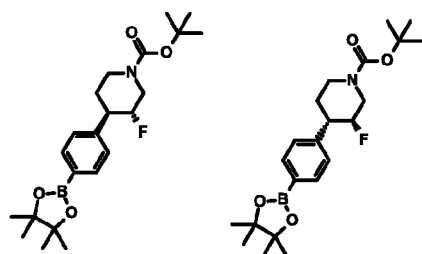
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A mixture of tert-butyl (3R,4R)-4-(4-bromophenyl)-3-hydroxy-piperidine-1-carboxylate and tert-butyl (3S,4S)-4-(4-bromophenyl)-3-hydroxy-piperidine-1-carboxylate (*Example 32, step 1*) (0.492 g, 1.31 mmol, Eq: 1; purity=95%) was dissolved in 13 ml of dichloromethane and cooled to -76°C . Bis(2-methoxyethyl)aminosulfur trifluoride (*CAS 202289-38-1*) (312 mg, 0.26 ml, 1.41 mmol, 1.07 equiv.) was added dropwise at -76°C . The reaction mixture was allowed to slowly warm to room temperature and stirred for 16 hours. The reaction mixture was quenched with saturated NaHCO_3 -solution and extracted three times with Dichloromethane. The organic layers were combined, dried over sodium sulfate, filtered and concentrated on isolute® to dryness. The crude product was purified by flash chromatography on a silica gel column eluting with an ethyl acetate:heptane 0:100 to 20:80 gradient. The desired products (300 mg, 61 % yield, purity = 95 %) were obtained as a colorless oil, MS: $m/e = 302.0/304.0$ ($\text{M-tBu}+\text{H}^+$).

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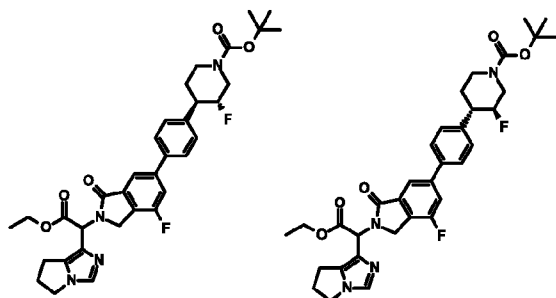
Step 3: tert-Butyl (3R,4R)-3-fluoro-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine-1-carboxylate and tert-butyl (3S,4S)-3-fluoro-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine-1-carboxylate



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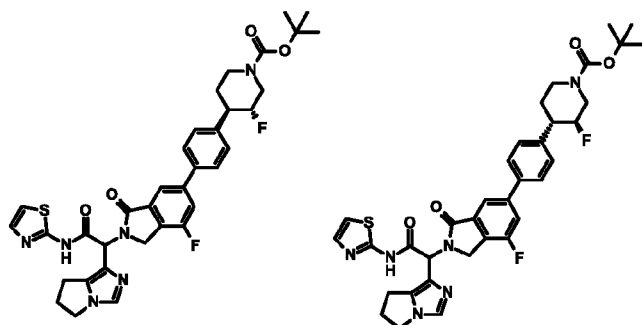
The title compounds were obtained as trans mixture and as an off-white foam, MS: $m/e = 350.0$ ($M-tBu+H^+$), using chemistry similar to that described in Example 19, step 2 starting from tert-butyl (3R,4R)-4-(4-bromophenyl)-3-fluoro-piperidine-1-carboxylate and tert-butyl (3S,4S)-4-(4-bromophenyl)-3-fluoro-piperidine-1-carboxylate (Example 32, step 2).

- 5 Step 4: tert-Butyl (3R,4R)-4-[4-[2-[(1RS)-1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-ethoxy-2-oxo-ethyl]-7-fluoro-3-oxo-isoindolin-5-yl]phenyl]-3-fluoro-piperidine-1-carboxylate and tert-butyl (3S,4S)-4-[4-[2-[(1RS)-1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-ethoxy-2-oxo-ethyl]-7-fluoro-3-oxo-isoindolin-5-yl]phenyl]-3-fluoro-piperidine-1-carboxylate



- 10 The title compounds were obtained as mixture and as a brown foam, MS: $m/e = 621.4$ ($M+H^+$), using chemistry similar to that described in Example 18, step 2 starting from ethyl (2RS)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-(4-fluoro-6-iodo-1-oxo-isoindolin-2-yl)acetate (Example 18, step 1) and tert-butyl (3R,4R)-3-fluoro-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine-1-carboxylate and tert-butyl (3S,4S)-3-fluoro-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine-1-carboxylate (Example 32, step 3).

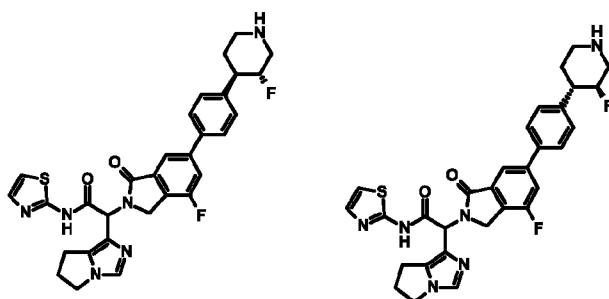
- 15 Step 5: tert-Butyl (3R,4R)-4-[4-[2-[(1RS)-1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-oxo-2-(thiazol-2-ylamino)ethyl]-7-fluoro-3-oxo-isoindolin-5-yl]phenyl]-3-fluoro-piperidine-1-carboxylate and tert-butyl (3S,4S)-4-[4-[2-[(1RS)-1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-oxo-2-(thiazol-2-ylamino)ethyl]-7-fluoro-3-oxo-isoindolin-5-yl]phenyl]-3-fluoro-
20 piperidine-1-carboxylate



The title compounds were obtained mixture and as a brown solid, MS: $m/e = 675.4$ ($M+H^+$), using chemistry similar to that described in Example 3, step 2 starting from a mixture of tert-butyl

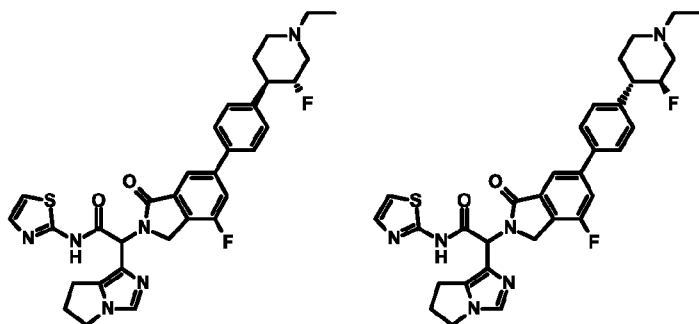
(3R,4R)-4-[4-[2-[(1RS)-1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-ethoxy-2-oxo-ethyl]-7-fluoro-3-oxo-isoindolin-5-yl]phenyl]-3-fluoro-piperidine-1-carboxylate and tert-butyl (3S,4S)-4-[4-[2-[(1RS)-1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-ethoxy-2-oxo-ethyl]-7-fluoro-3-oxo-isoindolin-5-yl]phenyl]-3-fluoro-piperidine-1-carboxylate (*Example 32, step 4*) and thiazol-2-amine.

Step 6: (2RS)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-6-[4-[(3R,4R)-3-fluoro-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide and (2RS)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-6-[4-[(3R,4R)-3-fluoro-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide



The title compounds were obtained as mixture and as a brown foam, MS: $m/e = 575.3$ ($M+H^+$), using chemistry similar to that described in Example 3, step 3 starting from a mixture of tert-butyl (3R,4R)-4-[4-[2-[(1RS)-1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-oxo-2-(thiazol-2-ylamino)ethyl]-7-fluoro-3-oxo-isoindolin-5-yl]phenyl]-3-fluoro-piperidine-1-carboxylate and tert-butyl (3S,4S)-4-[4-[2-[(1RS)-1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-oxo-2-(thiazol-2-ylamino)ethyl]-7-fluoro-3-oxo-isoindolin-5-yl]phenyl]-3-fluoro-piperidine-1-carboxylate (*Example 32, step 5*).

Step 7: (2RS)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[6-[4-[(3R,4R)-1-ethyl-3-fluoro-4-piperidyl]phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide and (2RS)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[6-[4-[(3S,4S)-1-ethyl-3-fluoro-4-piperidyl]phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide

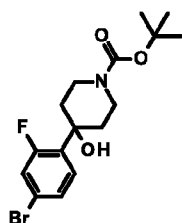


The title compounds were obtained as mixture and as an off-white foam, MS: m/e = 603.4 (M+H⁺), using chemistry similar to that described in Example 4, step 4 starting from a mixture of (2RS)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-6-[4-[(3R,4R)-3-fluoro-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide and (2RS)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-6-[4-[(3R,4R)-3-fluoro-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide (*Example 32, step 6*) and ethyl iodide.

Example 33

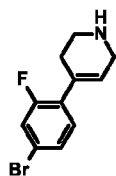
(2RS)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[6-[4-(1-ethyl-4-piperidyl)-3-fluoro-phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide

Step 1: tert-Butyl 4-(4-bromo-2-fluoro-phenyl)-4-hydroxy-piperidine-1-carboxylate



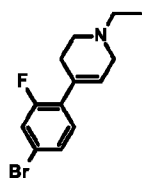
4-Bromo-2-fluoro-1-iodo-benzene (*CAS 105931-73-5*) (5 g, 16.6 mmol, 1.1 equiv.) was dissolved in 80 ml of THF and n-butyllithium (1.6 M solution in hexanes) (10.4 ml, 16.6 mmol, 1.1 equiv.) was added dropwise at -76 °C. The reaction mixture was stirred at -76 °C for 1 hour. A solution of tert-butyl 4-oxopiperidine-1-carboxylate (*CAS 79099-07-3*) (3 g, 15.1 mmol) dissolved in 40 ml of THF was added dropwise at -76 °C. After the addition was complete, the reaction mixture was stirred without cooling bath for 2 hours. The reaction mixture was extracted with ethyl acetate and saturated NaHCO₃-solution. The aqueous layer was backextracted with ethyl acetate. The organic layers were washed with water and brine. The organic layers were combined, dried over sodium sulfate, filtered and concentrated to dryness. The crude product was purified by flash chromatography on a silica gel column eluting with a heptane:ethyl acetate 100:0 to 0:100 gradient to obtain the desired tert-butyl 4-(4-bromo-2-fluoro-phenyl)-4-hydroxy-piperidine-1-carboxylate (5.3 g, 94 % yield) as a white solid, MS: m/e = 272.1/274.1 (M-BOC+H⁺).

Step 2: 4-(4-Bromo-2-fluoro-phenyl)-1,2,3,6-tetrahydropyridine



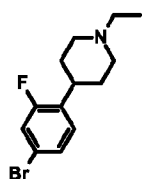
tert-Butyl 4-(4-bromo-2-fluoro-phenyl)-4-hydroxy-piperidine-1-carboxylate (*Example 33, step 1*) (5.3 g, 14.2 mmol) was dissolved in 55 ml of trifluoroacetic acid and triethylsilane (*CAS 617-86-7*) (4.12 g, 5.65 ml, 35.4 mmol, 2.5 equiv.) was added at room temperature. The reaction mixture was stirred at 60 °C for 3 hours. The reaction mixture was concentrated to dryness and then extracted with ethyl acetate and saturated NaHCO₃-solution. The aqueous layer was backextracted with ethyl acetate. The organic layers were washed with water. The organic layers were combined, dried over sodium sulfate, filtered and concentrated to dryness. The desired 4-(4-bromo-2-fluoro-phenyl)-1,2,3,6-tetrahydropyridine (4.5 g, quant.) was obtained as a yellow oil, MS: m/e = 255.9/257.9 (M+H⁺).

10 Step 3: 4-(4-Bromo-2-fluoro-phenyl)-1-ethyl-3,6-dihydro-2H-pyridine



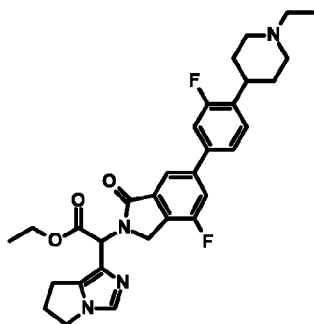
4-(4-Bromo-2-fluoro-phenyl)-1,2,3,6-tetrahydropyridine (*Example 33, step 2*) (1.80 g, 5.62 mmol, purity = 80 %) was dissolved in 20 ml of acetonitrile. Hunig's base (3.63 g, 4.91 ml, 28.1 mmol, 5 equiv.) and ethyl iodide (1.14 g, 591 µl, 7.31 mmol, 1.3 equiv.) were added at room temperature. The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was extracted with ethyl acetate and saturated NaHCO₃-solution. The aqueous layer was backextracted with ethyl acetate. The organic layers were washed with water and brine. The organic layers were combined, dried over sodium sulfate, filtered and concentrated to dryness. The crude product was purified by flash chromatography on a silica gel column eluting with a dichloromethane:methanol 100:0 to 85:15 gradient to obtain the desired 4-(4-bromo-2-fluoro-phenyl)-1-ethyl-3,6-dihydro-2H-pyridine (0.71 g, 44 % yield) as a yellow oil, MS: m/e = 283.9/285.9 (M+H⁺).

Step 4: 4-(4-Bromo-2-fluoro-phenyl)-1-ethyl-piperidine



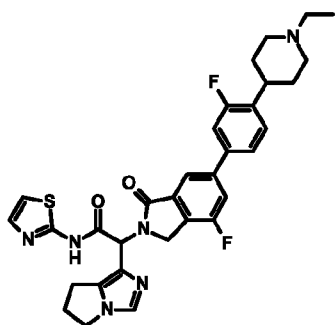
25 The title compound was obtained as a yellow oil, MS: m/e = 286.0/288.0 (M+H⁺), using chemistry similar to that described in Example 26, step 2 starting from 4-(4-bromo-2-fluoro-phenyl)-1-ethyl-3,6-dihydro-2H-pyridine (*Example 33, step 3*).

Step 5: Ethyl (2RS)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[6-[4-(1-ethyl-4-piperidyl)-3-fluoro-phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]acetate



Ethyl (2RS)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-1-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-2-yl]acetate (*Example 27, step 1*) (100 mg, 0.213 mmol) and 4-(4-bromo-2-fluoro-phenyl)-1-ethyl-piperidine (*Example 33, step 4*) (85 mg, 0.298 mmol, 1.4 equiv.) were dissolved in 2.0 ml of THF. Cesium carbonate (2M in water) (0.32 ml, 0.639 mmol, 3.0 equiv.) and PdCl₂(dppf)-CH₂Cl₂ adduct (16 mg, 0.021 mmol, 0.1 equiv.) were added and the reaction mixture was stirred at 50 °C for 1 hour. The reaction mixture was cooled to room temperature and then extracted with ethyl acetate and water. The aqueous layer was backextracted with ethyl acetate. The organic layers were washed with brine. The organic layers were combined, dried over sodium sulfate, filtered and concentrated to dryness. The crude product was purified by flash chromatography on a silica gel column eluting with a methanol:ethyl acetate 0:100 to 10:90 gradient. The desired ethyl (2RS)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[6-[4-(1-ethyl-4-piperidyl)-3-fluoro-phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]acetate (43 mg, 37 % yield) was obtained as a brown oil, MS: m/e = 549.4 (M+H⁺).

Step 6: (2RS)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[6-[4-(1-ethyl-4-piperidyl)-3-fluoro-phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide

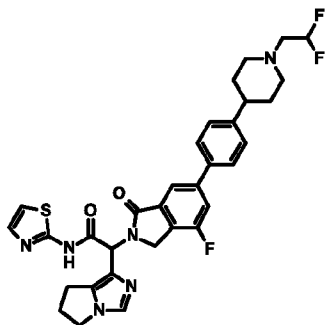


The title compound was obtained as a white solid, MS: m/e = 603.6 (M+H⁺), using chemistry similar to that described in Example 3, step 2 starting from ethyl (2RS)-2-(6,7-

dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[6-[4-(1-ethyl-4-piperidyl)-3-fluoro-phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]acetate (*Example 33, step 5*) and thiazol-2-amine.

Example 34

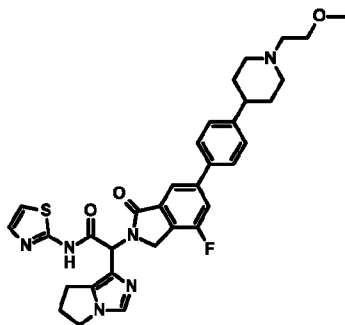
(2RS)-2-[6-[4-[1-(2,2-Difluoroethyl)-4-piperidyl]phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide



The title compound was obtained as a light yellow solid, MS: $m/e = 621.3$ ($M+H^+$), using chemistry similar to that described in Example 4, step 4 starting from (2RS)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-1-oxo-6-[4-(4-piperidyl)phenyl]isoindolin-2-yl]-N-thiazol-2-yl-acetamide hydrochloride (*Example 16, step 2*) and 2,2-difluoroethyl trifluoromethanesulfonate.

Example 35

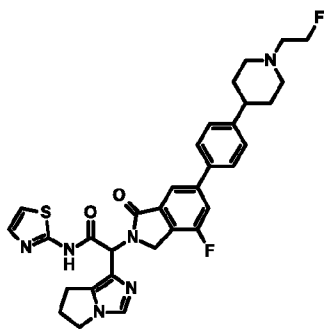
(2RS)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-6-[4-[1-(2-methoxyethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide



The title compound was obtained as a light yellow solid, MS: $m/e = 615.3$ ($M+H^+$), using chemistry similar to that described in Example 4, step 4 starting from (2RS)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-1-oxo-6-[4-(4-piperidyl)phenyl]isoindolin-2-yl]-N-thiazol-2-yl-acetamide hydrochloride (*Example 16, step 2*) and 1-bromo-2-methoxyethane.

Example 36

((2RS)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-6-[4-[1-(2-fluoroethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide

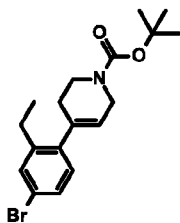


The title compound was obtained as a light yellow solid, MS: $m/e = 603.2$ ($M+H^+$), using chemistry similar to that described in Example 4, step 4 starting from (2RS)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-1-oxo-6-[4-(4-piperidyl)phenyl]isoindolin-2-yl]-N-thiazol-2-yl-acetamide hydrochloride (Example 16, step 2) and 2-fluoroethyl 4-methylbenzenesulfonate.

Example 37

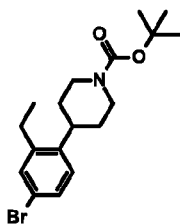
(2RS)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[6-[3-ethyl-4-(1-ethyl-4-piperidyl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide

Step 1: tert-Butyl 4-(4-bromo-2-ethyl-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylate



The title compound was obtained as a light yellow oil, MS: $m/e = 310.0/312.0$ ($M-tBu+H^+$), using chemistry similar to that described in Example 26, step 1 starting from 4-bromo-2-ethyl-1-iodobenzene (CAS 175278-30-5) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (CAS 286961-14-6).

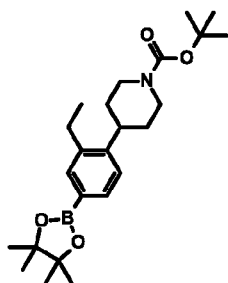
Step 2: tert-Butyl 4-(4-bromo-2-ethyl-phenyl)piperidine-1-carboxylate



tert-Butyl 4-(4-bromo-2-ethyl-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylate (Example 37, step 1) (1.29 g, 3.35 mmol, purity=95%) was dissolved in 7.0 ml of ethyl acetate and 14 ml of methanol. The flask was three times alternating evacuated and backfilled with argon. Platinum

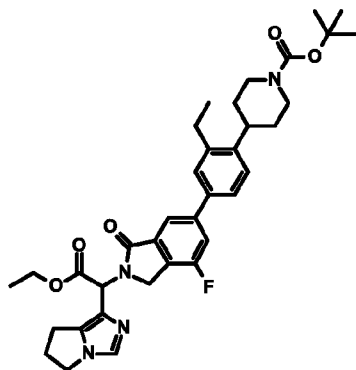
(IV) oxide (285 mg, 1 mmol, 0.3 equiv., purity = 80 %) was added carefully. The flask was evacuated, flushed with argon, evacuated and flushed with hydrogen. The reaction mixture was stirred under hydrogen atmosphere (balloon) at room temperature for 16 hours. The reaction mixture was filtered and the filtrate was concentrated on isolute® to dryness. The crude product was purified by flash chromatography on a silica gel column eluting with an ethyl acetate:heptane 0:100 to 10:90 gradient. The desired tert-butyl 4-(4-bromo-2-ethyl-phenyl)piperidine-1-carboxylate (445 mg, 33 % yield, purity = 90 %) was obtained as an off-white solid, MS: m/e = 312.0/314.0 (M-tBu+H⁺).

Step 3: tert-Butyl 4-[2-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine-1-carboxylate



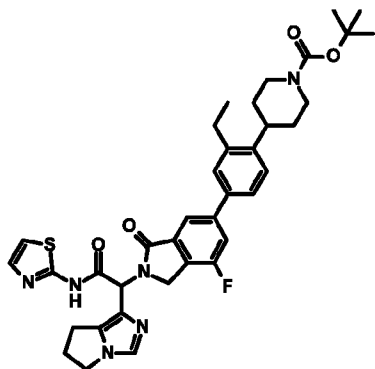
The title compound was obtained as an off-white foam, MS: m/e = 360.2 (M-tBu+H⁺), using chemistry similar to that described in Example 19, step 2 starting from tert-butyl 4-(4-bromo-2-ethyl-phenyl)piperidine-1-carboxylate (*Example 37, step 2*).

Step 4: tert-Butyl 4-[4-[2-[(1RS)-1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-ethoxy-2-oxo-ethyl]-7-fluoro-3-oxo-isoindolin-5-yl]-2-ethyl-phenyl]piperidine-1-carboxylate



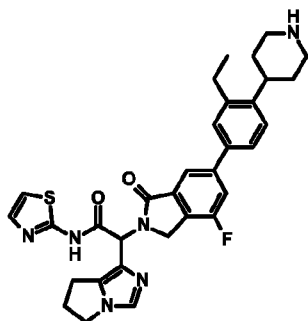
The title compound was obtained as a light brown foam, MS: m/e = 631.4 (M+H⁺), using chemistry similar to that described in Example 18, step 2 starting from ethyl (2RS)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-(4-fluoro-6-iodo-1-oxo-isoindolin-2-yl)acetate (*Example 18, step 1*) and tert-butyl 4-[2-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine-1-carboxylate (*Example 37, step 3*).

Step 5: tert-Butyl 4-[4-[2-[(1RS)-1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-oxo-2-(thiazol-2-ylamino)ethyl]-7-fluoro-3-oxo-isoindolin-5-yl]-2-ethyl-phenyl]piperidine-1-carboxylate



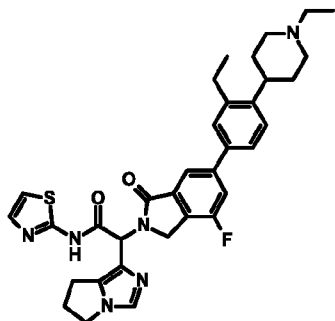
5 The title compound was obtained as a brown solid, MS: $m/e = 685.4$ ($M+H^+$), using chemistry similar to that described in Example 3, step 2 starting from tert-butyl 4-[4-[2-[(1RS)-1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-ethoxy-2-oxo-ethyl]-7-fluoro-3-oxo-isoindolin-5-yl]-2-ethyl-phenyl]piperidine-1-carboxylate (*Example 37, step 4*) and thiazol-2-amine.

10 Step 6: (2RS)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[6-[3-ethyl-4-(4-piperidyl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide



The title compound was obtained as a brown foam, MS: $m/e = 585.3$ ($M+H^+$), using chemistry similar to that described in Example 3, step 3 starting from tert-butyl 4-[4-[2-[(1RS)-1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-oxo-2-(thiazol-2-ylamino)ethyl]-7-fluoro-3-oxo-isoindolin-5-yl]-2-ethyl-phenyl]piperidine-1-carboxylate (*Example 37, step 5*).

Step 7: (2RS)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[6-[3-ethyl-4-(1-ethyl-4-piperidyl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide

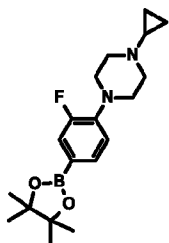


The title compound was obtained as a light brown foam, MS: $m/e = 613.5$ ($M+H^+$), using chemistry similar to that described in Example 4, step 4 starting from (2RS)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[6-[3-ethyl-4-(4-piperidyl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide (Example 37, step 6) and ethyl iodide.

Example 38

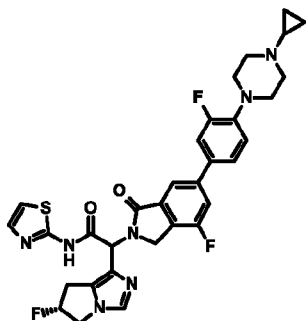
(2RS)-2-[6-[4-(4-Cyclopropylpiperazin-1-yl)-3-fluoro-phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide

10 Step 1: 1-Cyclopropyl-4-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine



The title compound was obtained as a yellow solid, MS: $m/e = 347.3$ ($M+H^+$), using chemistry similar to that described in Example 19, step 1 and step 2 starting from 4-bromo-2-fluoro-1-iodobenzene and 1-cyclopropylpiperazine dihydrochloride.

Step 2: (2RS)-2-[6-[4-(4-Cyclopropylpiperazin-1-yl)-3-fluoro-phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide

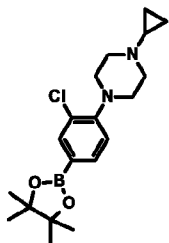


The title compound was obtained as a yellow solid, MS: $m/e = 613.3/615.3$ ($M+H^+$), using chemistry similar to that described in Example 18, step 2 and Example 3, step 2 starting from ethyl (2RS)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate (Example 17, step 9) and 1-cyclopropyl-4-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine (Example 38, step 1).

Example 39

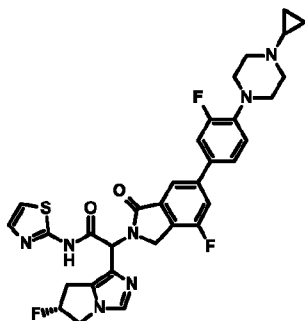
(2RS)-2-[6-[4-(4-Cyclopropylpiperazin-1-yl)-3-fluoro-phenyl]-4-chloro-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide

Step 1: 1-Cyclopropyl-4-[2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine



The title compound was obtained as a light brown solid, MS: $m/e = 363.0/365.0$ ($M+H^+$), using chemistry similar to that described in Example 19, step 1 and step 2 starting from 4-bromo-2-chloro-1-iodobenzene and 1-cyclopropylpiperazine dihydrochloride.

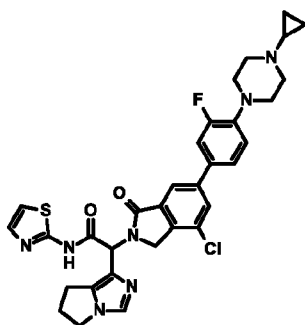
Step 2: (2RS)-2-[6-[4-(4-Cyclopropylpiperazin-1-yl)-3-fluoro-phenyl]-4-chloro-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide



The title compound was obtained as a light brown solid, MS: $m/e = 650.4/652.3$ ($M+H^+$), using chemistry similar to that described in Example 18, step 2 and Example 3, step 2 starting from ethyl (2RS)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate (Example 17, step 9) and 1-cyclopropyl-4-[2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine (Example 39, step 1).

Example 40

(2RS)-2-[4-Chloro-6-[4-(4-cyclopropylpiperazin-1-yl)-3-fluoro-phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide



10

The title compound was obtained as a white solid, MS: $m/e = 632.3/634.23$ ($M+H^+$), using chemistry similar to that described in Example 18, step 2 and Example 3, step 2 starting from ethyl (2RS)-2-(4-chloro-6-iodo-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (Example 9, step 4) and 1-cyclopropyl-4-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine (Example 38, step 1).

15

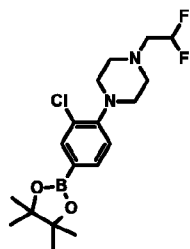
Example 41

(2RS)-2-[6-[3-Chloro-4-[4-(2,2-difluoroethyl)piperazin-1-yl]phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide

Step 1: 1-Cyclopropyl-4-[2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-

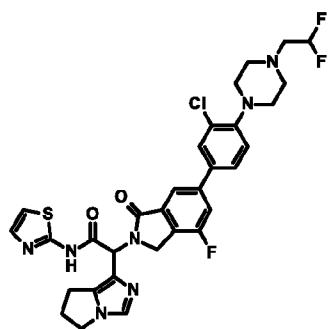
20

yl)phenyl]piperazine



The title compound was obtained as a yellow solid, MS: $m/e = 387.2/389.2$ ($M+H^+$), using chemistry similar to that described in Example 19, step 1 and step 2 starting from 4-bromo-2-chloro-1-iodobenzene and 1-(2,2-difluoroethyl)piperazine.

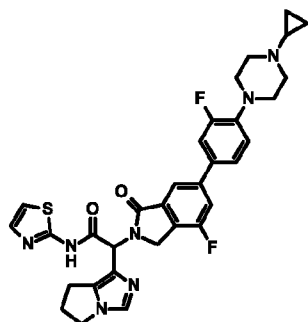
- 5 Step 2: (2RS)-2-[6-[3-Chloro-4-[4-(2,2-difluoroethyl)piperazin-1-yl]phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide



- 10 The title compound was obtained as a brown solid, MS: $m/e = 656.3/658.3$ ($M+H^+$), using chemistry similar to that described in Example 18, step 2 and Example 3, step 2 starting from ethyl (2RS)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-(4-fluoro-6-iodo-1-oxo-isoindolin-2-yl)acetate (*Example 18, step 1*) and 1-cyclopropyl-4-[2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine (*Example 41, step 1*).

Example 42

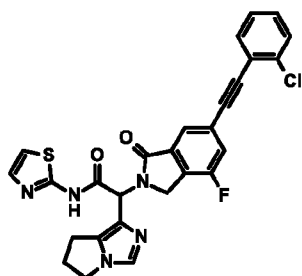
- 15 **(2RS)-2-[4-Fluoro-6-[4-(4-cyclopropylpiperazin-1-yl)-3-fluoro-phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide**



The title compound was obtained as a light brown foam, MS: $m/e = 616.4$ ($M+H^+$), using chemistry similar to that described in Example 18, step 2 and Example 3, step 2 starting from ethyl (2*RS*)-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-(4-fluoro-6-iodo-1-oxo-isoindolin-2-yl)acetate (*Example 18, step 1*) and 1-cyclopropyl-4-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine (*Example 38, step 1*).

Example 43

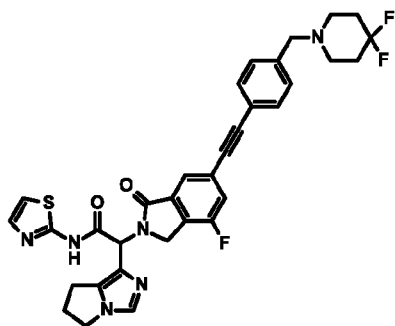
(2*RS*)-2-[6-[2-(2-Chlorophenyl)ethynyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide



The title compound was obtained as a white solid, MS: $m/e = 532.2/534.2$ ($M+H^+$), using chemistry similar to that described in Example 1, step 9 starting from (2*RS*)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide (*Example 1, step 8*) and 1-chloro-2-ethynylbenzene.

Example 44

(2*RS*)-2-[6-[2-[4-[(4,4-Difluoro-1-piperidyl)methyl]phenyl]ethynyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide



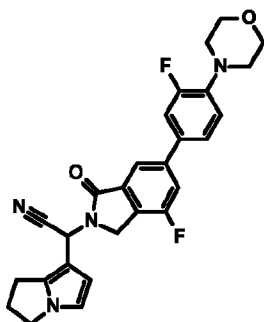
The title compound was obtained as a white solid, MS: $m/e = 631.3$ ($M+H^+$), using chemistry similar to that described in Example 1, step 10 starting from (2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-[4-fluoro-6-[2-(4-formylphenyl)ethynyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide (*Example 1, step 9*) and 4,4-difluoropiperidine hydrochloride.

Example 45

(2RS)-2-(6,7-Dihydro-5H-pyrrolizin-1-yl)-2-[4-fluoro-6-(3-fluoro-4-morpholino-phenyl)-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide

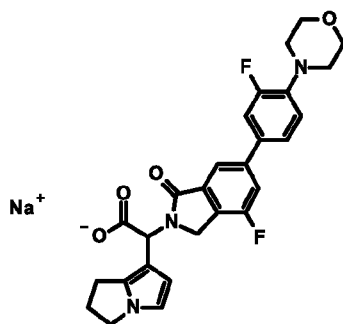
Step 1: (2RS)-2-(6,7-Dihydro-5H-pyrrolizin-1-yl)-2-[4-fluoro-6-(3-fluoro-4-morpholino-phenyl)-1-oxo-isoindolin-2-yl]acetonitrile

5



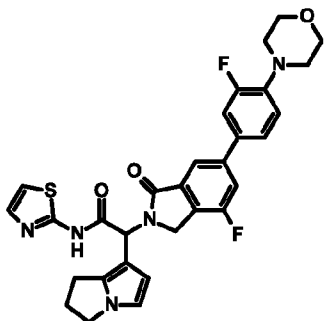
The title compound was obtained as a light brown oil, MS: $m/e = 475.3$ ($M+H^+$), using chemistry similar to that described in Example 18, step 2 starting from (2RS)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolizin-1-yl)acetonitrile (*Example 10, step 3*) and (3-fluoro-4-morpholinophenyl)boronic acid (*CAS 279262-09-8*).

10 Step 2: Sodium (2RS)-2-(6,7-dihydro-5H-pyrrolizin-1-yl)-2-[4-fluoro-6-(3-fluoro-4-morpholino-phenyl)-1-oxo-isoindolin-2-yl]acetate



15 The title compound was obtained as a yellow solid, MS: $m/e = 494.3$ ($M+H^+$), using chemistry similar to that described in Example 10, step 4 starting from (2RS)-2-(6,7-dihydro-5H-pyrrolizin-1-yl)-2-[4-fluoro-6-(3-fluoro-4-morpholino-phenyl)-1-oxo-isoindolin-2-yl]acetonitrile (*Example 45, step 1*).

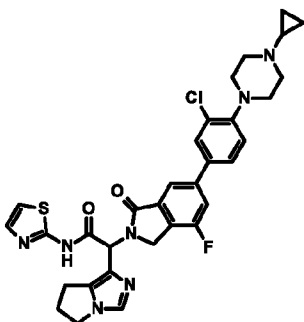
Step 3: (2RS)-2-(6,7-Dihydro-5H-pyrrolizin-1-yl)-2-[4-fluoro-6-(3-fluoro-4-morpholino-phenyl)-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide



The title compound was obtained as a yellow foam, MS: $m/e = 576.4$ ($M+H^+$), using chemistry similar to that described in Example 1, step 8 starting from sodium (2RS)-2-(6,7-dihydro-5H-pyrrolizin-1-yl)-2-[4-fluoro-6-(3-fluoro-4-morpholino-phenyl)-1-oxo-isoindolin-2-yl]acetate (Example 45, step 2) and thiazol-2-amine.

Example 46

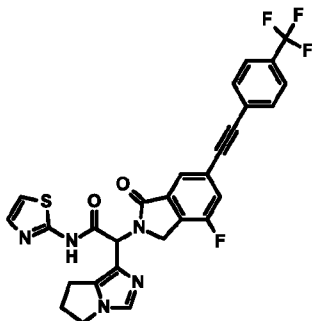
(2RS)-2-[6-[3-Chloro-4-(4-cyclopropylpiperazin-1-yl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide



The title compound was obtained as a white solid, MS: $m/e = 632.3/634.3$ ($M+H^+$), using chemistry similar to that described in Example 18, step 2 and Example 3, step 2 starting from ethyl (2RS)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-(4-fluoro-6-iodo-1-oxo-isoindolin-2-yl)acetate (Example 18, step 1) and 1-cyclopropyl-4-[2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine (Example 39, step 1).

Example 47

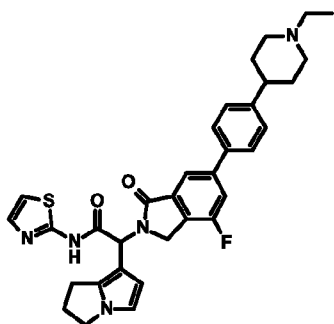
(2RS)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-1-oxo-6-[2-[4-(trifluoromethyl)phenyl]ethynyl]isoindolin-2-yl]-N-thiazol-2-yl-acetamide



The title compound was obtained as a light yellow solid, MS: $m/e = 566.1$ ($M+H^+$), using chemistry similar to that described in Example 1, step 9 starting from (2*RS*)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide (Example 1, step 8) and 1-ethynyl-4-(trifluoromethyl)benzene.

Example 48

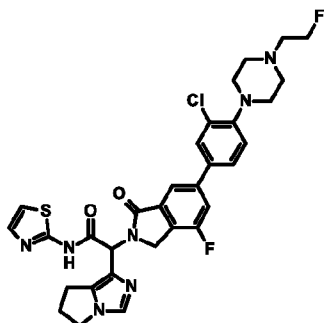
(2*RS*)-2-(6,7-Dihydro-5H-pyrrolizin-1-yl)-2-[6-[4-(1-ethyl-4-piperidyl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide



The title compound was obtained as a light brown solid, MS: $m/e = 584.5$ ($M+H^+$), using chemistry similar to that described in Example 18, step 2 starting from (2*RS*)-2-(6-bromo-4-fluoro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolizin-1-yl)-N-thiazol-2-yl-acetamide (Example 10, step 5) and 1-ethyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine (Example 29, step 1).

Example 49

(2*RS*)-2-[6-[3-Chloro-4-[4-(2-fluoroethyl)piperazin-1-yl]phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide

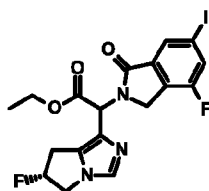


The title compound was obtained as a white solid, MS: $m/e = 638.2/640.2$ ($M+H^+$), using chemistry similar to that described in Example 4, step 4 starting from (2RS)-2-[6-(3-chloro-4-piperazin-1-yl-phenyl)-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide (Example 18, step 4) and 2-fluoroethyl 4-methylbenzenesulfonate.

Example 50

(2RS)-2-[6-[3-Ethyl-4-(1-ethyl-4-piperidyl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide

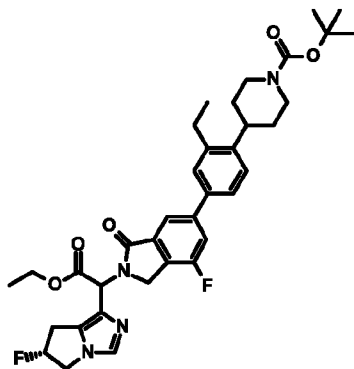
10 Step 1: Ethyl (2RS)-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-(4-fluoro-6-iodo-1-oxo-isoindolin-2-yl)acetate



The title compound was obtained as a light yellow solid, MS: $m/e = 488.0$ ($M+H^+$), using chemistry similar to that described in Example 1, step 5 and 6 starting from ethyl (2RS)-2-amino-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate (Example 17, step 8) and by using methyl 5-iodo-3-fluoro-2-methylbenzoate instead of methyl 5-bromo-3-fluoro-2-methylbenzoate.

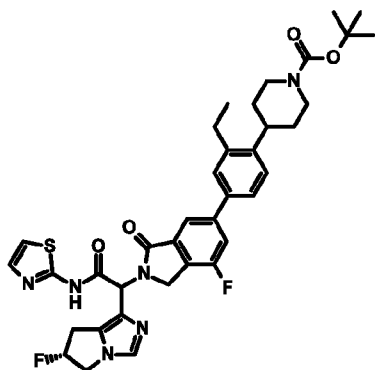
Step 2: tert-Butyl 4-[4-[2-[(1RS)-2-ethoxy-1-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-oxo-ethyl]-7-fluoro-3-oxo-isoindolin-5-yl]-2-ethyl-phenyl]piperidine-1-carboxylate

20



Ethyl (2RS)-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-(4-fluoro-6-iodo-1-oxo-isindolin-2-yl)acetate (*Example 50, step 1*) (200 mg, 0.41 mmol) and tert-butyl 4-[2-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine-1-carboxylate (*Example 37, step 3*) (233 mg, 0.534 mmol, 1.3 equiv., purity = 95 %) were dissolved in 3.0 ml of toluene. Cesium carbonate (401 mg, 1.23 mmol, 3 equiv.), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (45 mg, 0.062 mmol, 0.15 equiv.) and water (100 mg, 0.10 ml, 5.55 mmol, 13.5 equiv.) were added and the reaction mixture was stirred at 65 °C for 16 hours. The reaction mixture was cooled to room temperature and then extracted with ethyl acetate and water. The aqueous layer was backextracted with ethyl acetate. The organic layers were washed with water and brine. The organic layers were combined, dried over sodium sulfate, filtered and concentrated to dryness. The crude product was purified by flash chromatography on a silica gel column eluting with a dichloromethane:methanol 100:0 to 95:5 gradient. The desired tert-butyl 4-[4-[2-[(1RS)-2-ethoxy-1-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-oxo-ethyl]-7-fluoro-3-oxo-isindolin-5-yl]-2-ethyl-phenyl]piperidine-1-carboxylate (232 mg, 78 % yield, purity = 90 %) was obtained as a brown foam, MS: m/e = 649.4 (M+H⁺).

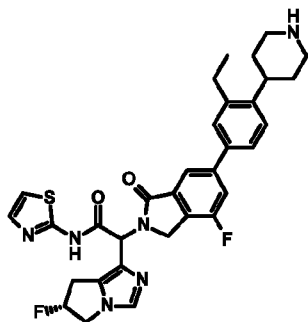
Step 3: tert-Butyl 4-[2-ethyl-4-[7-fluoro-2-[(1RS)-1-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-oxo-2-(thiazol-2-ylamino)ethyl]-3-oxo-isindolin-5-yl]phenyl]piperidine-1-carboxylate



The title compound was obtained as a brown solid, MS: m/e = 703.6 (M+H⁺), using chemistry similar to that described in Example 3, step 2 starting from tert-butyl 4-[4-[2-[(1RS)-

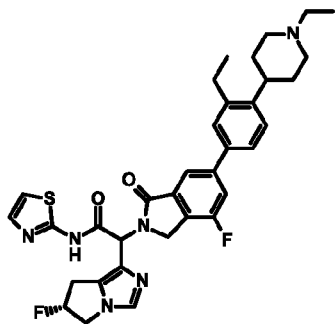
2-ethoxy-1-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-oxo-ethyl]-7-fluoro-3-oxo-isoindolin-5-yl]-2-ethyl-phenyl]piperidine-1-carboxylate (*Example 50, step 2*) and thiazol-2-amine.

Step 4: (2RS)-2-[6-[3-Ethyl-4-(4-piperidyl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide



The title compound was obtained as a dark brown solid, MS: $m/e = 603.4$ ($M+H^+$), using chemistry similar to that described in Example 3, step 3 starting from tert-butyl 4-[2-ethyl-4-[7-fluoro-2-[(1RS)-1-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-oxo-2-(thiazol-2-ylamino)ethyl]-3-oxo-isoindolin-5-yl]phenyl]piperidine-1-carboxylate (*Example 50, step 3*).

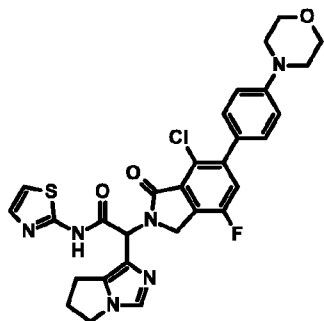
Step 5: (2RS)-2-[6-[3-Ethyl-4-(1-ethyl-4-piperidyl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide



The title compound was obtained as a brown foam, MS: $m/e = 631.3$ ($M+H^+$), using chemistry similar to that described in Example 4, step 4 starting from (2RS)-2-[6-[3-ethyl-4-(4-piperidyl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide (*Example 50, step 4*) and ethyl iodide.

Example 51

(2RS)-2-[7-Chloro-4-fluoro-6-(4-morpholinophenyl)-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide

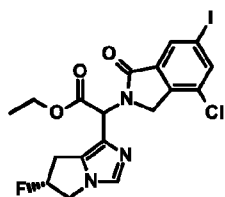


The title compound was obtained as a white solid, MS: $m/e = 593.2/595.2$ ($M+H^+$), using chemistry similar to that described in Example 18, step 2 and Example 3, step 2 starting from ethyl (2*RS*)-2-(7-chloro-4-fluoro-6-iodo-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)acetate (Example 13, step 6) and (4-morpholinophenyl)boronic acid.

Example 52

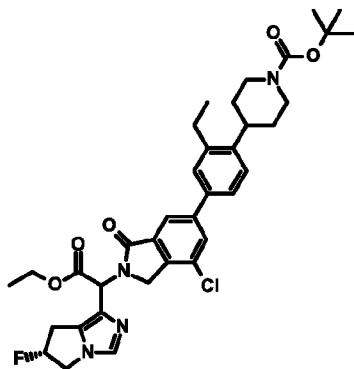
(2*RS*)-2-[4-Chloro-6-[3-ethyl-4-(1-ethyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-[(6*R*)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl]-N-thiazol-2-yl-acetamide

Step 1: Ethyl (2*RS*)-2-(4-chloro-6-iodo-1-oxo-isoindolin-2-yl)-2-[(6*R*)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl]acetate



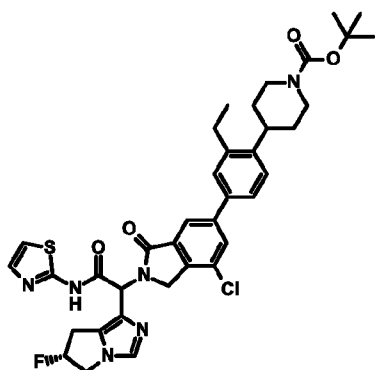
The title compound was obtained as a light brown foam, MS: $m/e = 504.0$ ($M+H^+$), using chemistry similar to that described in Example 1, step 6 starting from ethyl (2*RS*)-2-amino-2-[(6*R*)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl]acetate (Example 17, step 8) and methyl 2-(bromomethyl)-3-chloro-5-iodo-benzoate (Example 9, step 3).

Step 2: tert-Butyl 4-[4-[7-chloro-2-[(1*RS*)-2-ethoxy-1-[(6*R*)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl]-2-oxo-ethyl]-3-oxo-isoindolin-5-yl]-2-ethyl-phenyl]piperidine-1-carboxylate



Ethyl (2RS)-2-(4-chloro-6-iodo-1-oxo-isoindolin-2-yl)-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate (*Example 52, step 1*) (115 mg, 0.205 mmol, purity = 90 %) and tert-butyl 4-[2-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine-1-carboxylate (*Example 37, step 3*) (126 mg, 0.288 mmol, 1.4 equiv., purity = 95 %) were dissolved in 2.5 ml of THF. Cesium carbonate (201 mg, 0.616 mmol, 3 equiv.), PdCl₂(dppf)-CH₂Cl₂ adduct (25 mg, 0.031 mmol, 0.15 equiv.) and 0.50 ml of water were added and the reaction mixture was stirred at 65 °C for 3 hours. The reaction mixture was cooled to room temperature and then extracted with ethyl acetate and water. The aqueous layer was backextracted with ethyl acetate. The organic layers were washed with water and brine. The organic layers were combined, dried over sodium sulfate, filtered and concentrated on isolute® to dryness. The crude product was purified by flash chromatography on a silica gel column eluting with a dichloromethane:methanol 100:0 to 95:5 gradient. The desired tert-butyl 4-[4-[7-chloro-2-[(1RS)-2-ethoxy-1-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-oxo-ethyl]-3-oxo-isoindolin-5-yl]-2-ethyl-phenyl]piperidine-1-carboxylate (132 mg, 87 % yield, purity = 90 %) was obtained as a light brown oil, MS: m/e = 665.4 (M+H⁺).

Step 3: tert-Butyl 4-[4-[7-chloro-2-[(1RS)-1-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-oxo-2-(thiazol-2-ylamino)ethyl]-3-oxo-isoindolin-5-yl]-2-ethyl-phenyl]piperidine-1-carboxylate

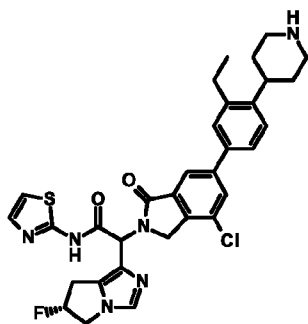


The title compound was obtained as a brown solid, MS: m/e = 719.5 (M+H⁺), using chemistry similar to that described in Example 3, step 2 starting from tert-butyl 4-[4-[7-chloro-2-[(1RS)-2-ethoxy-1-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-oxo-ethyl]-3-

oxo-isoindolin-5-yl]-2-ethyl-phenyl]piperidine-1-carboxylate (*Example 52, step 2*) and thiazol-2-amine.

Step 4: (2RS)-2-[4-Chloro-6-[3-ethyl-4-(4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide

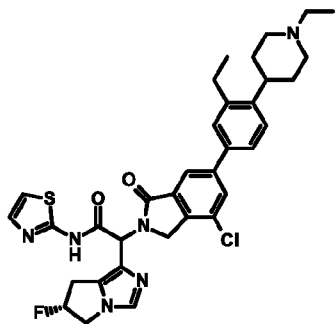
5



The title compound was obtained as a brown solid, MS: $m/e = 619.4$ ($M+H^+$), using chemistry similar to that described in Example 3, step 3 starting from tert-butyl 4-[4-[7-chloro-2-[(1RS)-1-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-oxo-2-(thiazol-2-ylamino)ethyl]-3-oxo-isoindolin-5-yl]-2-ethyl-phenyl]piperidine-1-carboxylate (*Example 52, step 3*).

10

Step 5: (2RS)-2-[4-chloro-6-[3-ethyl-4-(1-ethyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide



The title compound was obtained as a brown foam, MS: $m/e = 647.5$ ($M+H^+$), using chemistry similar to that described in Example 4, step 4 starting from (2RS)-2-[4-chloro-6-[3-ethyl-4-(4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide (*Example 52, step 4*) and ethyl iodide.

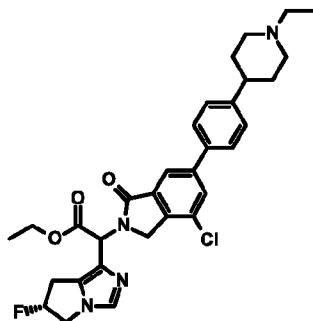
15

Example 53

(2RS)-2-[4-Chloro-6-[4-(1-ethyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide

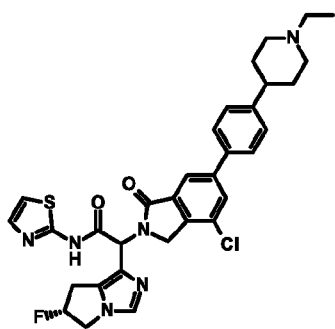
20

Step 1: Ethyl (2RS)-2-[4-chloro-6-[4-(1-ethyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate



The title compound was obtained as a white foam, MS: $m/e = 565.3$ ($M+H^+$), using chemistry similar to that described in Example 52, step 2 starting from ethyl (2RS)-2-(4-chloro-6-iodo-1-oxo-isoindolin-2-yl)-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate (*Example 52, step 1*) and 1-ethyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine (*Example 29, step 1*).

Step 2: (2RS)-2-[4-Chloro-6-[4-(1-ethyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide

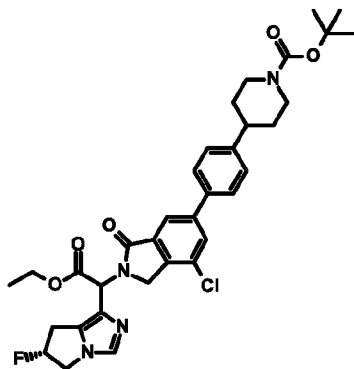


The title compound was obtained as a white solid, MS: $m/e = 619.3$ ($M+H^+$), using chemistry similar to that described in Example 3, step 2 starting from ethyl (2RS)-2-[4-chloro-6-[4-(1-ethyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate (*Example 53, step 1*) and thiazol-2-amine.

Example 54

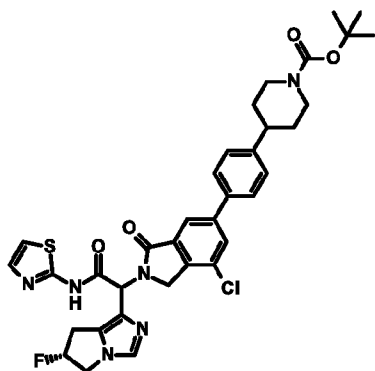
(2RS)-2-[4-Chloro-6-[4-(1-cyclopropyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide

Step 1: tert-Butyl 4-[4-[7-chloro-2-[(1RS)-2-ethoxy-1-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-oxo-ethyl]-3-oxo-isoindolin-5-yl]phenyl]piperidine-1-carboxylate



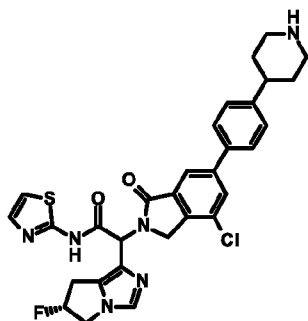
The title compound was obtained as a light brown foam, MS: $m/e = 637.3$ ($M+H^+$), using chemistry similar to that described in Example 52, step 2 starting from ethyl (2RS)-2-(4-chloro-6-iodo-1-oxo-isoindolin-2-yl)-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate (*Example 52, step 1*) and tert-butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine-1-carboxylate.

Step 2: tert-Butyl 4-[4-[7-chloro-2-[(1RS)-1-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-oxo-2-(thiazol-2-ylamino)ethyl]-3-oxo-isoindolin-5-yl]phenyl]piperidine-1-carboxylate



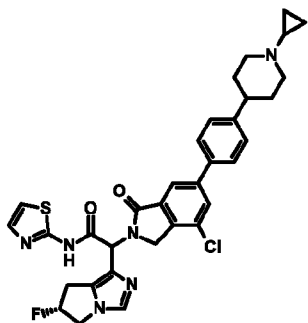
The title compound was obtained as a light brown foam, MS: $m/e = 691.3$ ($M+H^+$), using chemistry similar to that described in Example 3, step 2 starting from tert-butyl 4-[4-[7-chloro-2-[(1RS)-2-ethoxy-1-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-oxo-ethyl]-3-oxo-isoindolin-5-yl]phenyl]piperidine-1-carboxylate (*Example 54, step 1*) and thiazol-2-amine.

Step 3: (2RS)-2-[4-Chloro-1-oxo-6-[4-(4-piperidyl)phenyl]isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide



The title compound was obtained as a white solid, MS: $m/e = 591.3$ ($M+H^+$), using chemistry similar to that described in Example 3, step 3 starting from tert-butyl 4-[4-[7-chloro-2-[(1RS)-1-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-oxo-2-(thiazol-2-ylamino)ethyl]-3-oxo-isoindolin-5-yl]phenyl]piperidine-1-carboxylate (*Example 54, step 2*).

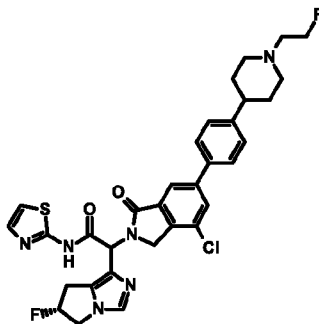
Step 4: (2RS)-2-[4-Chloro-6-[4-(1-cyclopropyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide



The title compound was obtained as a white solid, MS: $m/e = 631.3$ ($M+H^+$), using chemistry similar to that described in Example 27, step 2 starting from (2RS)-2-[4-chloro-1-oxo-6-[4-(4-piperidyl)phenyl]isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide (*Example 54, step 3*) and (1-ethoxycyclopropoxy)trimethylsilane.

Example 55

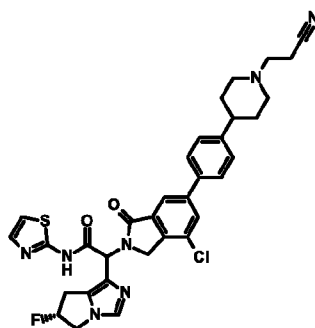
(2RS)-2-[4-Chloro-6-[4-[1-(2-fluoroethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide



The title compound was obtained as a light brown solid, MS: $m/e = 637.3$ ($M+H^+$), using chemistry similar to that described in Example 4, step 4 starting from (2RS)-2-[4-chloro-1-oxo-6-[4-(4-piperidyl)phenyl]isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide (*Example 54, step 3*) and 2-fluoroethyl 4-methylbenzenesulfonate.

Example 56

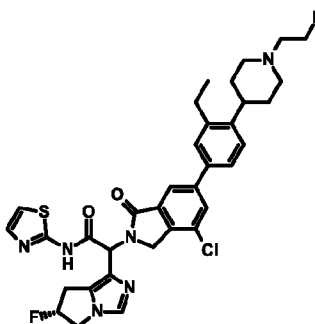
(2RS)-2-[4-Chloro-6-[4-[1-(2-cyanoethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide



The title compound was obtained as a white solid, MS: $m/e = 644.3$ ($M+H^+$), using chemistry similar to that described in Example 4, step 4 starting from (2RS)-2-[4-chloro-1-oxo-6-[4-(4-piperidyl)phenyl]isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide (*Example 54, step 3*) and 3-bromopropanenitrile.

Example 57

(2RS)-2-[4-Chloro-6-[3-ethyl-4-[1-(2-fluoroethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide

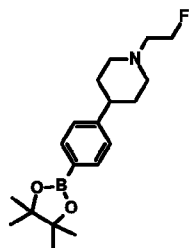


The title compound was obtained as a white foam, MS: $m/e = 665.4$ ($M+H^+$), using chemistry similar to that described in Example 4, step 4 starting from (2RS)-2-[4-chloro-6-[3-ethyl-4-(4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide (*Example 52, step 4*) and 2-fluoroethyl 4-methylbenzenesulfonate.

Example 58

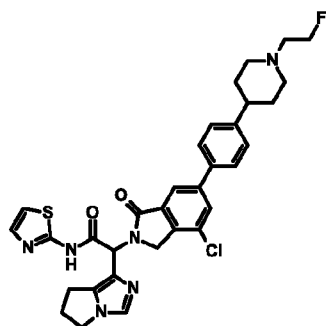
(2RS)-2-[4-Chloro-6-[4-[1-(2-fluoroethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide

Step 1: 1-(2-Fluoroethyl)-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine



- 5 The title compound was obtained as a dark red solid, MS: $m/e = 334.2$ ($M+H^+$), using chemistry similar to that described in Example 4, step 4 and Example 19, step 2 starting from 4-(4-bromophenyl)piperidine and 2-fluoroethyl 4-methylbenzenesulfonate.

Step 2: (2RS)-2-[4-Chloro-6-[4-[1-(2-fluoroethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide



10

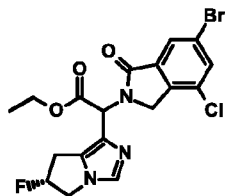
- The title compound was obtained as a light brown solid, MS: $m/e = 619.3$ ($M+H^+$), using chemistry similar to that described in Example 52, step 2 and Example 3, step 2 starting from ethyl (2RS)-2-(4-chloro-6-iodo-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (*Example 9, step 4*) and 1-(2-fluoroethyl)-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine (*Example 58, step 1*).
- 15

Example 59

(2RS)-2-[4-Chloro-6-[4-[1-(2,2-difluoroethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide

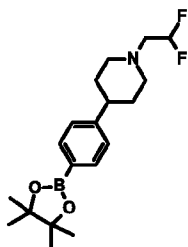
Step 1: Ethyl (2RS)-2-(4-chloro-6-bromo-1-oxo-isoindolin-2-yl)-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate

20



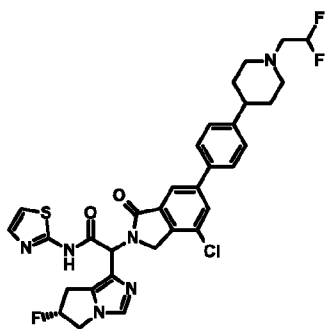
The title compound was obtained as a yellow oil, MS: $m/e = 474.0/476.0$ ($M+H^+$), using chemistry similar to that described in Example 1, step 6 starting from ethyl (2RS)-2-amino-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate (*Example 17, step 8*) and methyl 5-bromo-2-(bromomethyl)-3-chloro-benzoate (*Example 6, step 1*).

Step 2: 1-(2,2-Difluoroethyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine



The title compound was obtained as a light brown solid, MS: $m/e = 352.2$ ($M+H^+$), using chemistry similar to that described in Example 4, step 4 and Example 19, step 2 starting from 4-(4-bromophenyl)piperidine and 2,2-difluoroethyl trifluoromethanesulfonate.

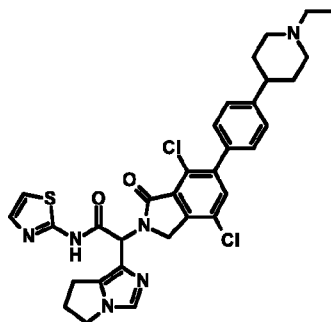
Step 3: (2RS)-2-[4-Chloro-6-[4-[1-(2,2-difluoroethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide



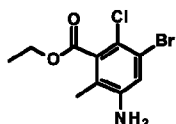
The title compound was obtained as a white solid, MS: $m/e = 655.2$ ($M+H^+$), using chemistry similar to that described in Example 52, step 2 and Example 3, step 2 starting from ethyl (2RS)-2-(4-chloro-6-bromo-1-oxo-isoindolin-2-yl)-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate (*Example 59, step 1*) and 1-(2,2-difluoroethyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine (*Example 59, step 2*).

Example 60

(2RS)-2-[4,7-Dichloro-6-[4-(1-ethyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide

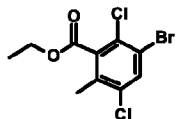


5 Step 1: Ethyl 5-amino-3-bromo-2-chloro-6-methyl-benzoate



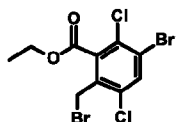
The title compound was obtained as a colorless oil, MS: $m/e = 293.7$ ($M+H^+$), using chemistry similar to that described in Example 13, step 3 starting from 6-chloro-2-methyl-3-nitrobenzoic acid and NBS.

10 Step 2: Ethyl 3-bromo-2,5-dichloro-6-methyl-benzoate



Ethyl 5-amino-3-bromo-2-chloro-6-methyl-benzoate (*Example 60, step 1*) (40 g, 136.7 mmol) was dissolved in 200 ml of dioxane and 40 ml of water. 200 ml of HCl 30% in water and sodium nitrite (10.4 g, 150.4 mmol, 1.1 equiv.) were added at 0-5 °C. The mixture was stirred for 1 hour and cuprous chloride (14.9 g, 150.4 mmol, 1.1 equiv.) was added. The mixture was stirred at 0-5°C for 1 hour. The reaction mixture was extracted with water and three times with ethyl acetate. The organic layers were dried over sodium sulfate and concentrated to dryness to obtain the desired product (35 g, 82 % yield) as a colorless oil.

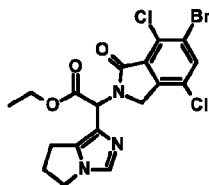
15 Step 3: Ethyl 5-bromo-2-(bromomethyl)-3,6-dichloro-benzoate



20

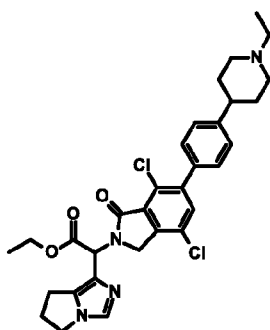
The title compound was obtained as a light green gum using chemistry similar to that described in Example 1, step 5 starting from ethyl 3-bromo-2,5-dichloro-6-methyl-benzoate (*Example 60, step 2*).

Step 4: Ethyl (2RS)-2-(6-bromo-4,7-dichloro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate



The title compound was obtained as a grey solid, MS: $m/e = 472.0$ ($M+H^+$), using chemistry similar to that described in Example 1, step 6 starting from ethyl (2RS)-2-amino-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (*Example 1, step 3*) and ethyl 5-bromo-2-(bromomethyl)-3,6-dichloro-benzoate (*Example 60, step 3*).

Step 5: Ethyl (2RS)-2-[4,7-dichloro-6-[4-(1-ethyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate

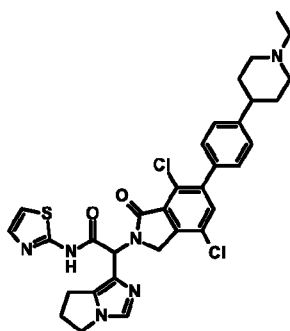


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The title compound was obtained as a brown waxy solid, MS: $m/e = 581.3$ ($M+H^+$), using chemistry similar to that described in Example 52, step 2 starting from ethyl (2RS)-2-(6-bromo-4,7-dichloro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (*Example 60, step 5*) and 1-ethyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine (*Example 29, step 1*).

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Step 6: (2RS)-2-[4,7-Dichloro-6-[4-(1-ethyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide



The title compound was obtained as a light yellow solid, MS: $m/e = 635.1$ ($M+H^+$), using chemistry similar to that described in Example 3, step 2 starting from ethyl (2RS)-2-[4,7-dichloro-

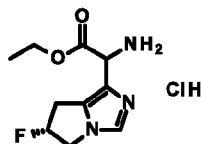
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6-[4-(1-ethyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (*Example 60, step 5*) and thiazol-2-amine.

Example 61

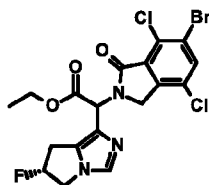
(2RS)-2-[4,7-Dichloro-6-[4-(1-ethyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide

Step 1: Ethyl (2RS)-2-amino-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate hydrochloride



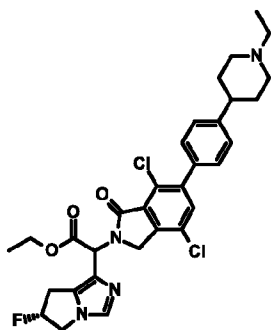
The title compound was obtained as a white solid, using chemistry similar to that described in Example 1, step 4 starting from ethyl (2RS)-2-amino-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate (*Example 17, step 8*).

Step 2: Ethyl (2RS)-2-(6-bromo-4,7-dichloro-1-oxo-isoindolin-2-yl)-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate



The title compound was obtained as an off-white solid, MS: $m/e = 492.1$ ($M+H^+$), using chemistry similar to that described in Example 1, step 6 starting from ethyl (2RS)-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate hydrochloride (*Example 61, step 1*) and ethyl 5-bromo-2-(bromomethyl)-3,6-dichloro-benzoate (*Example 60, step 3*).

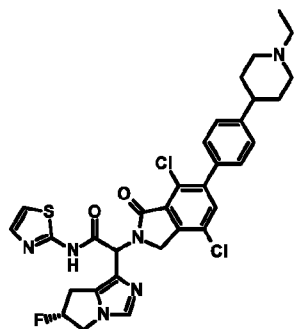
Step 3: Ethyl (2RS)-2-[4,7-dichloro-6-[4-(1-ethyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate



The title compound was obtained as a brown waxy solid, MS: $m/e = 599.3$ ($M+H^+$), using chemistry similar to that described in Example 52, step 2 starting from ethyl (2RS)-2-(6-bromo-

4,7-dichloro-1-oxo-isoindolin-2-yl)-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate (*Example 61, step 2*) and 1-ethyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine (*Example 29, step 1*).

Step 4: (2RS)-2-[4,7-Dichloro-6-[4-(1-ethyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide

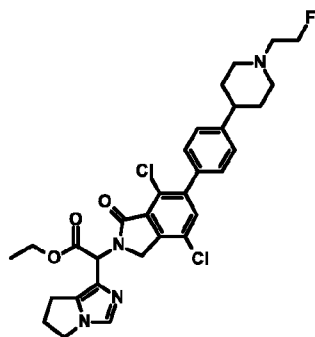


The title compound was obtained as a light brown solid, MS: $m/e = 655.2$ ($M+H^+$), using chemistry similar to that described in Example 3, step 2 starting from ethyl (2RS)-2-[4,7-dichloro-6-[4-(1-ethyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate (*Example 61, step 3*) and thiazol-2-amine.

Example 62

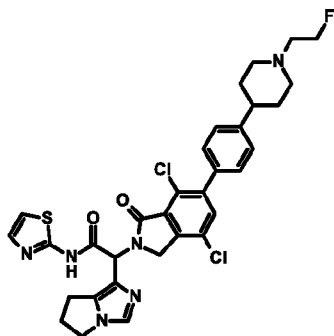
(2RS)-2-[4,7-Dichloro-6-[4-[1-(2-fluoroethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide

Step 1: Ethyl (2RS)-2-[4,7-dichloro-6-[4-[1-(2-fluoroethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate



The title compound was obtained as an off-white foam, MS: $m/e = 599.3$ ($M+H^+$), using chemistry similar to that described in Example 52, step 2 starting from ethyl (2RS)-2-(6-bromo-4,7-dichloro-1-oxo-isoindolin-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (*Example 60, step 4*) and 1-(2-fluoroethyl)-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine (*Example 58, step 1*).

Step 2: (2RS)-2-[4,7-Dichloro-6-[4-[1-(2-fluoroethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide

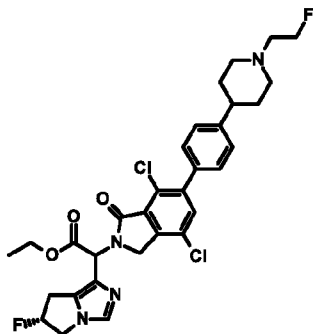


The title compound was obtained as a light brown solid, MS: $m/e = 653.3$ ($M+H^+$), using chemistry similar to that described in Example 3, step 2 starting from ethyl (2RS)-2-[4,7-dichloro-6-[4-[1-(2-fluoroethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (*Example 62, step 1*) and thiazol-2-amine.

Example 63

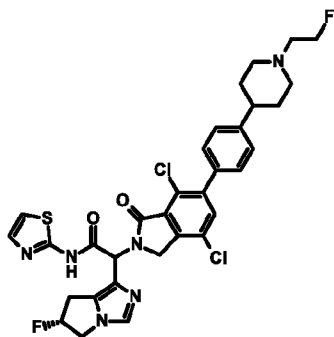
(2RS)-2-[4,7-Dichloro-6-[4-[1-(2-fluoroethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide

Step 1: Ethyl (2RS)-2-[4,7-dichloro-6-[4-[1-(2-fluoroethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate



The title compound was obtained as a light brown foam, MS: $m/e = 617.3$ ($M+H^+$), using chemistry similar to that described in Example 52, step 2 starting from ethyl (2RS)-2-(6-bromo-4,7-dichloro-1-oxo-isoindolin-2-yl)-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate (*Example 61, step 2*) and 1-(2-fluoroethyl)-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine (*Example 58, step 1*).

Step 2: (2RS)-2-[4,7-Dichloro-6-[4-[1-(2-fluoroethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide

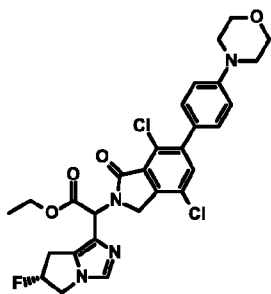


The title compound was obtained as an off-white solid, MS: $m/e = 673.2$ ($M+H^+$), using chemistry similar to that described in Example 3, step 2 starting from ethyl (2RS)-2-[4,7-dichloro-6-[4-[1-(2-fluoroethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate (*Example 63, step 1*) and thiazol-2-amine.

Example 64

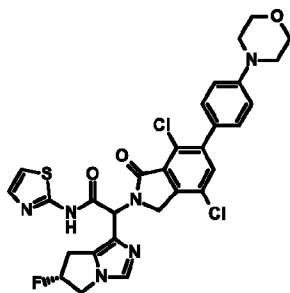
(2RS)-2-[4,7-Dichloro-6-(4-morpholinophenyl)-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide

Step 1: Ethyl (2RS)-2-[4,7-dichloro-6-(4-morpholinophenyl)-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate



The title compound was obtained as a light brown foam, MS: $m/e = 573.3$ ($M+H^+$), using chemistry similar to that described in Example 52, step 2 starting from ethyl (2RS)-2-(6-bromo-4,7-dichloro-1-oxo-isoindolin-2-yl)-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate (*Example 61, step 2*) and (4-morpholinophenyl)boronic acid.

Step 2: (2RS)-2-[4,7-Dichloro-6-(4-morpholinophenyl)-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide



The title compound was obtained as a brown solid, MS: $m/e = 627.3$ ($M+H^+$), using chemistry similar to that described in Example 3, step 2 starting from ethyl (2RS)-2-[4,7-dichloro-6-(4-morpholinophenyl)-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate (*Example 64, step 1*) and thiazol-2-amine.

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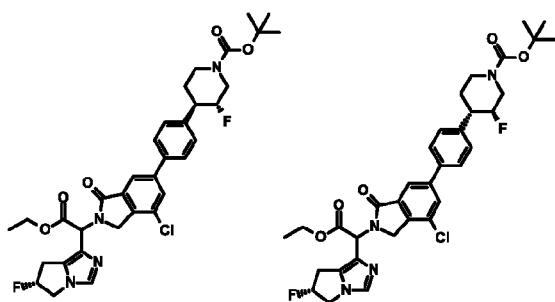
Example 65

(2RS)-2-[4-Chloro-6-[4-[(3R,4R)-1-ethyl-3-fluoro-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide and (2RS)-2-[4-chloro-6-[4-[(3S,4S)-1-ethyl-3-fluoro-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide

10

Step 1: tert-Butyl (3R,4R)-4-[4-[7-chloro-2-[(1RS)-2-ethoxy-1-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-oxo-ethyl]-3-oxo-isoindolin-5-yl]phenyl]-3-fluoro-piperidine-1-carboxylate and tert-butyl (3S,4S)-4-[4-[7-chloro-2-[(1RS)-2-ethoxy-1-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-oxo-ethyl]-3-oxo-isoindolin-5-yl]phenyl]-3-fluoro-piperidine-1-carboxylate

15

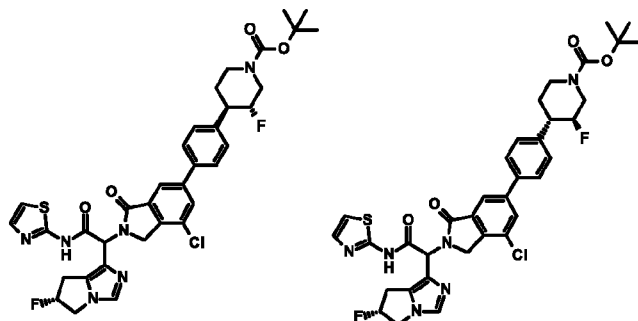


The title compounds were obtained as mixture and as a brown foam, MS: $m/e = 655.4$ ($M+H^+$), using chemistry similar to that described in Example 52, step 2 starting from ethyl (2RS)-2-(4-chloro-6-bromo-1-oxo-isoindolin-2-yl)-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate (*Example 59, step 1*) and a mixture of tert-butyl (3R,4R)-3-fluoro-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine-1-carboxylate and tert-butyl (3S,4S)-3-fluoro-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine-1-carboxylate (*Example 32, step 3*).

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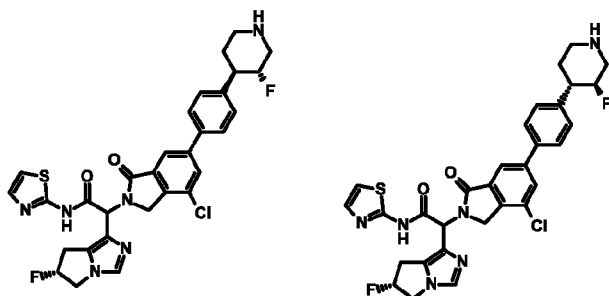
25

Step 2: tert-Butyl (3R,4R)-4-[4-[7-chloro-2-[(1RS)-1-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-oxo-2-(thiazol-2-ylamino)ethyl]-3-oxo-isoindolin-5-yl]phenyl]-3-fluoro-piperidine-1-carboxylate and tert-butyl (3S,4S)-4-[4-[7-chloro-2-[(1RS)-1-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-oxo-2-(thiazol-2-ylamino)ethyl]-3-oxo-isoindolin-5-yl]phenyl]-3-fluoro-piperidine-1-carboxylate



The title compounds were obtained as mixture and as a brown foam, MS: $m/e = 709.3$ ($M+H^+$), using chemistry similar to that described in Example 3, step 2 starting from a mixture of tert-butyl (3R,4R)-4-[4-[7-chloro-2-[(1RS)-2-ethoxy-1-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-oxo-ethyl]-3-oxo-isoindolin-5-yl]phenyl]-3-fluoro-piperidine-1-carboxylate and tert-butyl (3S,4S)-4-[4-[7-chloro-2-[(1RS)-2-ethoxy-1-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-oxo-ethyl]-3-oxo-isoindolin-5-yl]phenyl]-3-fluoro-piperidine-1-carboxylate (*Example 65, step 1*) and thiazol-2-amine.

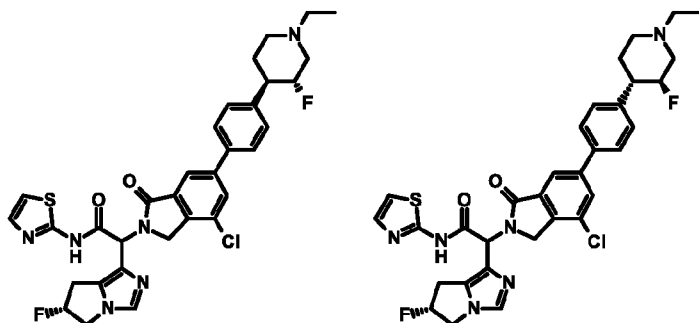
Step 3: (2RS)-2-[4-Chloro-6-[4-[(3R,4R)-3-fluoro-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide and (2RS)-2-[4-chloro-6-[4-[(3S,4S)-3-fluoro-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide



The title compounds were obtained as mixture and as a brown foam, MS: $m/e = 609.3$ ($M+H^+$), using chemistry similar to that described in Example 3, step 3 starting from a mixture of tert-butyl (3R,4R)-4-[4-[7-chloro-2-[(1RS)-1-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-oxo-2-(thiazol-2-ylamino)ethyl]-3-oxo-isoindolin-5-yl]phenyl]-3-fluoro-piperidine-1-carboxylate and tert-butyl (3S,4S)-4-[4-[7-chloro-2-[(1RS)-1-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-oxo-2-(thiazol-2-ylamino)ethyl]-3-oxo-isoindolin-5-yl]phenyl]-3-fluoro-piperidine-1-carboxylate (*Example 65, step 2*).

Step 4: (2RS)-2-[4-Chloro-6-[4-[(3R,4R)-1-ethyl-3-fluoro-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide and (2RS)-2-[4-chloro-6-[4-[(3S,4S)-1-ethyl-3-fluoro-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide

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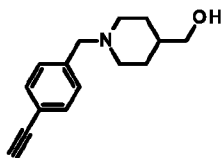


The title compounds were obtained as mixture and as a light brown foam, MS: $m/e = 637.5$ ($M+H^+$), using chemistry similar to that described in Example 4, step 4 starting from a mixture of (2RS)-2-[4-chloro-6-[4-[(3R,4R)-3-fluoro-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide and (2RS)-2-[4-chloro-6-[4-[(3S,4S)-3-fluoro-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide (*Example 65, step 3*) and ethyl iodide.

Example 66

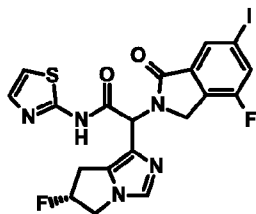
- 10 **(2RS)-2-[(6R)-6-Fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-[4-fluoro-6-[2-[4-[[4-(hydroxymethyl)-1-piperidyl]methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide**

Step 1: [1-[(4-Ethynylphenyl)methyl]-4-piperidyl]methanol



- 15 The title compound was obtained as an orange viscous oil, MS: $m/e = 230.2$ ($M+H^+$), using chemistry similar to that described in Example 1, step 10 starting from 4-ethynylbenzaldehyde and 4-piperidylmethanol.

Step 2: (2RS)-2-[(6R)-6-Fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-(4-fluoro-6-iodo-1-oxo-isoindolin-2-yl)-N-thiazol-2-yl-acetamide



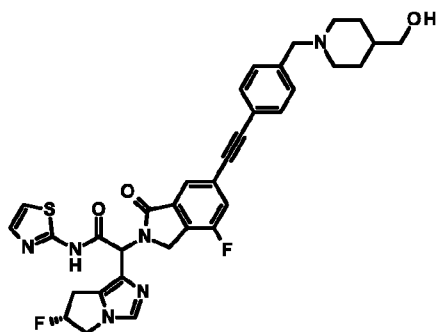
20

The title compound was obtained as a light brown foam, MS: $m/e = 542.0$ ($M+H^+$), using chemistry similar to that described in Example 3, step 2 starting from ethyl (2RS)-2-[(6R)-6-

fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-(4-fluoro-6-iodo-1-oxo-isoindolin-2-yl)acetate (*Example 50, step 1*) and thiazol-2-amine.

Step 3: (2RS)-2-[(6R)-6-Fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-[4-fluoro-6-[2-[4-[[4-(hydroxymethyl)-1-piperidyl]methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide

5



The title compound was obtained as an off-white solid, MS: $m/e = 643.5$ ($M+H^+$), using chemistry similar to that described in Example 1, step 9 starting from (2RS)-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-(4-fluoro-6-iodo-1-oxo-isoindolin-2-yl)-N-thiazol-2-yl-acetamide (*Example 66, step 2*) and [1-[(4-ethynylphenyl)methyl]-4-piperidyl]methanol (*Example 66, step 1*).

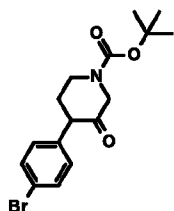
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Example 67

(2RS)-2-[4-Chloro-6-[4-(1-ethyl-3,3-difluoro-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide

15

Step 1: tert-Butyl 4-(4-bromophenyl)-3-oxo-piperidine-1-carboxylate



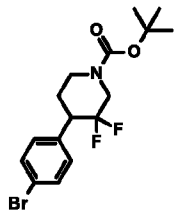
tert-Butyl 4-(4-bromophenyl)-3,6-dihydro-2H-pyridine-1-carboxylate (*CAS 273727-44-9*) (500 mg, 1.4 mmol) was combined with 15 ml of dichloromethane and cooled to 0 °C. Dess-Martin periodinane (15% solution in dichloromethane) (5.95 g, 4.37 ml, 2.11 mmol, 1.5 equiv.) was added at 0 °C and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into dichloromethane and extracted with water and saturated NaHCO_3 -solution. The aqueous layer was backextracted with dichloromethane. The organic layers were washed with $\text{Na}_2\text{S}_2\text{O}_3$ -solution. The organic layers were combined, dried over sodium sulfate, filtered and concentrated to dryness. The crude product was purified by flash chromatography on a silica gel column eluting with an ethyl acetate:heptane 0:100 to 50:50

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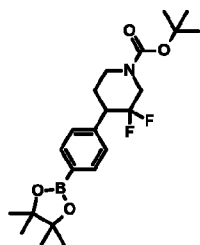
gradient. The desired tert-butyl 4-(4-bromophenyl)-3-oxo-piperidine-1-carboxylate (450 mg, 72 % yield, purity = 80 %) was obtained as a colorless oil, MS: m/e = 300.0 (M-tBu+H⁺).

Step 2: tert-Butyl 4-(4-bromophenyl)-3,3-difluoro-piperidine-1-carboxylate



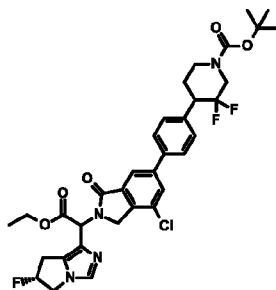
- 5 In a plastic 100 mL round-bottomed flask, a mixture of tert-Butyl 4-(4-bromophenyl)-3-oxo-piperidine-1-carboxylate (*Example 67, step 1*) (875 mg, 2.47 mmol), triethylamine trihydrofluoride (*CAS 73602-61-6*) (1.19 g, 1.21 ml, 7.41 mmol, 3 equiv.) and XtalFluor-E® (*CAS 63517-29-3*) (1.13 g, 4.94 mmol, 2 equiv.) in 40ml of dichloromethane was stirred at room temperature for 16 hours. The reaction mixture was quenched with saturated NaHCO₃-solution,
- 10 stirred for 10min and then extracted twice with dichloromethane. The organic layers were combined, dried over sodium sulfate, filtered and concentrated to dryness. The crude product was purified by flash chromatography on a silica gel column eluting with an ethyl acetate:heptane 0:100 to 30:70 gradient. The desired tert-butyl 4-(4-bromophenyl)-3,3-difluoro-piperidine-1-carboxylate (680 mg, 70 % yield, purity = 95 %) was obtained as a colorless oil,
- 15 MS: m/e = 320.0 (M-tBu+H⁺).

Step 3: tert-Butyl 3,3-difluoro-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine-1-carboxylate



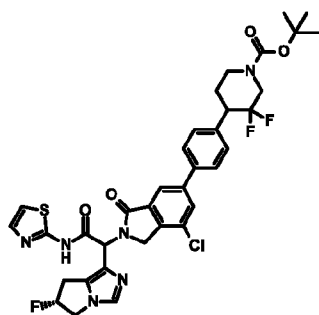
- The title compound was obtained as a colorless oil, MS: m/e = 324.1 (M-tBu+H⁺), using
- 20 chemistry similar to that described in Example 19, step 2 starting from tert-butyl 4-(4-bromophenyl)-3,3-difluoro-piperidine-1-carboxylate (*Example 67, step 2*).

Step 4: tert-Butyl 4-[4-[7-chloro-2-[(1R)-2-ethoxy-1-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-oxo-ethyl]-3-oxo-isoindolin-5-yl]phenyl]-3,3-difluoro-piperidine-1-carboxylate



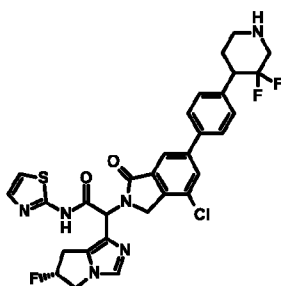
The title compound was obtained as an off-white foam, MS: $m/e = 673.3$ ($M+H^+$), using chemistry similar to that described in Example 52, step 2 starting from ethyl (2RS)-2-(4-chloro-6-bromo-1-oxo-isoindolin-2-yl)-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]acetate (*Example 59, step 1*) and tert-butyl 3,3-difluoro-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine-1-carboxylate (*Example 67, step 3*).

Step 5: tert-Butyl 4-[4-[7-chloro-2-[(1RS)-1-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-oxo-2-(thiazol-2-ylamino)ethyl]-3-oxo-isoindolin-5-yl]phenyl]-3,3-difluoro-piperidine-1-carboxylate



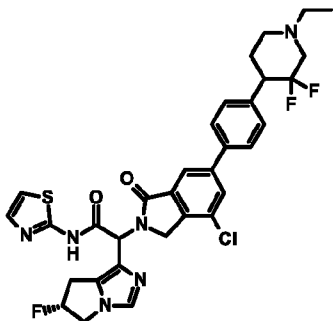
The title compound was obtained as a light brown foam, MS: $m/e = 727.3$ ($M+H^+$), using chemistry similar to that described in Example 3, step 2 starting from tert-butyl 4-[4-[7-chloro-2-[(1RS)-2-ethoxy-1-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-oxo-ethyl]-3-oxo-isoindolin-5-yl]phenyl]-3,3-difluoro-piperidine-1-carboxylate (*Example 67, step 4*) and thiazol-2-amine.

Step 6: (2RS)-2-[4-Chloro-6-[4-(3,3-difluoro-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide



The title compound was obtained as a brown foam, MS: $m/e = 627.2$ ($M+H^+$), using chemistry similar to that described in Example 3, step 3 starting from tert-butyl 4-[4-[7-chloro-2-[(1RS)-1-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-2-oxo-2-(thiazol-2-ylamino)ethyl]-3-oxo-isoindolin-5-yl]phenyl]-3,3-difluoro-piperidine-1-carboxylate (*Example 67, step 5*).

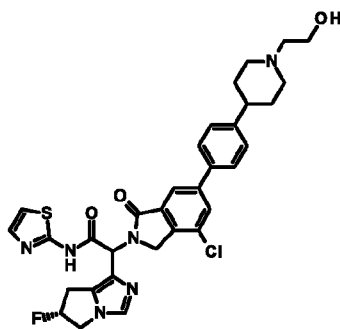
Step 7: (2RS)-2-[4-Chloro-6-[4-(1-ethyl-3,3-difluoro-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide



The title compound was obtained as an off-white solid, MS: $m/e = 655.2$ ($M+H^+$), using chemistry similar to that described in Example 1, step 10 starting from (2RS)-2-[4-chloro-6-[4-(3,3-difluoro-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide (*Example 67, step 6*) and acetaldehyde.

Example 68

(2RS)-2-[4-Chloro-6-[4-[1-(2-hydroxyethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide

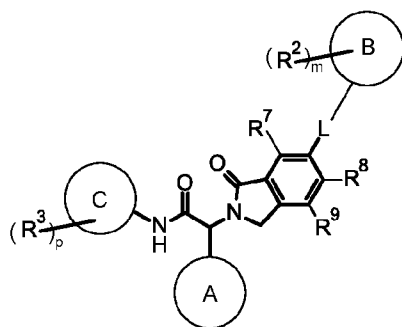


The title compound was obtained as a white solid, MS: $m/e = 635.4$ ($M+H^+$), using chemistry similar to that described in Example 1, step 10 starting from (2RS)-2-[4-chloro-1-oxo-6-[4-(4-piperidyl)phenyl]isoindolin-2-yl]-2-[(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide (*Example 54, step 3*) and 2-hydroxyacetaldehyde.

- ¹ Yarden, Y., Sliwkowski, MX. Untangling the ErbB signalling network. *Nature Review Mol Cell Biol.* 2001 Feb;2(2): 127-37
- ² Ciardiello, F., and Tortora, G. (2008). EGFR antagonists in cancer treatment. *The New England journal of medicine* 358, 1160-1174
- ³ Paez, J. *et al.* (2004). EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* (New York, NY 304, 1497-1500
- ⁴ Sharma SV, Bell DW, Settleman J, Haber DA. Epidermal growth factor receptor mutations in lung cancer. *Nat Rev Cancer.* 2007 Mar;7(3): 169-81
- ⁵ Thress, K. S. *et al.* Acquired EGFR C797S mutation mediates resistance to AZD9291 in non-small cell lung cancer harboring EGFR T790M. *Nat. Med.* 21, 560–562 (2015)
- ⁶ Wang *et al.* EGFR C797S mutation mediates resistance to third-generation inhibitors in T790M-positive non-small cell lung cancer, *J Hematol Oncol.* 2016; 9: 59
- ⁷ Yang *et al.*, Investigating Novel Resistance Mechanisms to Third-Generation EGFR Tyrosine Kinase Inhibitor Osimertinib in Non–Small Cell Lung Cancer Patients, *Clinical Cancer Research*, DOI: 10.1158/1078-0432.CCR-17-2310
- ⁸ Lu *et al.* Targeting EGFR^{L858R/T790M} and EGFR^{L858R/T790M/C797S} resistance mutations in NSCLC: Current developments in medicinal chemistry, <https://doi.org/10.1002/med.21488>, *Med Res Rev* 2018; 1-32
- ⁹ Jia *et al.* Overcoming EGFR(T790M) and EGFR(C797S) resistance with mutant-selective allosteric inhibitors, June 2016, *Nature* 534, 129-132
- ¹⁰ WO2009158369
- ¹¹ WO2016183534
- ¹² *Biochem. Pharmacol.* (1973) 22:3099
- ¹³ IUPAC - Compendium of Chemical Terminology, 2nd, A. D. McNaught & A. Wilkinson (Eds). Blackwell Scientific Publications, Oxford (1997)
- ¹⁴ CAS 869113-97-3
- ¹⁵ CAS 2090424-20-5
- ¹⁶ CAS 457613-78-4
- ¹⁷ CAS 919347-67-4
- ¹⁸ CAS 1522778-35-3
- ¹⁹ CAS 656257-45-3
- ²⁰ CAS 1430472-07-3
- ²¹ CAS 1702698-94-9
- ²² CAS 27628-46-2
- ²³ CAS 899821-27-3

Claims

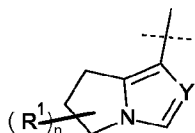
1. A compound of formula I,



I

wherein

- 5 L is absent or $-(C\equiv C)-$,
A is



- B is aryl or heteroaryl,
C is heteroaryl,
10 Y is N, C(OH) or CH,
R¹ is each independently selected from the group consisting of
- i) amino,
 - ii) C₁₋₆-alkyl,
 - iii) C₁₋₆-alkoxy,
 - 15 iv) cyano,
 - v) halogen,
 - vi) halogen-C₁₋₆-alkyl,
 - vii) halogen-C₁₋₆-alkoxy, and
 - viii) hydroxy;
- 20 R² is each independently selected from the group consisting of
- i) $-(CH_2)_k-N(R^4, R^5)$,
 - ii) $-(C=O)-N(R^4, R^5)$,
 - iii) halogen,
 - iv) halogen-C₁₋₆-alkyl,
 - 25 v) $-NH-(C=O)-C_{1-6}$ -alkyl, and
 - vi) C₁₋₆-alkyl, optionally substituted by OH;

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;

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;

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

R⁶ is each independently selected from the group consisting of

- ix) -OH,
- x) halogen,
- xi) C₃₋₈-cycloalkyl,
- xii) halogen-C₁₋₆-alkyl,
- xiii) C₁₋₆-alkoxy-C₁₋₆-alkyl,
- xiv) cyano-C₁₋₆-alkyl,
- xv) C₁₋₆-alkyl, and
- xvi) -(C=O)-C₁₋₆-alkyl;

R⁷ is each independently selected from the group consisting of

- vi) H,
- vii) halogen,
- viii) halogen-C₁₋₆-alkoxy,
- ix) C₁₋₆-alkoxy, and
- x) C₁₋₆-alkyl;

R⁸ is each independently selected from the group consisting of

- v) H,
- vi) halogen,
- vii) C₁₋₆-alkoxy, and
- viii) C₁₋₆-alkyl;

R⁹ is each independently selected from the group consisting of

- vi) H,

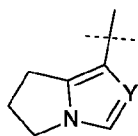
- vii) halogen,
- viii) halogen-C₁₋₆-alkoxy,
- ix) C₁₋₆-alkoxy, and
- x) C₁₋₆-alkyl;

- 5 k is 0, 1 or 2,
 n is 0, 1, 2, 3 or 4;
 m is 0, 1 or 2;
 p is 0 or 1;

or a pharmaceutically acceptable salt thereof.

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

- L is absent or $-(C\equiv C)-$,
 A is



- 15 B is aryl or heteroaryl,
 C is heteroaryl,
 Y is N or CH,
 R² is each independently selected from the group consisting of
- iv) $-(CH_2)_k-N(R^4, R^5)$,
 - 20 v) halogen-C₁₋₆-alkyl, and
 - vi) C₁₋₆-alkyl, optionally substituted by OH;

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

R⁶ is each independently selected from the group consisting of

- 25 vi) $-OH$,
 vii) halogen,
 viii) C₃₋₈-cycloalkyl,
 ix) halogen-C₁₋₆-alkyl,
 x) C₁₋₆-alkoxy-C₁₋₆-alkyl,
 30 xi) cyano-C₁₋₆-alkyl, and
 xii) C₁₋₆-alkyl;

R⁷ is H or halogen;

R⁸ is H;

R⁹ is halogen;

k is 0 or 1;
 n is 0;
 m is 1;
 p is 0.

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



, in particular

wherein

Y is N or CH, and

- R^a, R^b, R^c or R^d is each independently selected from the group consisting of

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

- more particularly, wherein A is 6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl or 6,7-Dihydro-5H-pyrrolizin-1-yl.

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.

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

8. The compound of formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-7, wherein m is 1.
9. The compound of formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-8, wherein p is 0.
- 5 10. The compound of formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-8, wherein R² is -(CH₂)_k-N(R⁴,R⁵), k is 0 or 1 and R⁴ and R⁵ form together with the N they are attached to a heterocyclyl, which heterocyclyl is optionally substituted by R⁶.
- 10 11. The compound of formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-8, wherein R² is -(CH₂)_k-N(R⁴,R⁵), k is 0 or 1 and R⁴ and R⁵ form together with the N they are attached to piperazinyl, piperidinyl or morpholino, which piperazinyl, piperidinyl or morpholino are optionally substituted by R⁶.
12. 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
 - 15 (2*RS*)-2-(6,7-Dihydro-5H-pyrrolizin-1-yl)-2-[4-fluoro-6-[2-[4-[(4-hydroxy-1-piperidyl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide,
 - (2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-6-[2-[4-[(4-methylpiperazin-1-yl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide,
 - 20 (2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-6-[2-[4-[(4-hydroxy-1-piperidyl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide,
 - (2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-1-oxo-6-(4-piperazin-1-yl)phenyl]isoindolin-2-yl]-N-thiazol-2-yl-acetamide,
 - (2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-6-[4-(4-hydroxy-1-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide,
 - 25 (2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-6-[2-[4-(hydroxymethyl)phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide,
 - (2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-1-oxo-6-[2-[4-(1-piperidylmethyl)phenyl]ethynyl]isoindolin-2-yl]-N-thiazol-2-yl-acetamide,
 - 30 (2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[6-[4-(4-ethylpiperazin-1-yl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide,
 - (2*RS*)-2-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[6-[6-(4-ethylpiperazin-1-yl)-3-pyridyl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide,
 - (2*RS*)-2-[4-Chloro-6-[2-[4-[(4-hydroxy-1-piperidyl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide,
 - 35

(2*RS*)-2-[4-Chloro-6-[4-(4-ethylpiperazin-1-yl)phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide,
 (2*RS*)-2-[4-Chloro-6-[4-(4-hydroxy-1-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide,
 5 (2*RS*)-2-[4-Chloro-6-[6-(4-hydroxy-1-piperidyl)-3-pyridyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide, and
 (2*RS*)-2-[7-chloro-4-fluoro-6-[2-[4-[(4-hydroxy-1-piperidyl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide.

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

2-[4-chloro-1-oxo-6-[2-[4-(1-piperidylmethyl)phenyl]ethynyl]isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-2-[6-[4-(1-ethyl-4-piperidyl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide;

15 2-[4-fluoro-6-[2-[4-[(4-hydroxy-1-piperidyl)methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-2-[rac-(6*R*)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

2-[6-[3-chloro-4-(4-ethylpiperazin-1-yl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

20 2-[6-[3-chloro-4-[rac-(3*R*)-3-methylpiperazin-1-yl]phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

2-[6-[3-chloro-4-[rac-(3*R*)-4-ethyl-3-methylpiperazin-1-yl]phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

2-[4-chloro-6-[4-[(1-ethyl-4-piperidyl)oxy]phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

25 2-[6-(3-chloro-4-morpholino-phenyl)-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

2-[6-[3-chloro-4-(4-ethylpiperazin-1-yl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-[rac-(6*R*)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

30 2-[6-(3-chloro-4-morpholino-phenyl)-4-fluoro-1-oxo-isoindolin-2-yl]-2-[rac-(6*R*)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-*c*]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

2-[6-[3-chloro-4-[rac-(3R)-4-ethyl-3-methyl-piperazin-1-yl]phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

2-[6-[4-(1-ethyl-4-piperidyl)-3-fluoro-phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

2-[6-[4-(1-cyclopropyl-4-piperidyl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

2-[4-chloro-6-[4-(1-cyclopropyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

2-[4-chloro-6-[4-(1-ethyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

2-[6-[3-chloro-4-(1-ethyl-4-piperidyl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

2-[6-[4-(1-ethyl-4-piperidyl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-1-oxo-6-[4-[rac-(3R,4R)-1-ethyl-3-fluoro-4-piperidyl]phenyl]isoindolin-2-yl]-N-thiazol-2-yl-acetamide;

2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[6-[4-(1-ethyl-4-piperidyl)-3-fluoro-phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide;

2-[6-[4-[1-(2,2-difluoroethyl)-4-piperidyl]phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-6-[4-[1-(2-methoxyethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide;

2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-6-[4-[1-(2-fluoroethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide;

2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[6-[3-ethyl-4-(1-ethyl-4-piperidyl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide;

2-[6-[4-(4-cyclopropylpiperazin-1-yl)-3-fluoro-phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

2-[6-[3-chloro-4-(4-cyclopropylpiperazin-1-yl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

2-[4-chloro-6-[4-(4-cyclopropylpiperazin-1-yl)-3-fluoro-phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

5 2-[6-[3-chloro-4-[4-(2,2-difluoroethyl)piperazin-1-yl]phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

2-[6-[4-(4-cyclopropylpiperazin-1-yl)-3-fluoro-phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

10 2-[6-[2-(2-chlorophenyl)ethynyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

2-[6-[2-[4-[(4,4-difluoro-1-piperidyl)methyl]phenyl]ethynyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

2-(6,7-dihydro-5H-pyrrolizin-1-yl)-2-[4-fluoro-6-(3-fluoro-4-morpholino-phenyl)-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide;

15 2-[6-[3-chloro-4-(4-cyclopropylpiperazin-1-yl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-[4-fluoro-1-oxo-6-[2-[4-(trifluoromethyl)phenyl]ethynyl]isoindolin-2-yl]-N-thiazol-2-yl-acetamide;

20 2-(6,7-dihydro-5H-pyrrolizin-1-yl)-2-[6-[4-(1-ethyl-4-piperidyl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-thiazol-2-yl-acetamide;

2-[6-[3-chloro-4-[4-(2-fluoroethyl)piperazin-1-yl]phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

2-[6-[3-ethyl-4-(1-ethyl-4-piperidyl)phenyl]-4-fluoro-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

25 2-[7-chloro-4-fluoro-6-(4-morpholinophenyl)-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

2-[4-chloro-6-[3-ethyl-4-(1-ethyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

30 2-[4-chloro-6-[4-(1-ethyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

2-[4-chloro-6-[4-(1-cyclopropyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

2-[4-chloro-6-[4-[1-(2-fluoroethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

5 2-[4-chloro-6-[4-[1-(2-cyanoethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

2-[4-chloro-6-[3-ethyl-4-[1-(2-fluoroethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

10 2-[4-chloro-6-[4-[1-(2-fluoroethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

2-[4-chloro-6-[4-[1-(2,2-difluoroethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

2-[4,7-dichloro-6-[4-(1-ethyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

15 2-[4,7-dichloro-6-[4-(1-ethyl-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

2-[4,7-dichloro-6-[4-[1-(2-fluoroethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide;

20 2-[4,7-dichloro-6-[4-[1-(2-fluoroethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

2-[4,7-dichloro-6-(4-morpholinophenyl)-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

2-[4-chloro-1-oxo-6-[4-[rac-(3R,4R)-1-ethyl-3-fluoro-4-piperidyl]phenyl]isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

25 2-[4-fluoro-6-[2-[4-[4-(hydroxymethyl)-1-piperidyl]methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

2-[4-chloro-6-[4-(1-ethyl-3,3-difluoro-4-piperidyl)phenyl]-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

2-[4-chloro-6-[4-[1-(2-hydroxyethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide.

14. 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

5 2-[4-chloro-6-[3-ethyl-4-[1-(2-fluoroethyl)-4-piperidyl]phenyl]-1-oxo-isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide;

2-[4-chloro-1-oxo-6-[4-[rac-(3R,4R)-1-ethyl-3-fluoro-4-piperidyl]phenyl]isoindolin-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-thiazol-2-yl-acetamide.

10 15. The compound of formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-11, for use as therapeutically active substance.

16. The compound of formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-11, for the use in the therapeutic and/or prophylactic treatment of cancer, in particular non-small-cell lung cancer.

15 17. The compound of formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-11, 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.

18. A pharmaceutical composition comprising the compound of formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-11 and a pharmaceutically acceptable auxiliary substance.

20