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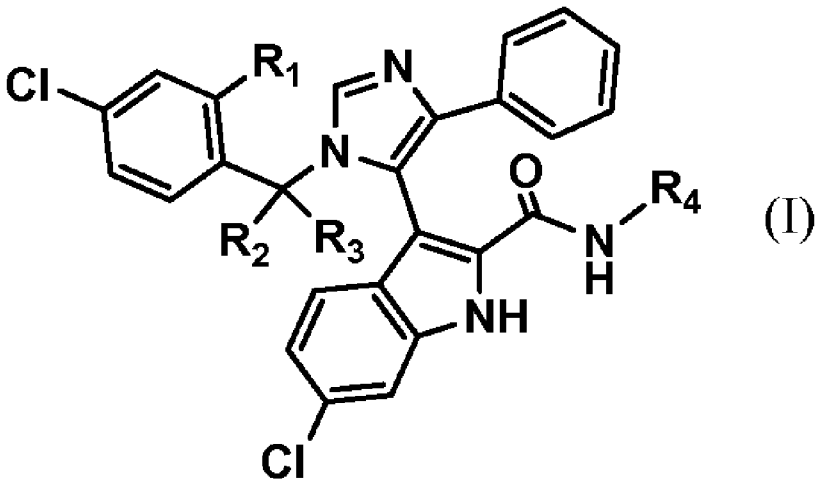
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(54) **Title**: 3 - IMIDAZOLYL- INDOLES FOR THE TREATMENT OF PROLIFERATIVE DISEASES



(I)

(57) **Abstract**: The invention relates to 3-heterocyclyl indolyl compounds capable of inhibiting the interaction between p53, or variants thereof, and MDM2 and/or MDM4, or variants thereof, respectively, said compounds having the formula (I), in which: R^1, R^2, R^3 and R^4 are as defined in the Summary of the Invention. Due to their activity, the compounds are useful in the treatment of various disorders and diseases mediated by the activity of MDM2 and/or MDM4, or variants thereof, such as inflammatory or proliferative diseases or in the protection of cells.

3-IMIDAZOLYL-INDOLES FOR THE TREATMENT OF PROLIFERATIVE DISEASES

BACKGROUND

Field of the Invention

[0001] The present invention relates to compounds capable of inhibiting the interaction between p53 and HDM2 and/or HDM4 (or variants thereof). In particular, compounds of the invention are capable of interfering with the binding of p53 and HDM2 and/or HDM4. The invention further provides a process for the preparation of compounds of the invention, pharmaceutical preparations comprising such compounds and methods of using such compounds in the treatment inflammatory and proliferative diseases.

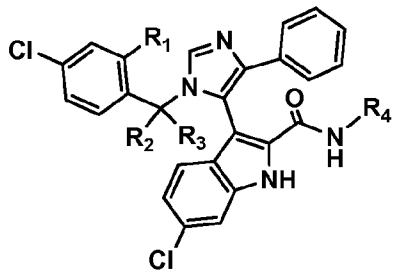
Background of the Invention

[0002] The transcription factor, p53, is known as a tumor suppressor protein which helps to control cellular integrity and prevents the proliferation of permanently damaged cells by initiating growth arrest or apoptosis (controlled cell death). p53 mediaties its effects by regulating a number of genes that control cell cycle and apoptosis. The oncoproteins, MDM2 and MDM4, are key negative regulators of the p53 tumor suppressor. MDM2 and MDM4 are capable of inhibiting p53 tumor suppressor activity, resulting in the inhibition of regulatory mechanisms that impede cells from uncontrolled proliferation. As a consequence, uncontrolled proliferation can take place, leading to tumors, leukemias or other proliferative diseases. Dysregulation of the ratio of MDM2 and p53, for example, due to mutations or molecular defects in the affected cells, can thus be found in many proliferative diseases. Indeed, levels of MDM2 are elevated in several human tumor and proliferative disease types including soft tissue sarcomas, bone cancer (for example osteosarcomas), breast tumors, bladder cancer, Li-Fraumeni syndrome, brain tumor, rhabdomyosarcoma and adrenocortical carcinoma and the like.

[0003] Thus there is a need for new drugs that are capable of interfering with the interaction between p53 and MDM2 and/or p53 and MDM4, especially oncogenic variants thereof, to restore the beneficial effects of p53 in regulating apoptosis.

Summary of the invention

[0004] In one aspect , the present invention provides compounds of Formula I:



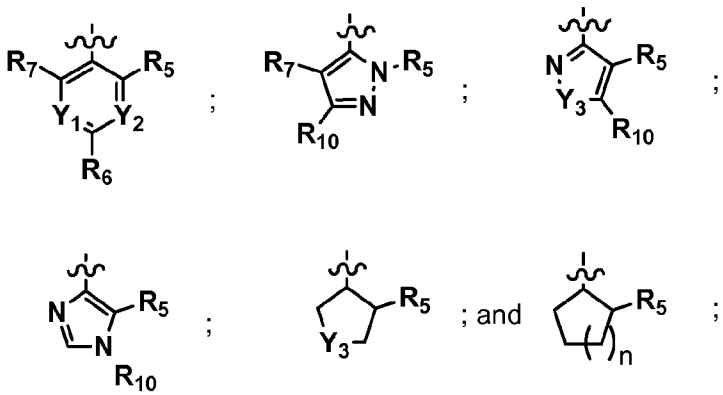
[0005] in which:

[0006] R_1 is selected from hydrogen and chloro;

[0007] R_2 is selected from hydrogen, deuterium and methyl;

[0008] R_3 is selected from hydrogen and deuterium;

[0009] R_4 is selected from:



[0010] wherein:

[0011] n is selected from 1 and 2;

[0012] R_5 is selected from methyl, phenyl, piperidinyl, piperazinyl, 3-oxopiperazin-1-yl, 3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl, 2,4-dioxo-1,3,8-triazaspiro[4.5]decan-8-yl, 3-oxo-1,2,8-triazaspiro[4.5]decan-8-yl, pyrrolidin-1-ylmethyl, piperidin-1-ylmethyl, benzyl, pyridin-4-ylmethyl, pyridin-3-ylmethyl, pyridin-2-ylmethyl, isopentyl, cyclopentyl, cyclohexyl, cyclohexyl-methyl, isobutyl, benzyloxy, pyrrolidin-2-ylmethoxy, 3-(piperazin-1-yl)propoxy, 3-(1,1-dioxidothiomorpholino)propoxy, 3-(diethylamino)propoxy, 3-(pyrrolidin-1-yl)propoxy, 3-(piperidin-1-yl)propoxy, 3-(azepan-1-yl)propoxy, 3-(2-oxopyrrolidin-1-yl)propoxy, pyrrolidin-3-yloxy, 3-(piperazin-1-yl)propoxy, (tetrahydro-2H-pyran-4-yl)methoxy, piperidin-4-ylmethoxy, piperidin-3-ylmethoxy, morpholino-ethoxy, piperidin-4-ylethoxy, 2-(tert-butoxy)ethoxy, 2-isobutoxyethoxy, 2-(2,2,2-trifluoroethoxy)ethoxy, phenoxy-ethoxy, piperidin-3-yloxy, piperidin-4-yloxy, cyclohexyloxy, cyclopropyl-methoxy, 2-amino-ethoxy, pyrrolidinyl-ethoxy, 3-amino-propoxy, and 3-(dimethylamino)-2,2-dimethylpropoxy;

[0013] wherein said phenyl, piperidinyl, piperazinyl, 3-oxopiperazin-1-yl, 3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl, 2,4-dioxo-1,3,8-triazaspiro[4.5]decan-8-yl, 3-oxo-1,2,8-triazaspiro[4.5]decan-8-yl, pyrrolidin-1-ylmethyl, piperidin-1-ylmethyl, benzyl, pyridin-4-ylmethyl, pyridin-3-ylmethyl, pyridin-2-ylmethyl, cyclopentyl, cyclohexyl, cyclohexyl-, benzyloxy, pyrrolidin-2-ylmethoxy, 3-(piperazin-1-yl)propoxy, 3-(1,1-dioxidothiomorpholino)propoxy, 3-(pyrrolidin-1-yl)propoxy, 3-(piperidin-1-yl)propoxy, 3-(azepan-1-yl)propoxy, 3-(2-oxopyrrolidin-1-yl)propoxy, pyrrolidin-3-yloxy, 3-(piperazin-1-yl)propoxy, (tetrahydro-2H-pyran-4-yl)methoxy, piperidin-4-ylmethoxy, piperidin-3-ylmethoxy, morpholino-ethoxy, piperidin-4-ylethoxy, 2-(tert-butoxy)ethoxy, phenoxy-ethoxy, piperidin-3-yloxy, piperidin-4-yloxy, cyclohexyloxy, cyclopropyl-methoxy, pyrrolidinyl-ethoxy, 2-amino-ethoxy, 3-amino-propoxy, or 3-(dimethylamino)-2,2-dimethylpropoxy of R_5 can be unsubstituted or substituted with 1 to 2 groups selected from $-NR_{13}C(O)OR_{14}$, $-NR_{13}S(O)_{0-2}R_{14}$, $-NR_{13}C(O)X_1OR_{14}$, $-NR_{13}C(O)OX_1OR_{14}$, $-NR_{13}C(O)NR_{13}R_{14}$, $-NR_{13}R_{14}$, $-X_1NR_{13}R_{14}$, $-NR_{13}C(O)R_{14}$, $-C(O)R_{14}$, $-C(O)OR_{14}$, $-C(O)NR_{13}R_{14}$, $-C(O)OX_1OR_{14}$, $C(O)NR_{13}X_1OR_{14}$, $-OR_{14}$, $-X_1R_{14}$, $-X_1OR_{14}$, $-NR_{13}X_1R_{14}$, hydroxyl, cyano, branched or unbranched C_{1-6}alkyl, piperidinyl, cyclohexyl, pyridinyl, piperazinyl, phenyl, pyrimidinyl, 4H-1,2,4-triazol-4-yl, 1,3,4-oxadiazol-2-

yl, 1H-1,2,4-triazol-3-yl, 5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl, tetrahydro-2H-pyran-4-yl, 2-oxopyrrolidin-1-yl, 2-oxo-1,3-oxazinan-3-yl, 2-oxopiperidin-1-yl, isoxazol-4-yl, 2-oxoimidazolidin-1-yl, 2-oxooxazolidin-3-yl, 1,1-dioxidoisothiazolidin-2-yl, 3-oxomorpholino, 1,1-dioxido-1,2-thiazinan-2-yl, 1,1-dioxido-1,2,6-thiadiazinan-2-yl, 2-oxotetrahydropyrimidin-1(2H)-yl, 2-oxo-1,3-oxazinan-3-yl, 2-oxopiperidin-1-yl, 2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl, 1,1-dioxidothiomorpholino, 2-oxo-1,4-diazepan-1-yl, 7-oxo-1,4-diazepan-1-yl and 2-oxoazepan-1-yl; wherein R_{13} at each occurrence is independently selected from hydrogen, methyl (see compound 91) and ethyl; and R_{14} at each occurrence is independently selected from hydrogen, branched or unbranched C_{1-6}alkyl, branched or unbranched hydroxy-substituted-C_{1-6}alkyl (see compounds 93/4), branched or unbranched halo-substituted-C_{1-6}alkyl, phenyl, pyridinyl, pyrazinyl, pyrimidinyl, tetrahydrofuranyl, cyclopentyl, trideuterated-methyl (see example 70), cyclopropyl, pyrrolidinyl, tetrahydro-2H-pyran-4-yl, azetidin-1-yl and cyclobutyl; wherein each R_{14} can be optionally further substituted with halo, hydroxy, $-X_1OR_{15}$, $-C(O)OR_{15}$ and $-C(O)R_{15}$; wherein R_{15} at each occurrence is independently selected from hydrogen and branched or unbranched C_{1-6}alkyl;

[0014] wherein said piperidinyl, cyclohexyl, pyridinyl, piperazinyl, phenyl, pyrimidinyl, 4H-1,2,4-triazol-4-yl, 1,3,4-oxadiazol-2-yl, 1H-1,2,4-triazol-3-yl, 5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl, tetrahydro-2H-pyran-4-yl, tetrahydrofuranyl, 2-oxopyrrolidin-1-yl, 2-oxo-1,3-oxazinan-3-yl, 2-oxopiperidin-1-yl, isoxazol-4-yl, 2-oxoimidazolidin-1-yl, 2-oxooxazolidin-3-yl, 1,1-dioxidoisothiazolidin-2-yl, 3-oxomorpholino, 1,1-dioxido-1,2-thiazinan-2-yl, 1,1-dioxido-1,2,6-thiadiazinan-2-yl, 2-oxotetrahydropyrimidin-1(2H)-yl, 2-oxo-1,3-oxazinan-3-yl, 2-oxopiperidin-1-yl, 2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl, 2-oxo-1,4-diazepan-1-yl, 7-oxo-1,4-diazepan-1-yl and 2-oxoazepan-1-yl substituents of R_5 can be optionally further substituted, where substituents are permitted, by 1 to 3 groups selected from halo, C_{1-4}alkyl, amino, tetrahydrofuranyl and hydroxy-substituted-C_{1-4}alkyl;

[0015] R_6 is selected from hydrogen, halo, C_{1-4}alkyl and C_{1-4}alkoxy;

[0016] R_7 is selected from hydrogen, C_{1-4}alkyl and C_{1-4}alkoxy;

[0017] Y_1 and Y_2 are independently selected from CR_8 and N; wherein R_8 is selected from hydrogen, halo, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, $-OX_1OR_{9a}$ (see compounds 230-233), $-X_1OR_{9a}$

(see compound 235), $-C(O)OR_{9a}$, $-X_1C(O)OR_{9a}$ (see compound 270), $-C(O)NR_{9a}R_{9b}$, $-X_1C(O)NR_{9a}R_{9b}$ and $-C(O)NR_{9a}X_1OR_{9b}$ (see compound 211); wherein X_1 is at each occurrence is independently selected from branched or unbranched C_{1-6}alkylene; R_{9a} and R_{9b} are independently selected from hydrogen, C_{1-4}alkyl, deutorated-C_{1-4}alkyl (see compound 186), halo-substituted-C_{1-4}alkyl and hydroxy-substituted-C_{1-4}alkyl; or R_{9a} and R_{9b} together with the nitrogen to which they are both attached form a 4-7 member saturated ring containing up to 2 heteroatoms selected from N, O and S; wherein said ring formed by R_{9a} and R_{9b} can be unsubstituted or substituted with a group selected from hydroxyl (see compound 212) and C_{1-4}alkyl;

[0018] R_{10} is selected from hydrogen and C_{1-4}alkyl;

[0019] Y_3 is selected from NR_{11} and O; wherein R_{11} is selected from hydrogen, C_{1-4}alkyl, $-S(O)_{0-2}R_{12}$, $-C(O)X_2OR_{12}$ and $-C(O)R_{12}$; and R_{12} is selected from hydrogen and C_{1-4}alkyl; and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof; and the pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds.

[0020] In a second aspect, the present invention provides a pharmaceutical composition which contains a compound of Formula I or a N-oxide derivative, individual isomers and mixture of isomers thereof; or a pharmaceutically acceptable salt thereof, in admixture with one or more suitable excipients.

[0021] In a third aspect, the present invention provides a method of treating a disease in an animal in which modulation of p53 (particularly a disease or disorder which is mediated by the activity of MDM2 and/or MDM4), can prevent, inhibit or ameliorate the pathology and/or symptomology of the diseases, which method comprises administering to the animal a therapeutically effective amount of a compound of Formula I or a N-oxide derivative, individual isomers and mixture of isomers thereof, or a pharmaceutically acceptable salt thereof.

[0022] In a fourth aspect, the present invention provides the use of a compound of Formula I in the manufacture of a medicament for treating a disease in an animal in which p53 activity (particularly a disease or disorder which is mediated by the activity of MDM2 and/or MDM4), contributes to the pathology and/or symptomology of the disease.

[0023] In a fifth aspect, the present invention provides a process for preparing compounds of Formula I and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, and the pharmaceutically acceptable salts thereof.

Definitions

[0024] The general terms used hereinbefore and hereinafter preferably have within the context of this disclosure the following meanings, unless otherwise indicated, where more general terms whereever used may, independently of each other, be replaced by more specific definitions or remain, thus defining more detailed embodiments of the invention:

[0025] "Alkyl" as a group and as a structural element of other groups, for example halo-substituted-alkyl and alkoxy, can be either straight-chained or branched. C_{1-4}-alkoxy includes, methoxy, ethoxy, and the like. Halo-substituted alkyl includes trifluoromethyl, pentafluoroethyl, and the like.

[0026] "Aryl" means a monocyclic or fused bicyclic aromatic ring assembly containing six to ten ring carbon atoms. For example, aryl may be phenyl or naphthyl, preferably phenyl. "Arylene" means a divalent radical derived from an aryl group.

[0027] "Heteroaryl" is as defined for aryl above where one or more of the ring members is a heteroatom. For example C_{5-10}heteroaryl is a minimum of 5 members as indicated by the carbon atoms but that these carbon atoms can be replaced by a heteroatom. Consequently, C_{5-10}heteroaryl includes pyridyl, indolyl, indazolyl, quinoxalinyl, quinolinyl, benzofuranyl, benzopyranyl, benzothiopyranyl, benzo[1,3]dioxole, imidazolyl, benzo-imidazolyl, pyrimidinyl, furanyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl, thienyl, etc.

[0028] "Cycloalkyl" means a saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly containing the number of ring atoms indicated. For example, C_{3-10}cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

[0029] "Heterocycloalkyl" means cycloalkyl, as defined in this application, provided that one or more of the ring carbons indicated, are replaced by a moiety selected

from -O-, -N=, -NR-, -C(O)-, -S-, -S(O) - or -$S(O)_2$-, wherein R is hydrogen, C_{1-4}alkyl or a nitrogen protecting group. For example, C_{3-8}heterocycloalkyl as used in this application to describe compounds of the invention includes morpholino, pyrrolidinyl, pyrrolidinyl-2-one, piperazinyl, piperidinyl, piperidinylone, 1,4-dioxa-8-aza-spiro[4.5]dec-8-yl, thiomorpholino, sulfanomorpholino, sulfonomorpholino, etc.

[0030] "Halogen" (or halo) preferably represents chloro or fluoro, but may also be bromo or iodo.

[0031] Compounds of the formula I may have different isomeric forms. For example, any asymmetric carbon atom may be present in the (R)-, (S)- or (R,S)-configuration, preferably in the (R)- or (S)-configuration. Substituents at a double bond or especially a ring may be present in cis- (= Z-) or trans (= E-) form. The compounds may thus be present as mixtures of isomers or preferably as pure isomers, preferably as pure diastereomers or pure enantiomers.

[0032] Where the plural form (e.g. compounds, salts) is used, this includes the singular (e.g. a single compound, a single salt). "A compound" does not exclude that (e.g. in a pharmaceutical formulation) more than one compound of the formula I (or a salt thereof) is present, the "a" merely representing the indefinite article. "A" can thus preferably be read as "one or more", less preferably alternatively as "one".

[0033] Wherever a compound or compounds of the formula I are mentioned, this is further also intended to include N-oxides of such compounds and/or tautomers thereof.

[0034] The term "and/or an N-oxide thereof, a tautomer thereof and/or a (preferably pharmaceutically acceptable) salt thereof" especially means that a compound of the formula I may be present as such or in mixture with its N-oxide, as tautomer (e.g. due to keto-enol, lactam-lactim, amide-imidic acid or enamine-imine tautomerism) or in (e.g. equivalency reaction caused) mixture with its tautomer, or as a salt of the compound of the formula I and/or any of these forms or mixtures of two or more of such forms.

[0035] p53 refers to the human protein itself as described by Matlashewski et al. in EMBO J. 3, 3257-62 (1984) (named also p53 wild type herein) or to any variant (e.g. a mutant, fragment or isoform due to deletion, insertion and/or exchange of one or more, e.g. one to 200, of the amino acids) thereof that is still capable to retain preferably at least 1 %, more preferably at

least 5 %, yet more preferably at least 10%, 20%, 30%, 40%, 50% or more than 50% of the p53 activity in growth suppression, e.g. in the growth suppression assay described in Pietenpol et al., Proc. Nat. Acad. Sci. USA 91, 1998-2002 (1994) and, if compared with the corresponding sequence of p53 wild type, shows at least 20 %, more preferably at least 25 % identity with the full sequence, e.g. at least 90% identity with a partial sequence thereof.

[0036] MDM2 or variants thereof) generally refers to all genes and/or proteins encoded thereof with the names MDM2, Mdm2, HDM2, Hdm2, or a variant thereof. MDM4 (especially when mentioned as MDM4 or variants thereof) refers to all genes and/or proteins encoded thereof with the names MDM4, Mdm4, HDM4, Hdm4, MDMX, MdmX, HDMX, HdmX, or a variant thereof.

[0037] MDM2 specifically relates to MDM2 as described in EMBO J. 10, 1565-9, Fakharzadeh et al., 1991, a variant thereof refers to a variant thereof which still binds to p53 in the assay system described below (e.g. an isoform, fragment, mutant or oncogene due to deletion, insertion and/or exchange of one or more, e.g. one to 430, of the amino acids), corresponding to the full length proteins as originally described, preferably at least with 0.5 %, more preferably at least with 5%, 10%, 20%, 30%, 40% or especially 50% or more of the affinity of MDM2 to p53, and have at least 20%, more preferably at least 25%, sequence identity to MDM2 or to HDM2 as originally described or as mentioned below specifically. Where not mentioned otherwise, MDM2 generally relates to MDM2, Mdm2, HDM2 or Hdm2, or variants thereof, respectively, as just defined.

[0038] MDM4 specifically relates to MDM4 as described in Genomics 43, 34-42, Shvarts et al., 1997, a variant thereof refers to a variant thereof which still binds to p53 in the assay system described below (e.g. an isoform, fragment, mutant or oncogene due to deletion, insertion and/or exchange of one or more, e.g. one to 430, of the amino acids), corresponding to the full length proteins as originally described, preferably at least with 0.5 %, more preferably at least with 5%, 10%, 20%, 30%, 40% or especially 50% or more of the affinity of MDM4 to p53, and have at least 20%, more preferably at least 25%, sequence identity to MDM4, to MDMX, to HDM4 or to HDM2 as originally described or as mentioned below specifically. Where not

mentioned otherwise, MDM4 generally relates to MDM4, Mdm4, HDM4, Hdm4, MDMX, MdmX, HDMX or HdmX, or variants thereof, respectively, as just defined.

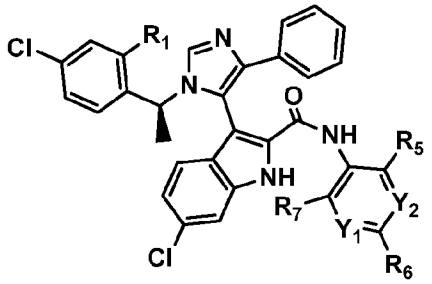
[0039] The percentage of sequence identity, often also termed homology, between a protein and a variant thereof is preferably determined by a computer program commonly employed for this purpose, such as the Gap program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Reseach Park, Madison Wisconsin, USA, which uses the algorithm of Smith and Waterman (Adv. Appl. Math. 2: 482-489 (1981)., especially using an affine gap search with a gap open penalty of 12 and a gap extension penalty of 1.

[0040] "Variants thereof" where mentioned means one or more variant(s).

[0041] A proto-oncogene is a normal gene that can become an oncogene, either after mutation or increased expression. Proto-oncogenes code for proteins that help to regulate cell growth and differentiation. Proto-oncogenes are often involved in signal transduction and execution of mitogenic signals, usually through their protein products. Upon activation, a proto-oncogene (or its product) becomes a tumor inducing agent, an oncogene.

Description of Preferred Embodiments

[0042] The present invention relates to the discovery of compounds of Formula I capable of inhibiting the interaction between p53 and MDM2 and/or MDM4, especially binding to MDM2 and/or MDM4. In one embodiment, with respect to compounds of Formula I, are compounds of Formula Ia:



Ia

[0043] in which:

[0044] R_1 is selected from hydrogen and chloro;

[0045] Y_1 and Y_2 are independently selected from CR_8 and N;

[0046] R_6 is selected from hydrogen, halo, C_{1-4}alkyl and C_{1-4}alkoxy;

[0047] R_5 is selected from methyl, piperidinyl, piperazinyl, 3-oxopiperazin-1-yl, 3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl, 3-oxo-1,2,8-triazaspiro[4.5]decan-8-yl, 2,4-dioxo-1,3,8-triazaspiro[4.5]decan-8-yl, pyrrolidin-1-ylmethyl, piperidin-1-ylmethyl, pyrrolidin-2-ylmethoxy, 3-(piperazin-1-yl)propoxy, 3-(1,1-dioxidothiomorpholino)propoxy, 3-(diethylamino)propoxy, 3-(azepan-1-yl)propoxy, 3-(2-oxopyrrolidin-1-yl)propoxy, pyrrolidin-3-yloxy, 3-(piperazin-1-yl)propoxy, (tetrahydro-2H-pyran-4-yl)methoxy, piperidin-4-ylmethoxy, piperidin-3-ylmethoxy, 2-(tert-butoxy)ethoxy, 2-isobutoxyethoxy, 2-(2,2,2-trifluoroethoxy)ethoxy, phenoxy-ethoxy, piperidin-3-yloxy, piperidin-4-yloxy, cyclohexyloxy, cyclopropyl-methoxy, 2-amino-ethoxy, pyrrolidinyl-ethoxy, 3-amino-propoxy, and 3-(dimethylamino)-2,2-dimethylpropoxy; wherein said piperidinyl, piperazinyl, 3-oxopiperazin-1-yl, 3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl, 3-oxo-1,2,8-triazaspiro[4.5]decan-8-yl, 2,4-dioxo-1,3,8-triazaspiro[4.5]decan-8-yl, pyrrolidin-1-ylmethyl, piperidin-1-ylmethyl, pyrrolidin-2-ylmethoxy, 3-(piperazin-1-yl)propoxy, 3-(1,1-dioxidothiomorpholino)propoxy, 3-(diethylamino)propoxy, 3-(azepan-1-yl)propoxy, 3-(2-oxopyrrolidin-1-yl)propoxy, pyrrolidin-3-yloxy, 3-(piperazin-1-yl)propoxy, (tetrahydro-2H-pyran-4-yl)methoxy, piperidin-4-ylmethoxy, piperidin-3-ylmethoxy, 2-(tert-butoxy)ethoxy, 2-isobutoxyethoxy, 2-(2,2,2-trifluoroethoxy)ethoxy, phenoxy-ethoxy, piperidin-3-yloxy, piperidin-4-yloxy, cyclohexyloxy, cyclopropyl-methoxy, 2-amino-ethoxy, pyrrolidinyl-ethoxy, 3-amino-propoxy, or 3-(dimethylamino)-2,2-dimethylpropoxy of R_5 can be unsubstituted or substituted

with a group selected from -$NR_{13}C(O)OR_{14}$, -$NR_{13}S(O)_{0-2}R_{14}$, -$NR_{13}C(O)X_1OR_{14}$, -$NR_{13}C(O)OX_1OR_{14}$, -$NR_{13}C(O)NR_{13}R_{14}$, -$NR_{13}R_{14}$, -$X_1NR_{13}R_{14}$, -$NR_{13}C(O)R_{14}$, -$C(O)R_{14}$, -$C(O)OR_{14}$, -$C(O)NR_{13}R_{14}$, - $C(O)OX_1OR_{14}$, $C(O)NR_{13}X_1OR_{14}$, -OR_{14}, -X_1R_{14}, -X_1OR_{14}, -$NR_{13}X_1R_{14}$, hydroxyl, cyano, branched or unbranched C_{1-6}alkyl, piperidinyl, cyclohexyl, pyridinyl, piperazinyl, phenyl, pyrimidinyl, 4H-1,2,4-triazol-4-yl, 1,3,4-oxadiazol-2-yl, 1H-1,2,4-triazol-3-yl, 5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl, tetrahydro-2H-pyran-4-yl, 2-oxopyrrolidin-1-yl, 2-oxo-1,3-oxazinan-3-yl, 2-oxopiperidin-1-yl, isoxazol-4-yl, 2-oxoimidazolidin-1-yl, 2-oxooxazolidin-3-yl, 1,1-dioxidoisothiazolidin-2-yl, 3-oxomorpholino, 1,1-dioxido-1,2-thiazinan-2-yl, 1,1-dioxido-1,2,6-thiadiazinan-2-yl, 2-oxotetrahydropyrimidin-1(2H)-yl, 2-oxo-1,3-oxazinan-3-yl, 2-oxopiperidin-1-yl, 2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl, 1,1-dioxidothiomorpholino, 2-oxo-1,4-diazepan-1-yl, 7-oxo-1,4-diazepan-1-yl and 2-oxoazepan-1-yl; wherein R_{13} at each occurrence is independently selected from hydrogen, methyl and ethyl; and R_{14} at each occurrence is independently selected from hydrogen, branched or unbranched C_{1-6}alkyl, branched or unbranched hydroxy-substituted-C_{1-6}alkyl, branched or unbranched halo-substituted-C_{1-6}alkyl, phenyl, pyridinyl, pyrazinyl, pyrimidinyl, tetrahydrofuranyl, cyclopentyl, trideuterated-methyl, cyclopropyl, pyrrolidinyl, tetrahydro-2H-pyran-4-yl, azetidin-1-yl and cyclobutyl; wherein each R_{14} can be optionally further substituted with halo, hydroxy, -X_1OR_{15}, -$C(O)OR_{15}$ and -$C(O)R_{15}$; wherein R_{15} at each occurrence is independently selected from hydrogen and branched or unbranched C_{1-6}alkyl; wherein said piperidinyl, cyclohexyl, pyridinyl, piperazinyl, phenyl, pyrimidinyl, 4H-1,2,4-triazol-4-yl, 1,3,4-oxadiazol-2-yl, 1H-1,2,4-triazol-3-yl, 5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl, tetrahydro-2H-pyran-4-yl, tetrahydrofuranyl, 2-oxopyrrolidin-1-yl, 2-oxo-1,3-oxazinan-3-yl, 2-oxopiperidin-1-yl, isoxazol-4-yl, 2-oxoimidazolidin-1-yl, 2-oxooxazolidin-3-yl, 1,1-dioxidoisothiazolidin-2-yl, 3-oxomorpholino, 1,1-dioxido-1,2-thiazinan-2-yl, 1,1-dioxido-1,2,6-thiadiazinan-2-yl, 2-oxotetrahydropyrimidin-1(2H)-yl, 2-oxo-1,3-oxazinan-3-yl, 2-oxopiperidin-1-yl, 2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl, 2-oxo-1,4-diazepan-1-yl, 7-oxo-1,4-diazepan-1-yl and 2-oxoazepan-1-yl substituents of R_5 can be optionally further substituted by 1 to 2 groups selected from halo, C_{1-4}alkyl, amino, tetrahydrofuranyl and hydroxy-substituted-C_{1-4}alkyl;

[0048] R_7 is selected from hydrogen, C_{1-4}alkyl and C_{1-4}alkoxy;

[0049] R_8 is selected from hydrogen, halo, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, $-OX_1OR_{9a}$, $-X_1OR_{9a}$, $-C(O)OR_{9a}$, $-X_1C(O)OR_{9a}$, $-C(O)NR_{9a}R_{9b}$, $-X_1C(O)NR_{9a}R_{9b}$ and $-C(O)NR_{9a}X_1OR_{9b}$; wherein X_1 is at each occurrence is independently selected from branched or unbranched C_{1-6}alkylene; and R_{9a} and R_{9b} are independently selected from hydrogen, C_{1-4}alkyl, deutorated-C_{1-4}alkyl, halo-substituted-C_{1-4}alkyl and hydroxy-substituted-C_{1-4}alkyl; or R_{9a} and R_{9b} together with the nitrogen to which they are both attached form a 4-7 member saturated ring containing up to 2 heteroatoms selected from N, O and S; wherein said ring formed by R_{9a} and R_{9b} can be unsubstituted or substituted with a group selected from hydroxyl and C_{1-4}alkyl ; or the pharmaceutically acceptable salts thereof.

[0050] In a further embodiment, Y_1 is selected from N and CR_8; Y_2 is selected from N and CR_8; R_6 is selected from hydrogen, methoxy, methyl, fluoro; R_7 is selected from hydrogen, methyl and methoxy; and R_8 is selected from hydrogen, chloro, fluoro, cyano, methoxy, hydroxy-methyl, hydroxy-ethoxy, trifluoromethyl, methoxy-ethoxy, methoxy-methyl, 2-hydroxy-2-methylpropyl, carboxy-methyl, hydroxy-carbonyl-methyl, methyl-amino-carbonyl-methyl, dimethylamino-carbonyl-methyl, $-C(O)NR_{9a}R_{9b}$, $-C(O)OR_{9a}$ and $-C(O)NR_{9a}R_{9b}$; wherein R_{9a} is selected from hydrogen, methyl and trideuterated-methyl; and R_{9b} is selected from methyl, trideuterated-methyl, methoxy-ethyl and hydroxy-ethyl; or R_{9a} and R_{9b} together with the nitrogen to which they are both attached form azetidin-1-yl optionally substituted with hydroxyl; or the pharmaceutically acceptable salts thereof.

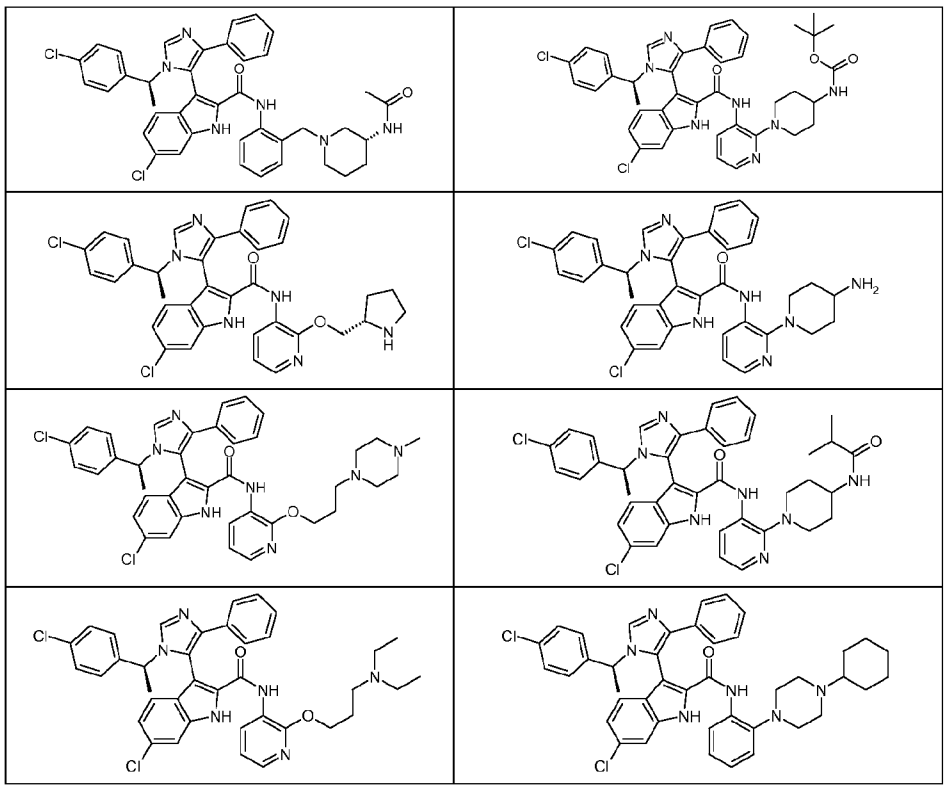
[0051] In a further embodiment, R_5 is selected from methyl, piperidinyl, piperazinyl, 3-oxopiperazin-1-yl, 3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl, 3-oxo-1,2,8-triazaspiro[4.5]decan-8-yl, 2,4-dioxo-1,3,8-triazaspiro[4.5]decan-8-yl, pyrrolidin-1-ylmethyl, piperidin-1-ylmethyl, pyrrolidin-2-ylmethoxy, 3-(piperazin-1-yl)propoxy, 3-(1,1-dioxidothiomorpholino)propoxy, 3-(diethylamino)propoxy, 3-(azepan-1-yl)propoxy, 3-(2-oxopyrrolidin-1-yl)propoxy, pyrrolidin-3-yloxy, 3-(piperazin-1-yl)propoxy, (tetrahydro-2H-pyran-4-yl)methoxy, piperidin-4-ylmethoxy, piperidin-3-ylmethoxy, 2-(tert-butoxy)ethoxy, 2-isobutoxyethoxy, 2-(2,2,2-trifluoroethoxy)ethoxy, phenoxy-ethoxy, piperidin-3-yloxy, piperidin-4-yloxy, cyclohexyloxy, cyclopropyl-methoxy, 2-amino-ethoxy, pyrrolidinyl-ethoxy, 3-amino-propoxy, and 3-(dimethylamino)-2,2-dimethylpropoxy;

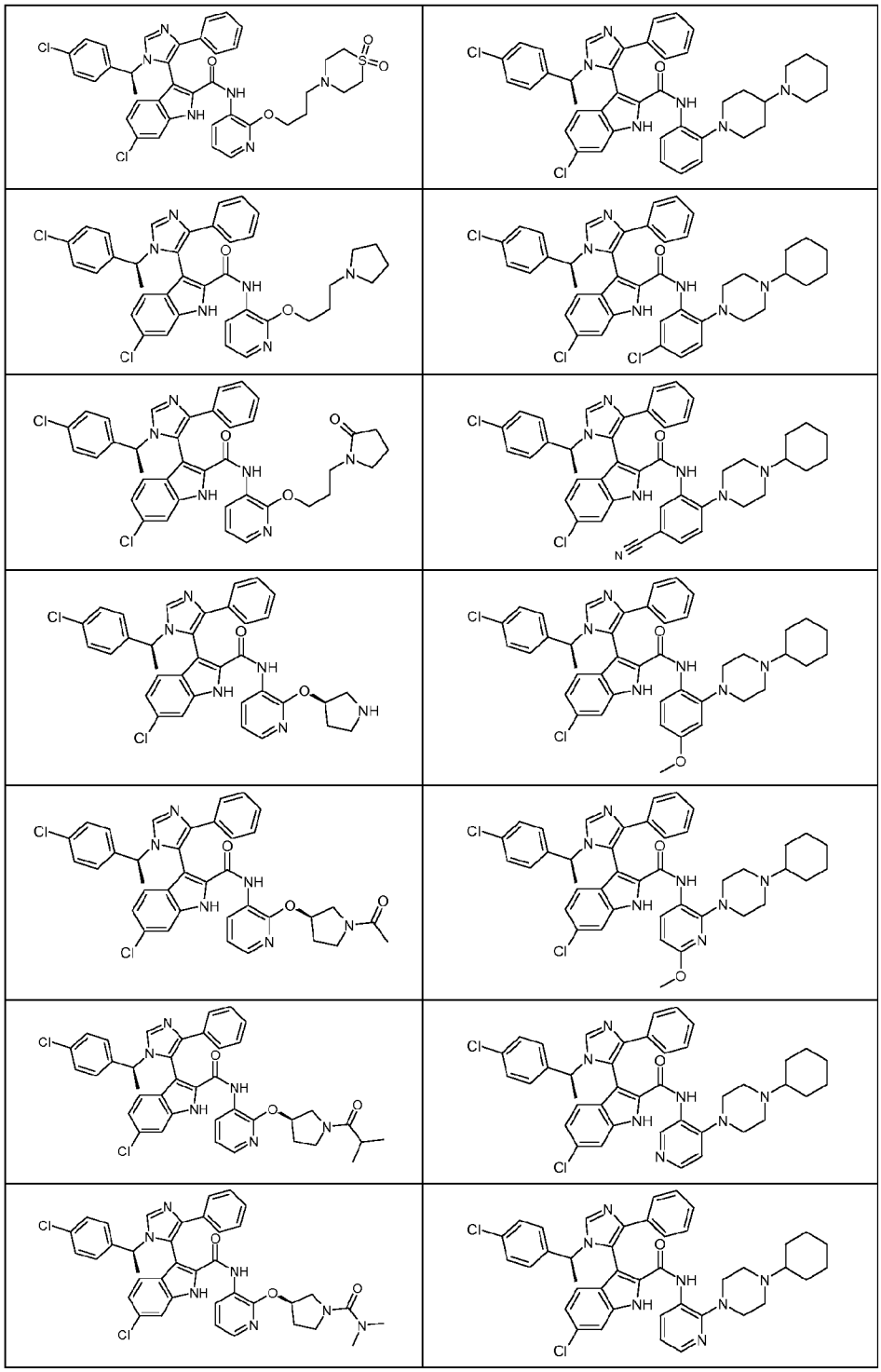
[0052] wherein said piperidinyl, piperazinyl, 3-oxopiperazin-1-yl, 3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl, 3-oxo-1,2,8-triazaspiro[4.5]decan-8-yl, 2,4-dioxo-1,3,8-triazaspiro[4.5]decan-8-yl, pyrrolidin-1-ylmethyl, piperidin-1-ylmethyl, pyrrolidin-2-ylmethoxy, 3-(piperazin-1-yl)propoxy, 3-(1,1-dioxidothiomorpholino)propoxy, 3-(diethylamino)propoxy, 3-(azepan-1-yl)propoxy, 3-(2-oxopyrrolidin-1-yl)propoxy, pyrrolidin-3-yloxy, 3-(piperazin-1-yl)propoxy, (tetrahydro-2H-pyran-4-yl)methoxy, piperidin-4-ylmethoxy, piperidin-3-ylmethoxy, 2-(tert-butoxy)ethoxy, 2-isobutoxyethoxy, 2-(2,2,2-trifluoroethoxy)ethoxy, phenoxy-ethoxy, piperidin-3-yloxy, piperidin-4-yloxy, cyclohexyloxy, cyclopropyl-methoxy, 2-amino-ethoxy, pyrrolidinyl-ethoxy, 3-amino-propoxy, or 3-(dimethylamino)-2,2-dimethylpropoxy of R_5 can be unsubstituted or substituted with a group selected from $-NR_{13}C(O)OR_{14}$, $-NR_{13}S(O)_{0-2}R_{14}$, $-NR_{13}C(O)X_1OR_{14}$, $-NR_{13}C(O)OX_1OR_{14}$, $-NR_{13}C(O)NR_{13}R_{14}$, $-NR_{13}R_{14}$, $-X_1NR_{13}R_{14}$, $-NR_{13}C(O)R_{14}$, $-C(O)R_{14}$, $-C(O)OR_{14}$, $-C(O)NR_{13}R_{14}$, $-C(O)OX_1OR_{14}$, $C(O)NR_{13}X_1OR_{14}$, $-OR_{14}$, $-X_1R_{14}$, $-X_1OR_{14}$, $-NR_{13}X_1R_{14}$, hydroxyl, cyano, branched or unbranched C_{1-6}alkyl, piperidinyl, cyclohexyl, pyridinyl, piperazinyl, phenyl, pyrimidinyl, 4H-1,2,4-triazol-4-yl, 1,3,4-oxadiazol-2-yl, 1H-1,2,4-triazol-3-yl, 5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl, tetrahydro-2H-pyran-4-yl, 2-oxopyrrolidin-1-yl, 2-oxo-1,3-oxazinan-3-yl, 2-oxopiperidin-1-yl, isoxazol-4-yl, 2-oxoimidazolidin-1-yl, 2-oxooxazolidin-3-yl, 1,1-dioxidoisothiazolidin-2-yl, 3-oxomorpholino, 1,1-dioxido-1,2-thiazinan-2-yl, 1,1-dioxido-1,2,6-thiadiazinan-2-yl, 2-oxotetrahydropyrimidin-1(2H)-yl, 2-oxo-1,3-oxazinan-3-yl, 2-oxopiperidin-1-yl, 2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl, 1,1-dioxidothiomorpholino, 2-oxo-1,4-diazepan-1-yl, 7-oxo-1,4-diazepan-1-yl and 2-oxoazepan-1-yl; wherein R_{13} at each occurrence is independently selected from hydrogen, methyl and ethyl; and R_{14} at each occurrence is independently selected from hydrogen, t-butyl, isopropyl, methyl, ethyl, pentan-3-yl, trideuterated-methyl, neopentyl, trifluoromethyl, phenyl, pyridinyl, pyrazinyl, pyrimidinyl, tetrahydrofuranyl, cyclopentyl, trideuterated-methyl, cyclopropyl, pyrrolidinyl, tetrahydro-2H-pyran-4-yl, azetidin-1-yl and cyclobutyl; wherein each R_{14} can be optionally further substituted with halo, hydroxy, $-X_1OR_{15}$, $-C(O)OR_{15}$ and $-C(O)R_{15}$; wherein R_{15} at each occurrence is independently selected from hydrogen, methyl, ethyl and t-butyl;

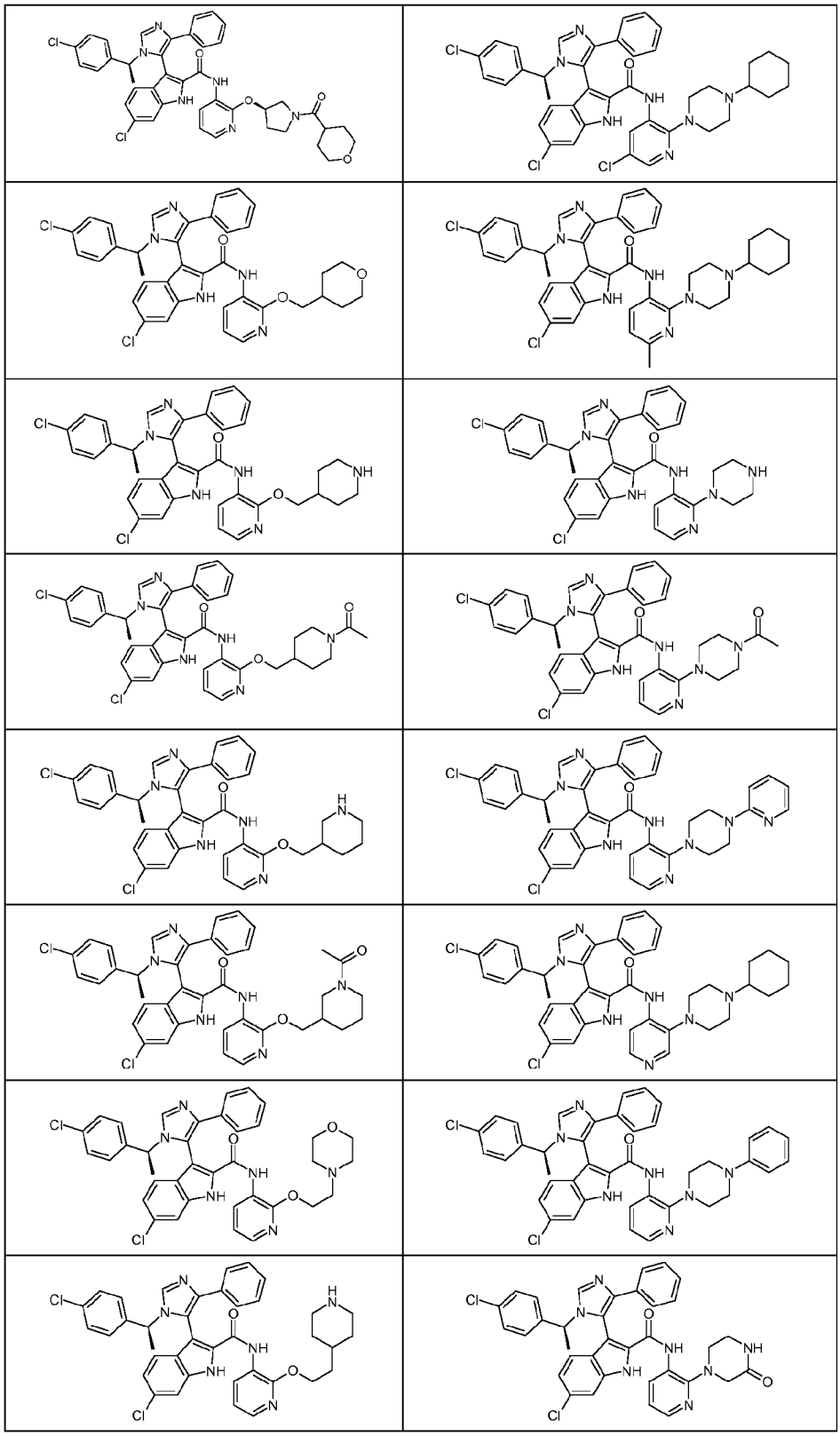
[0053] wherein said piperidinyl, cyclohexyl, pyridinyl, piperazinyl, phenyl, pyrimidinyl, 4H-1,2,4-triazol-4-yl, 1,3,4-oxadiazol-2-yl, 1H-1,2,4-triazol-3-yl, 5-oxo-4,5-dihydro-

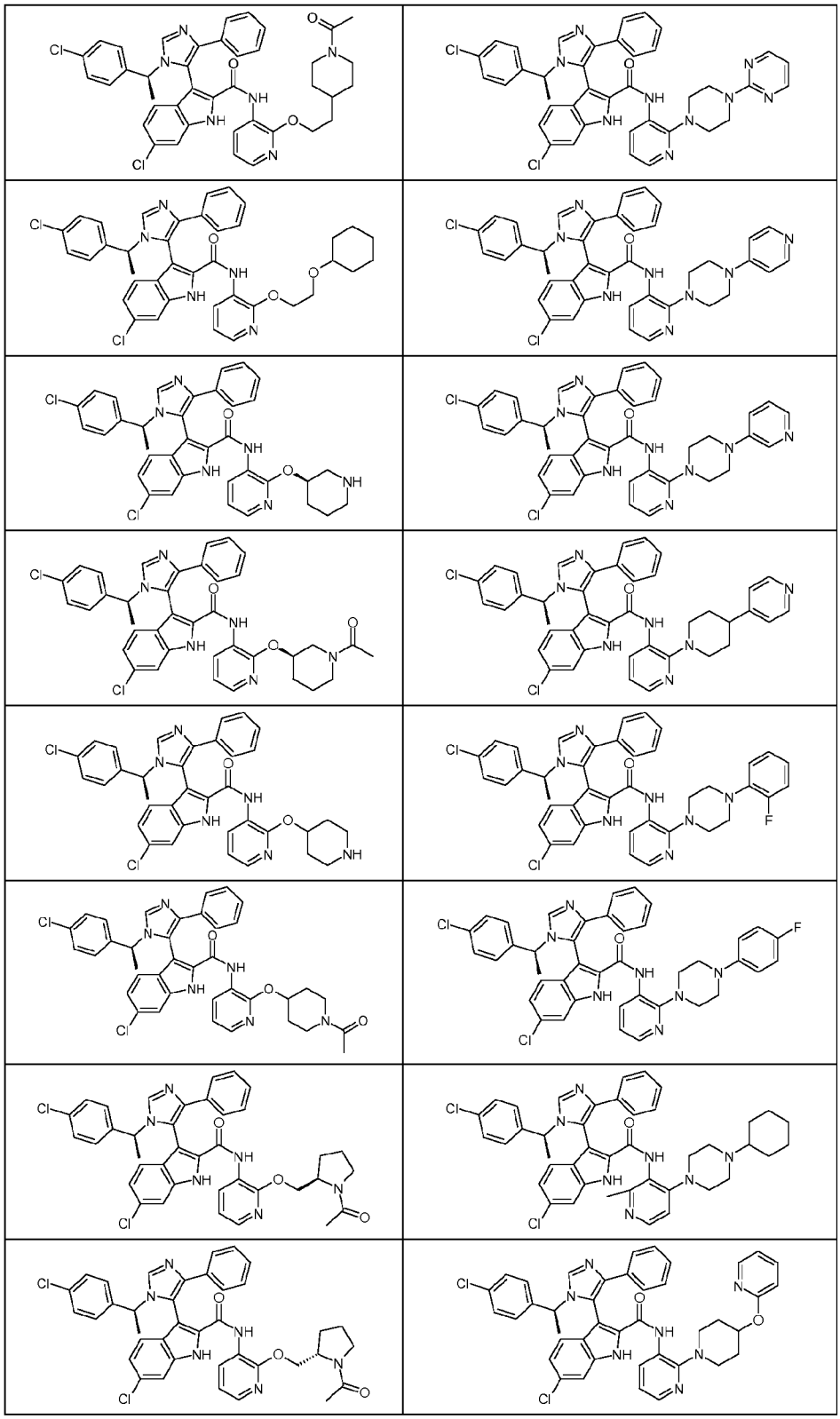
1,3,4-oxadiazol-2-yl, tetrahydro-2H-pyran-4-yl, tetrahydrofuranyl, 2-oxopyrrolidin-1-yl, 2-oxo-1,3-oxazinan-3-yl, 2-oxopiperidin-1-yl, isoxazol-4-yl, 2-oxoimidazolidin-1-yl, 2-oxooxazolidin-3-yl, 1,1-dioxidoisothiazolidin-2-yl, 3-oxomorpholino, 1,1-dioxido-1,2-thiazinan-2-yl, 1,1-dioxido-1,2,6-thiadiazinan-2-yl, 2-oxotetrahydropyrimidin-1(2H)-yl, 2-oxo-1,3-oxazinan-3-yl, 2-oxopiperidin-1-yl, 2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl, 2-oxo-1,4-diazepan-1-yl, 7-oxo-1,4-diazepan-1-yl and 2-oxoazepan-1-yl substituents of R_5 can be optionally further substituted by 1 to 2 groups selected from fluoro, methyl, amino, tetrahydrofuranyl and hydroxy-ethyl; and X_1 at each occurrence is independently selected from methylene, ethylene and propylene; or the pharmaceutically acceptable salts thereof.

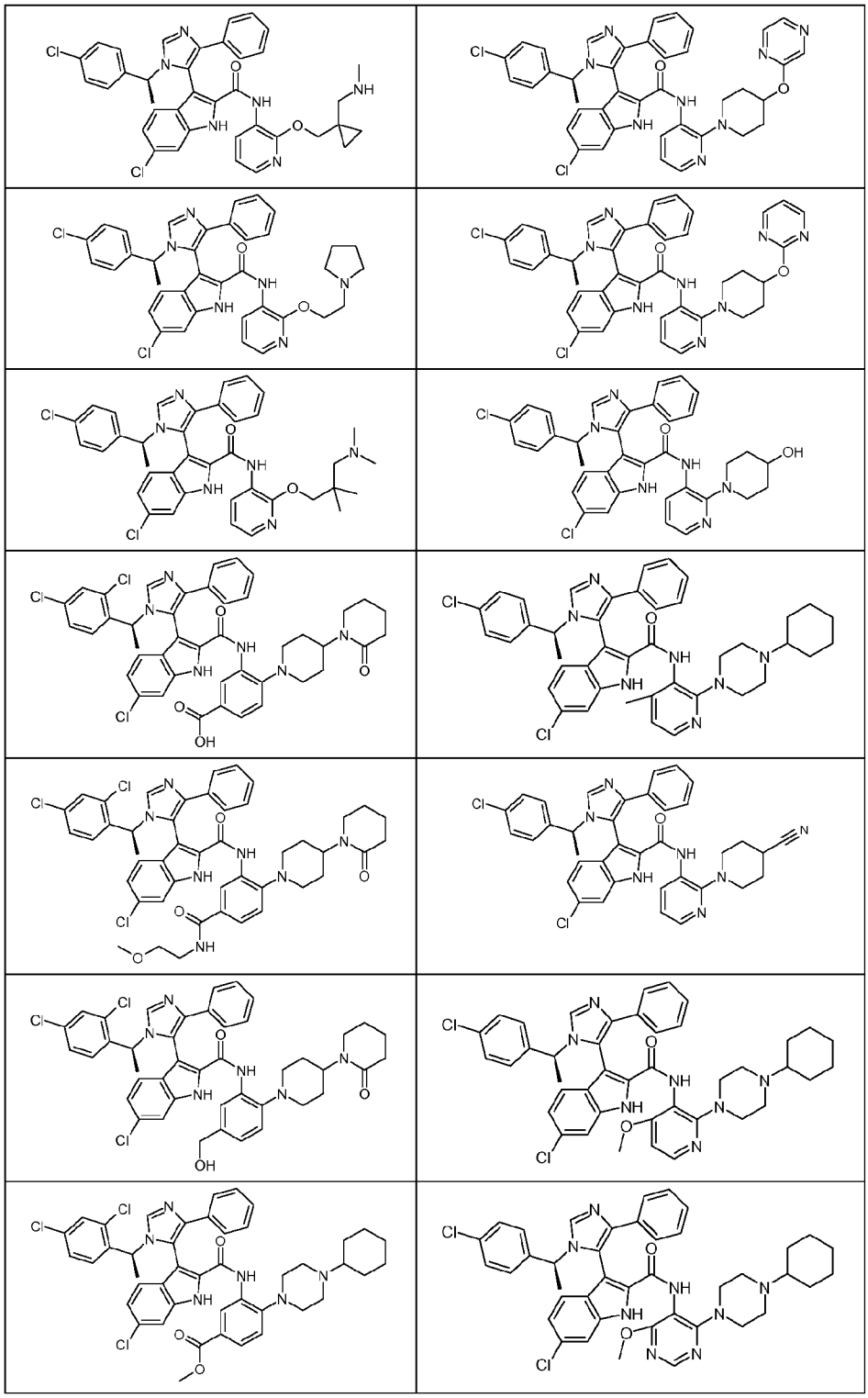
[0054] In a further embodiment are compounds (and the pharmaceutically acceptable salts thereof) selected from:

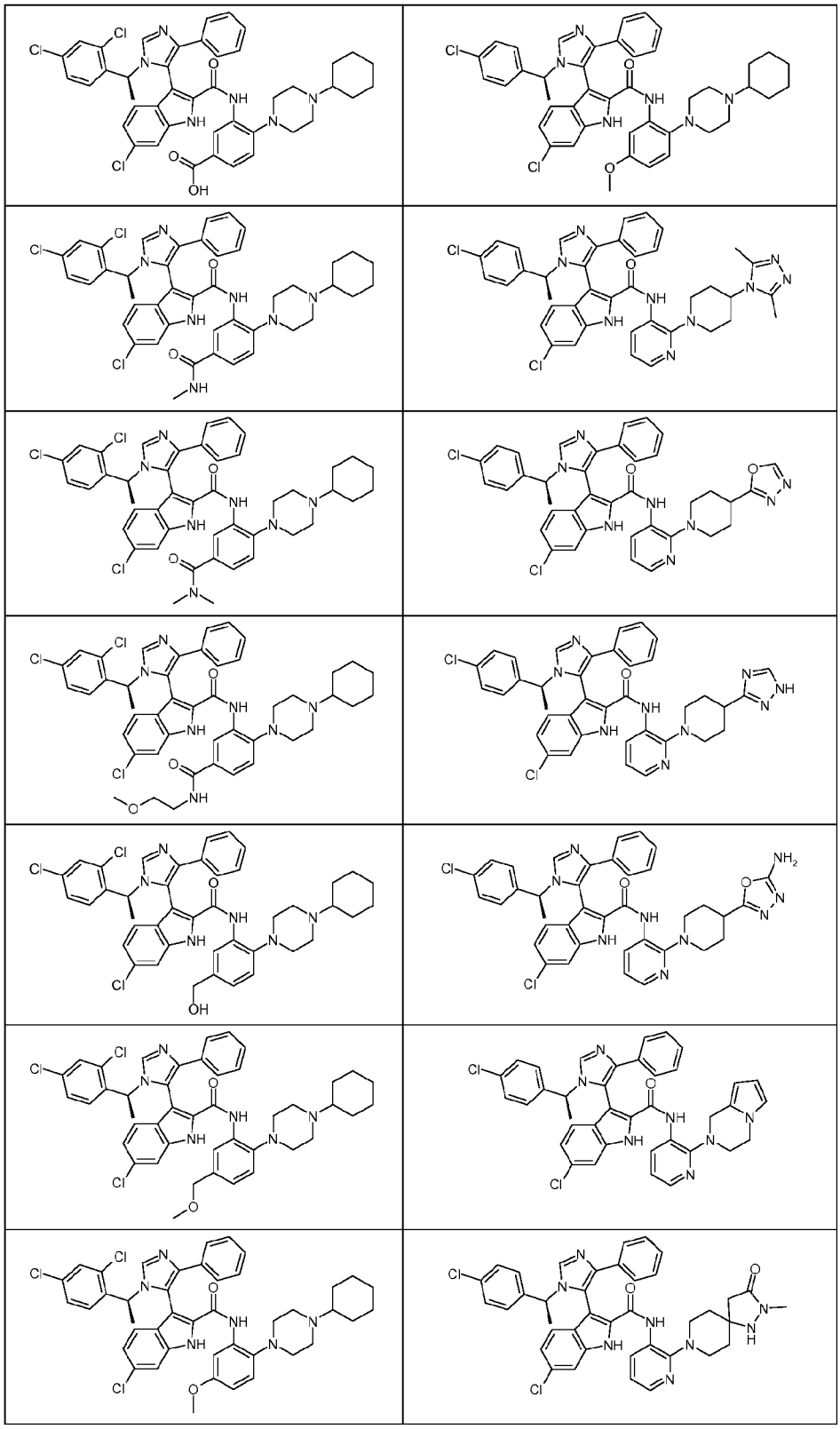


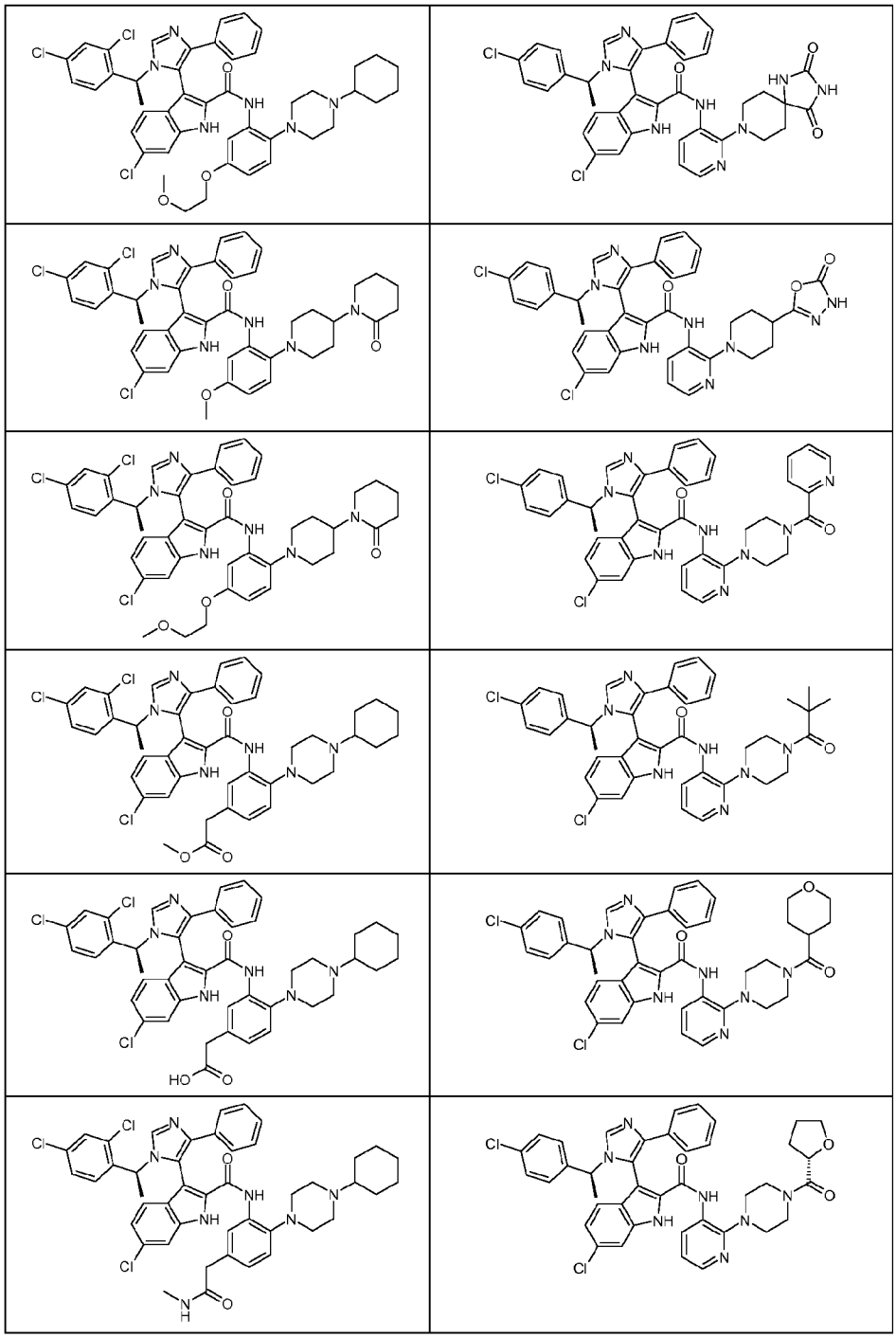


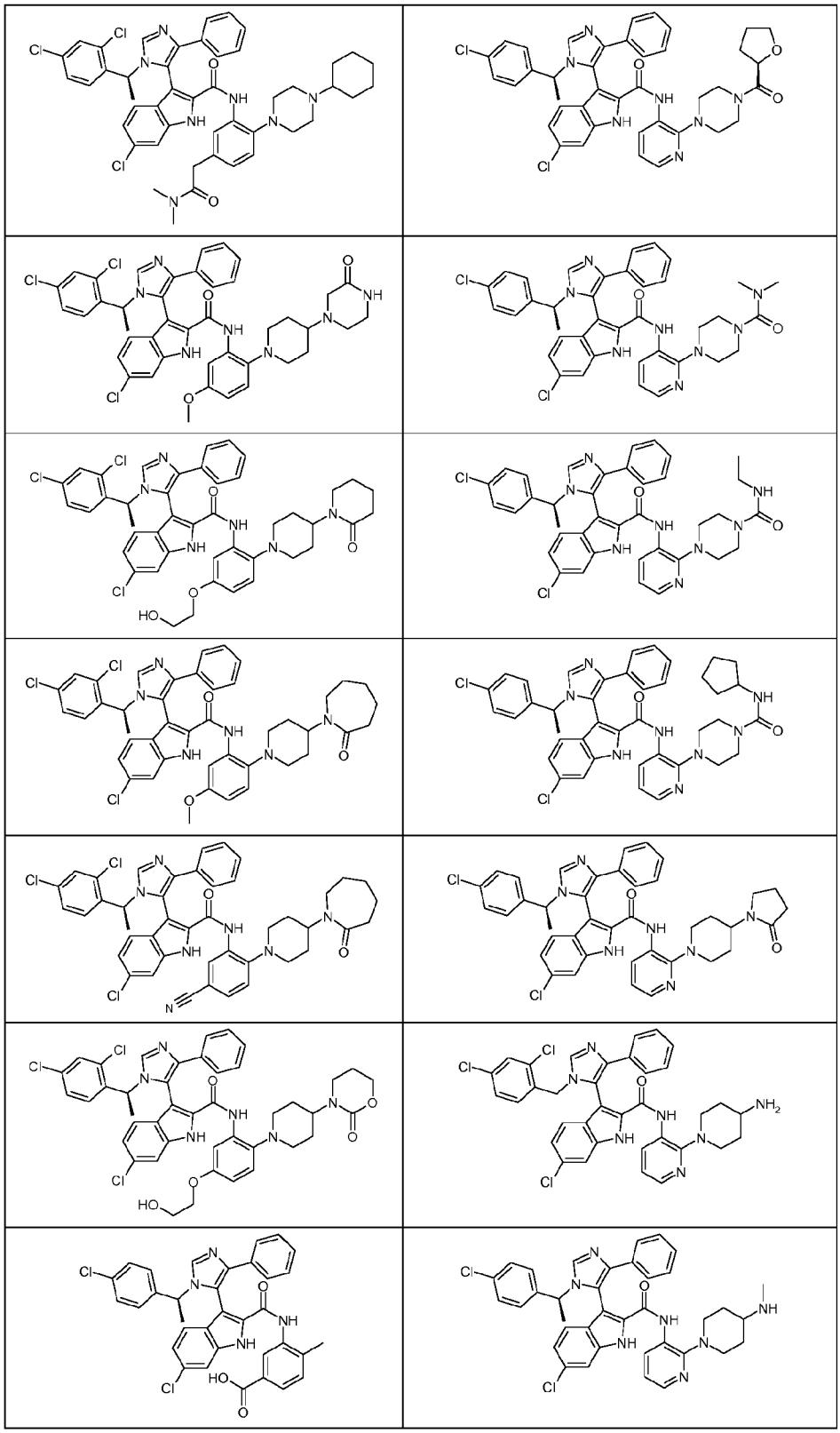


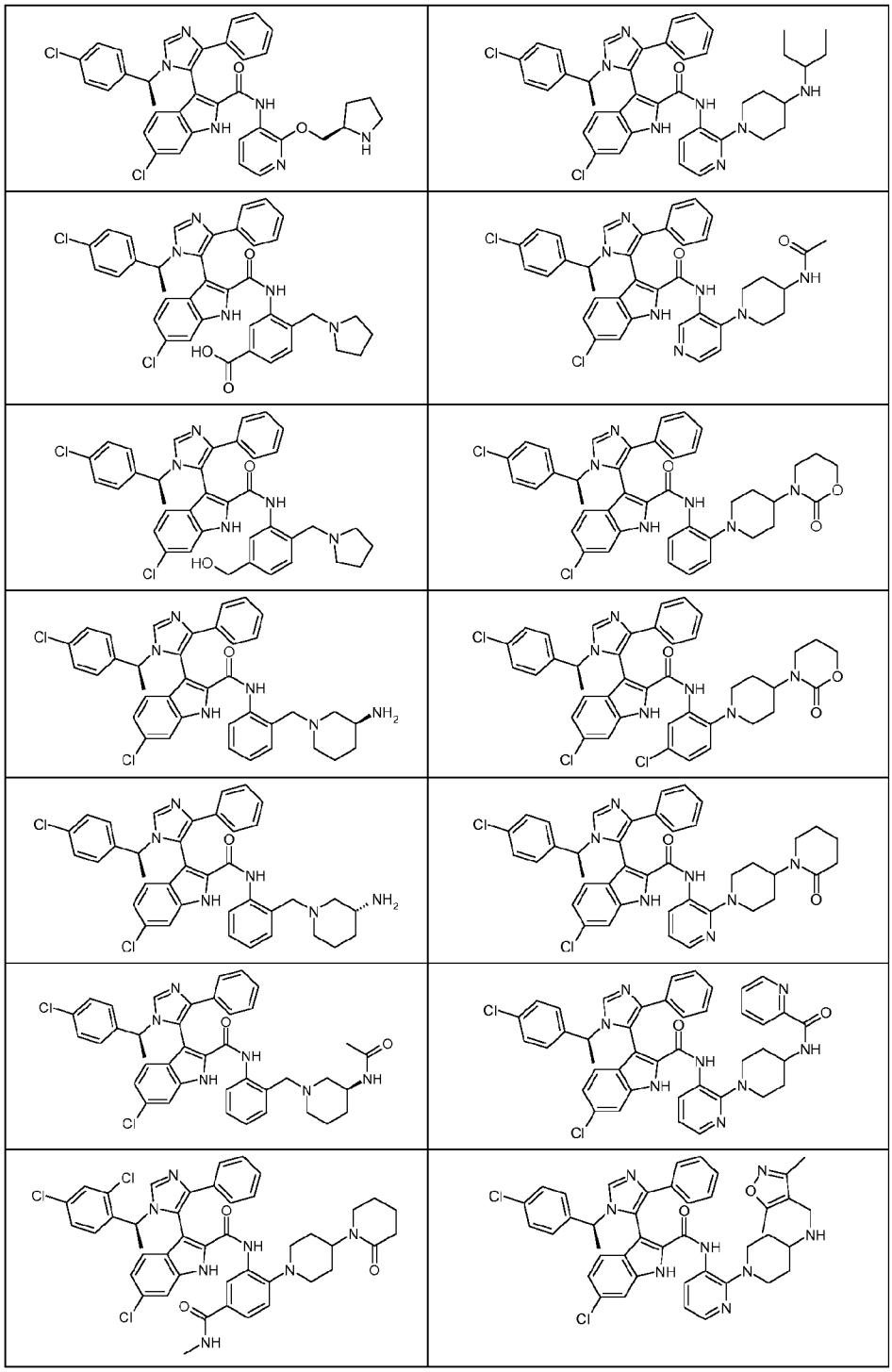


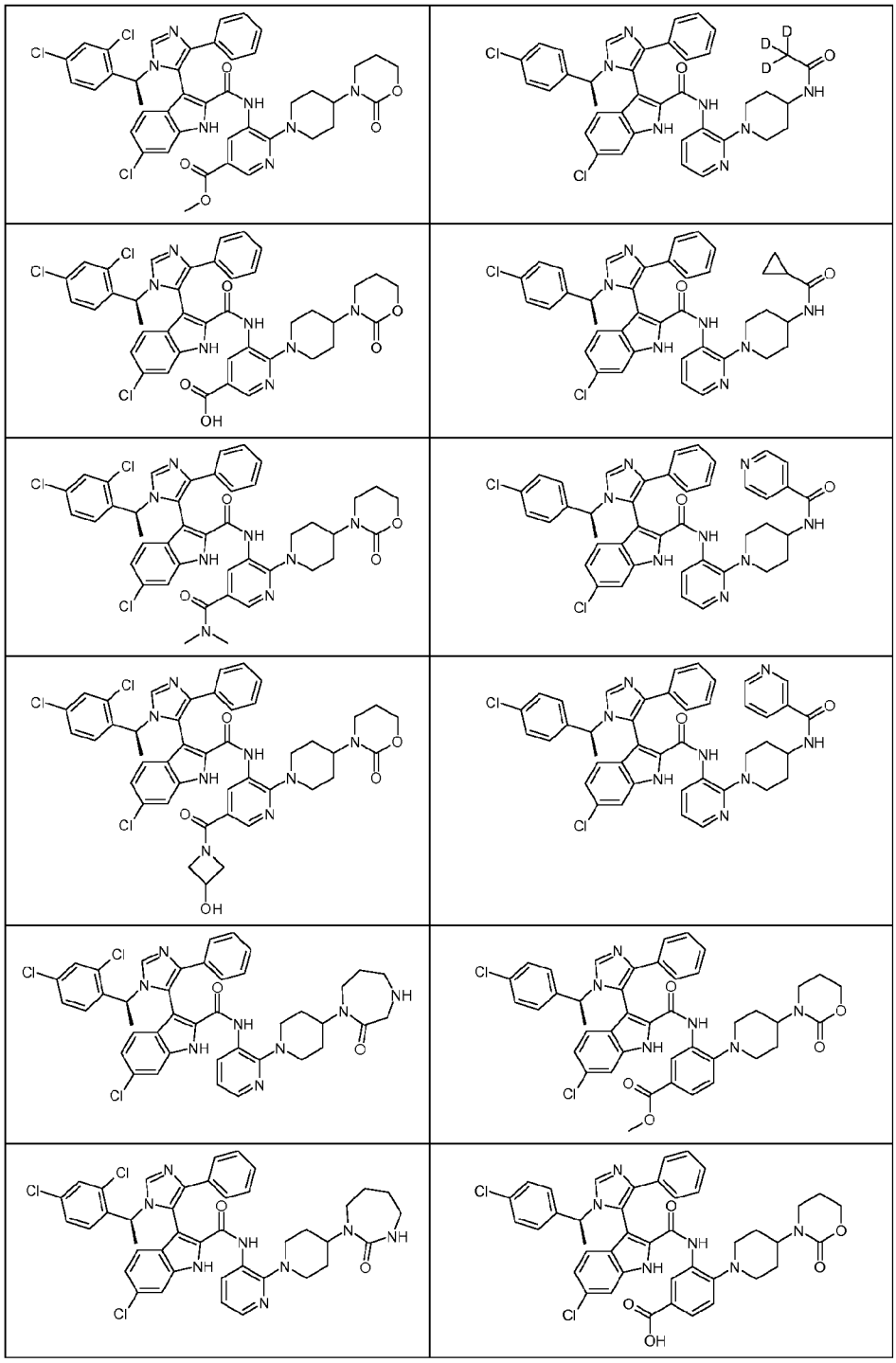


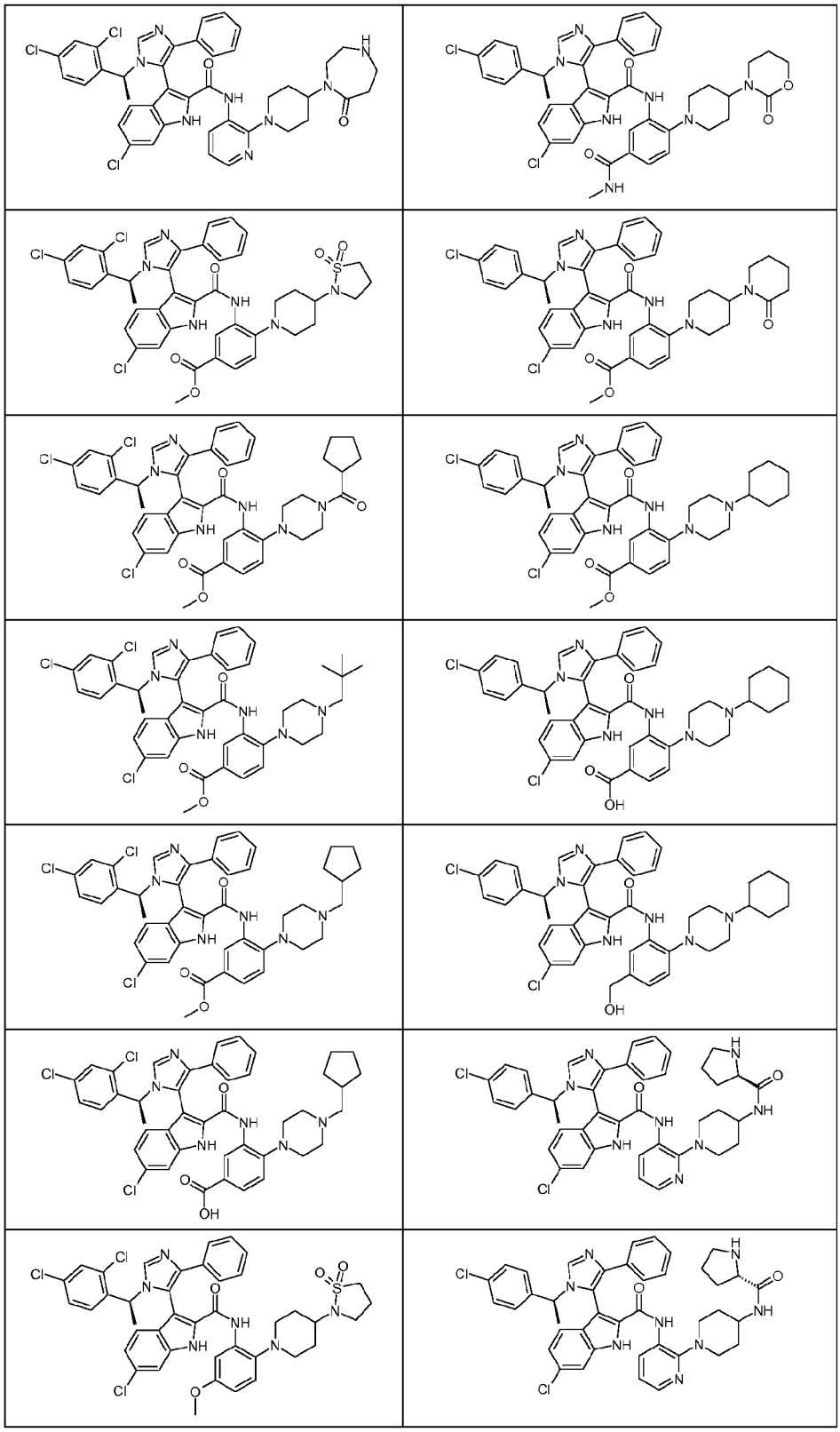


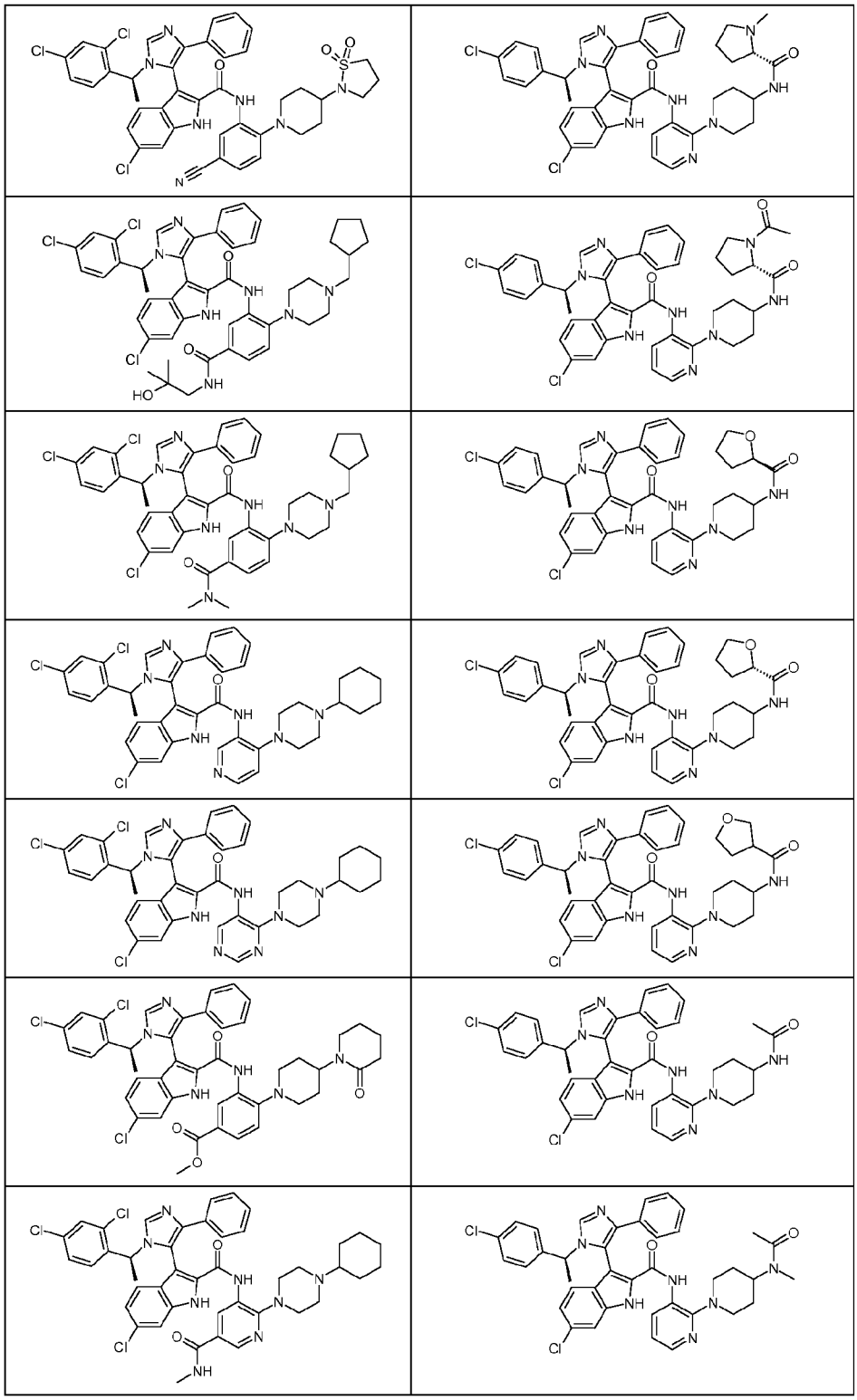


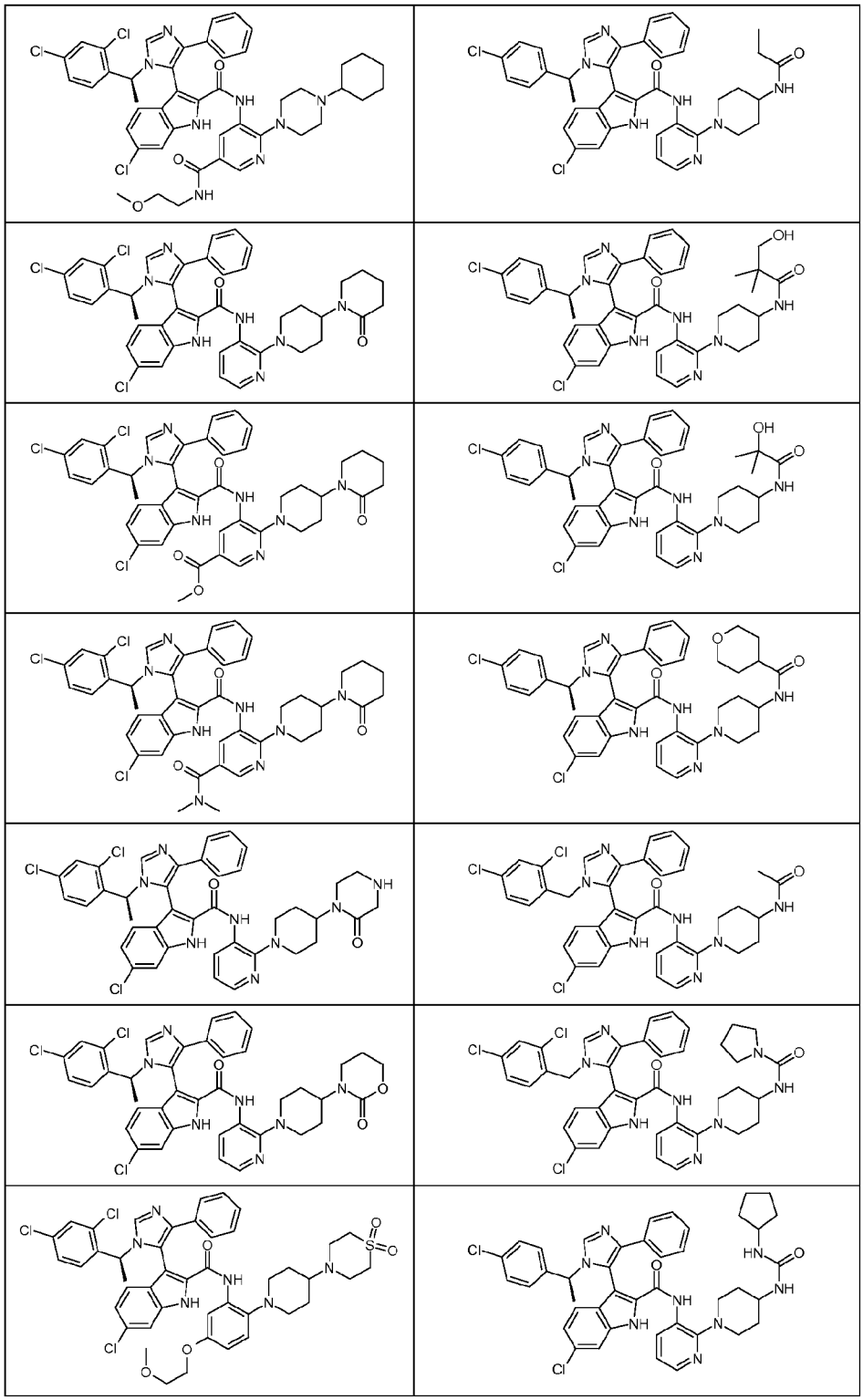


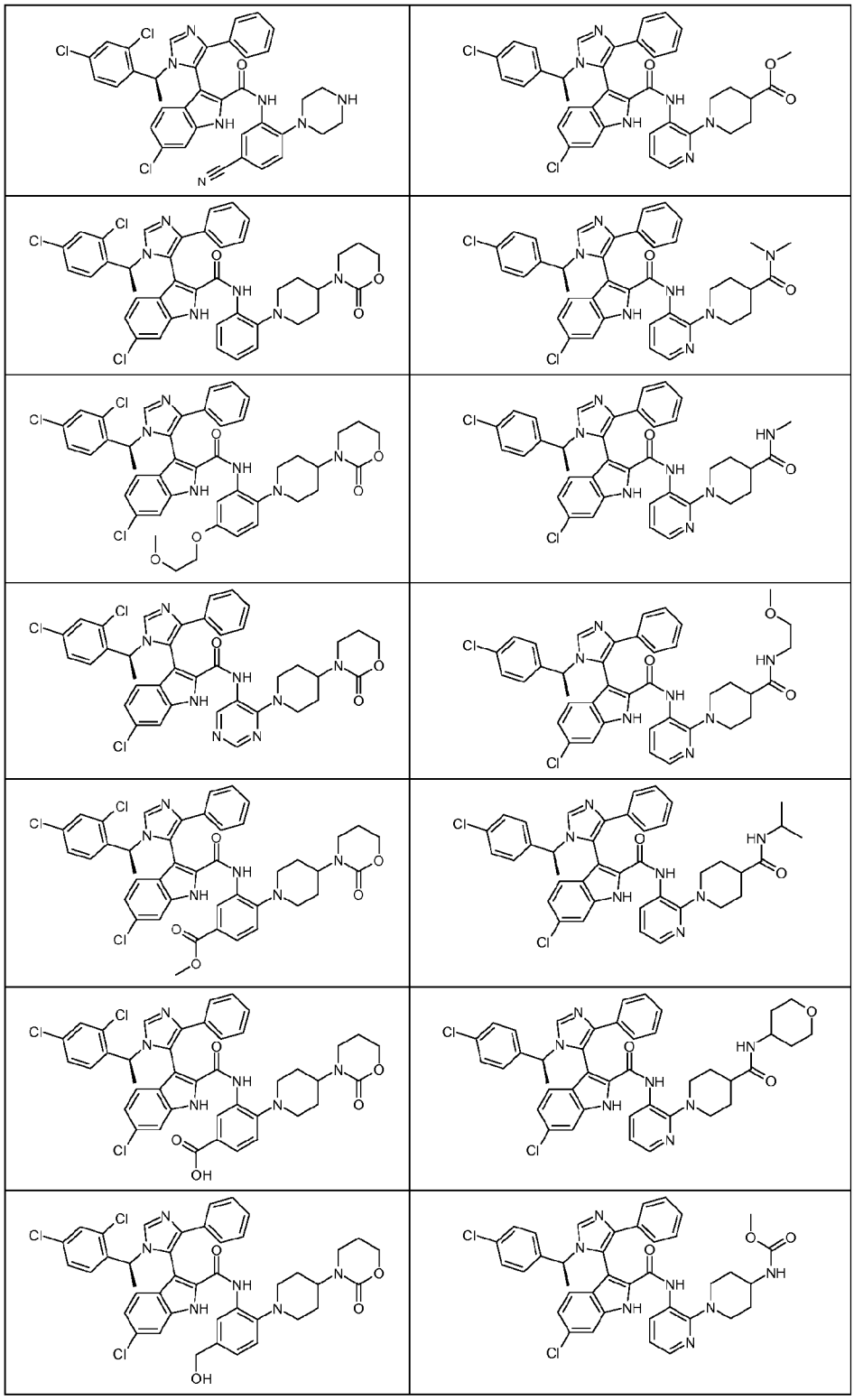


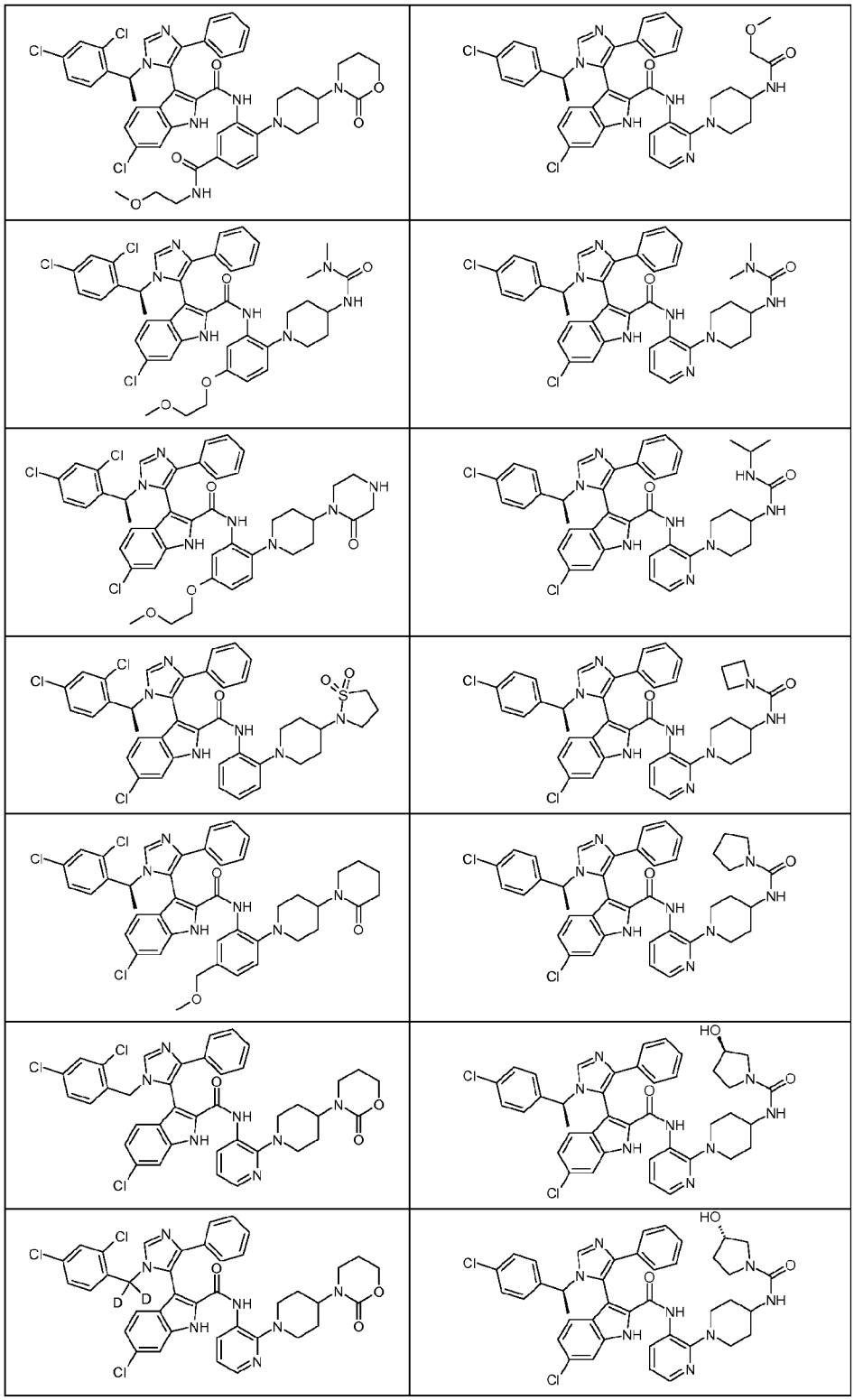


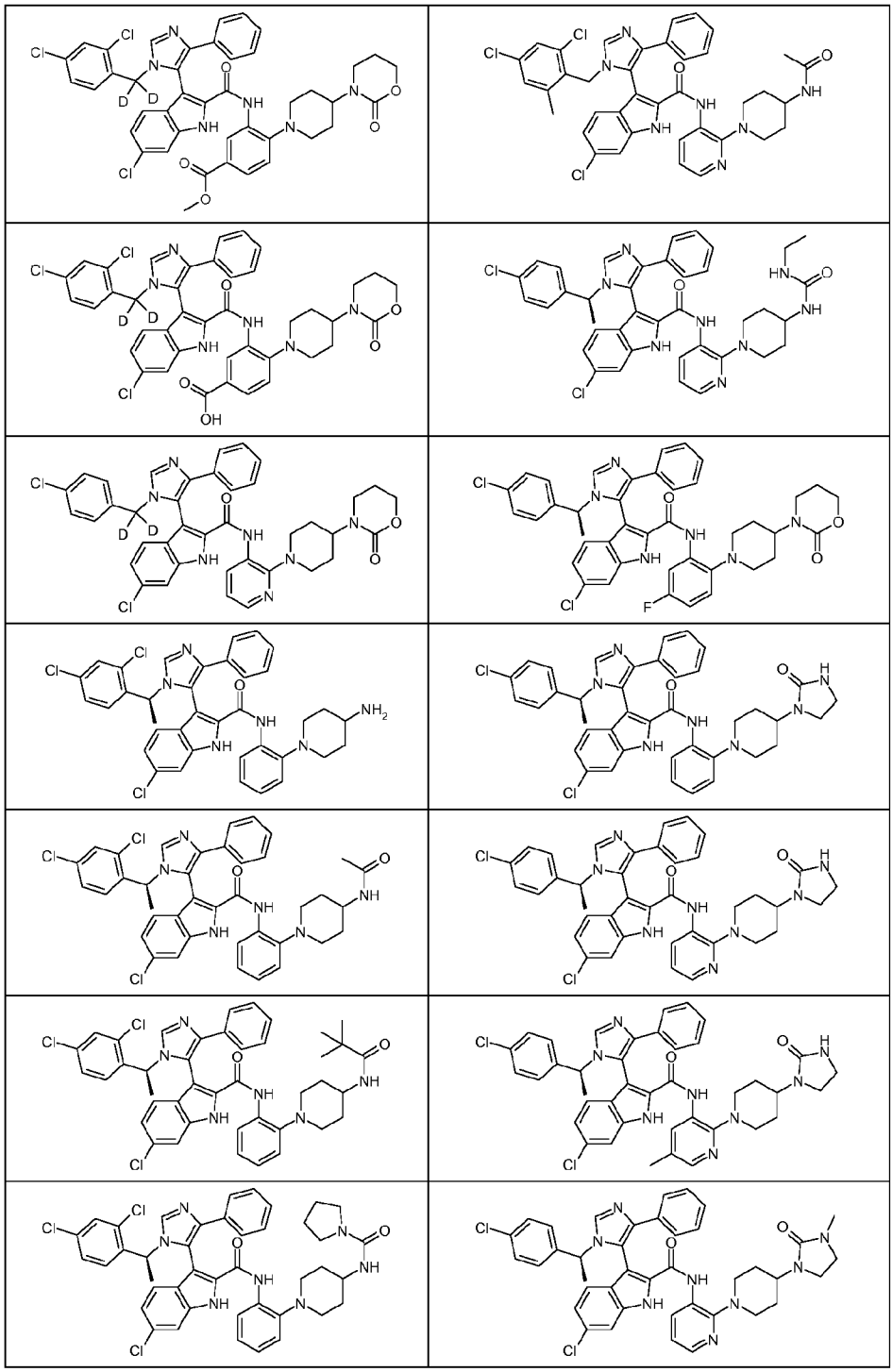


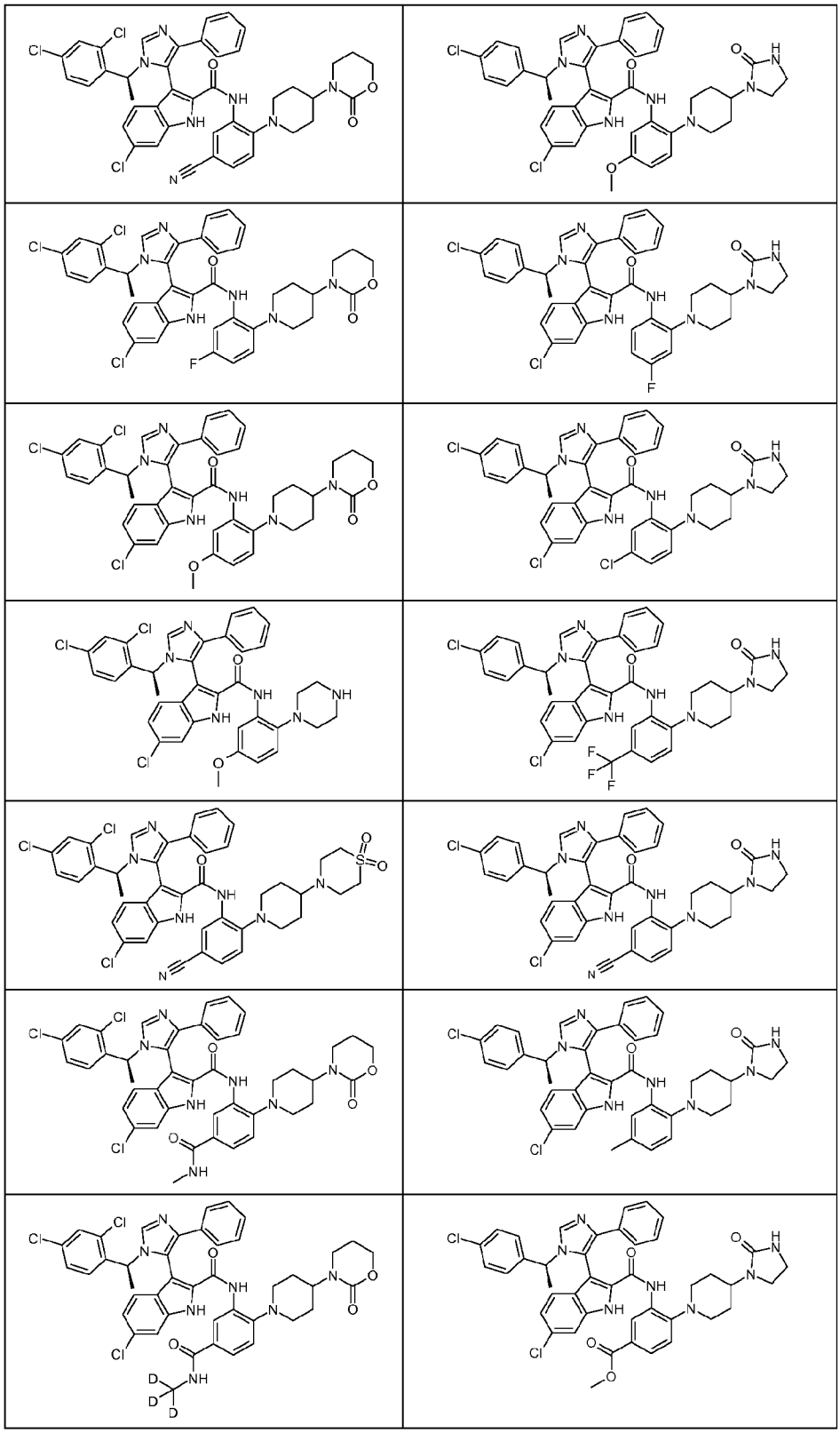


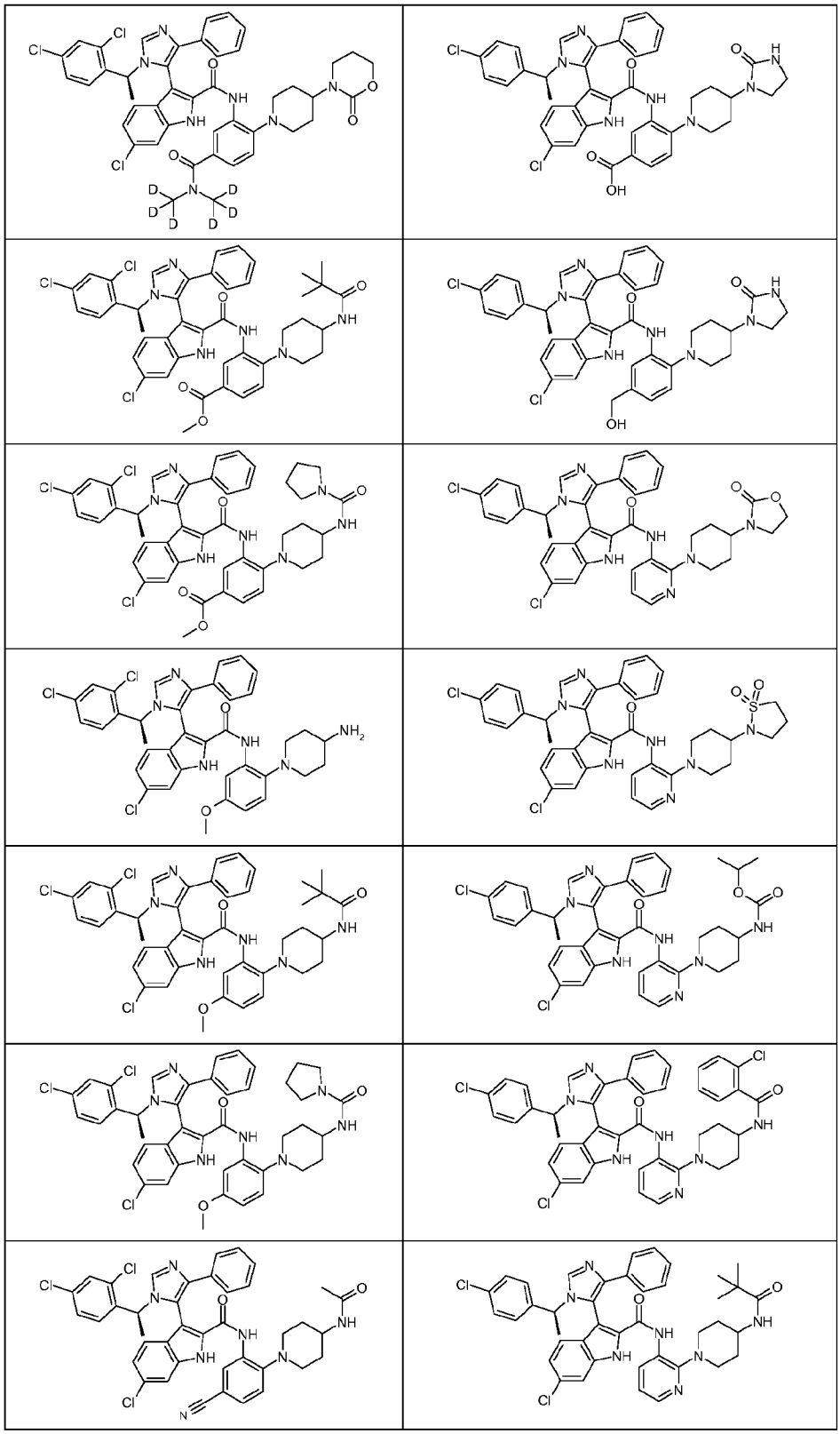


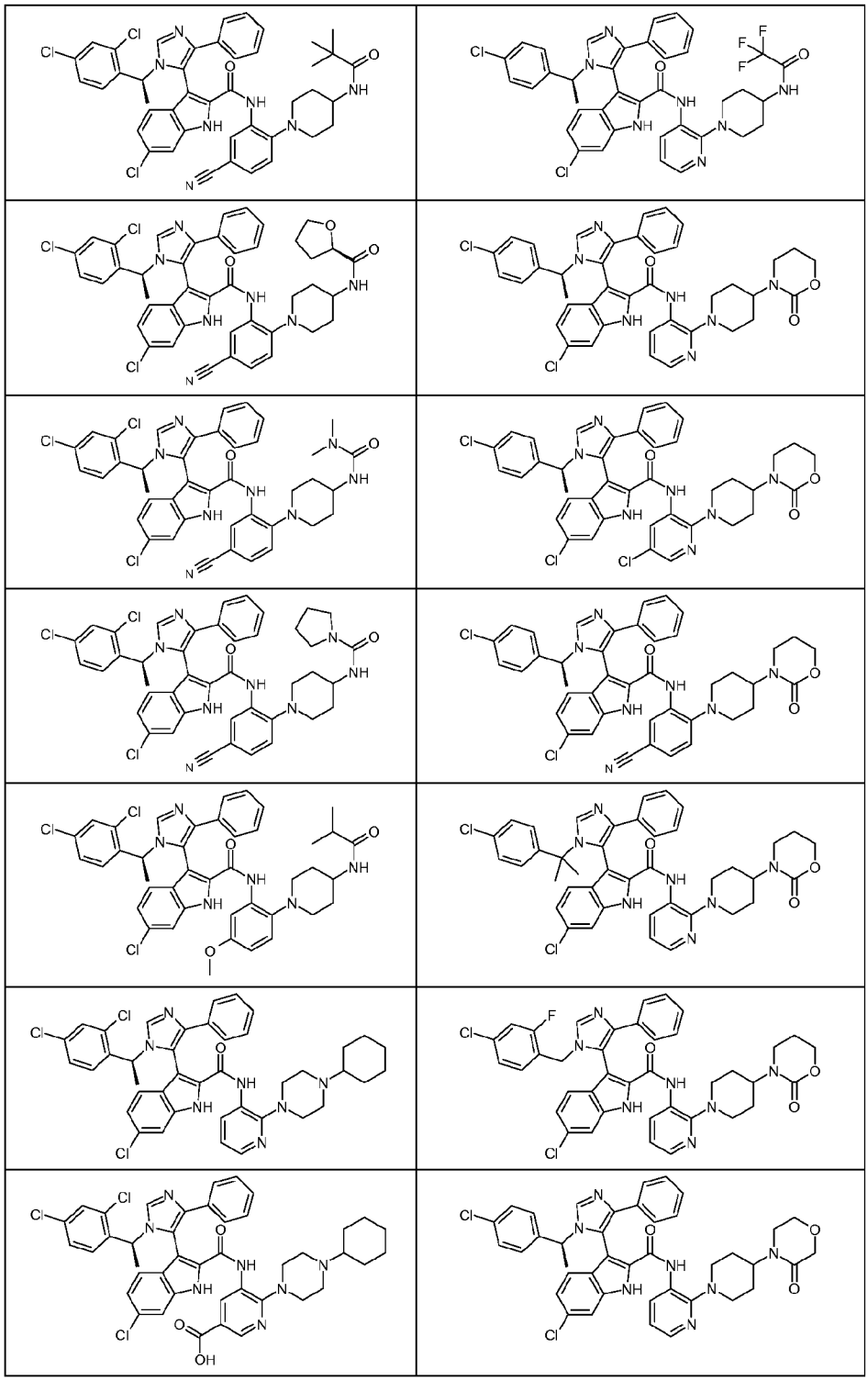


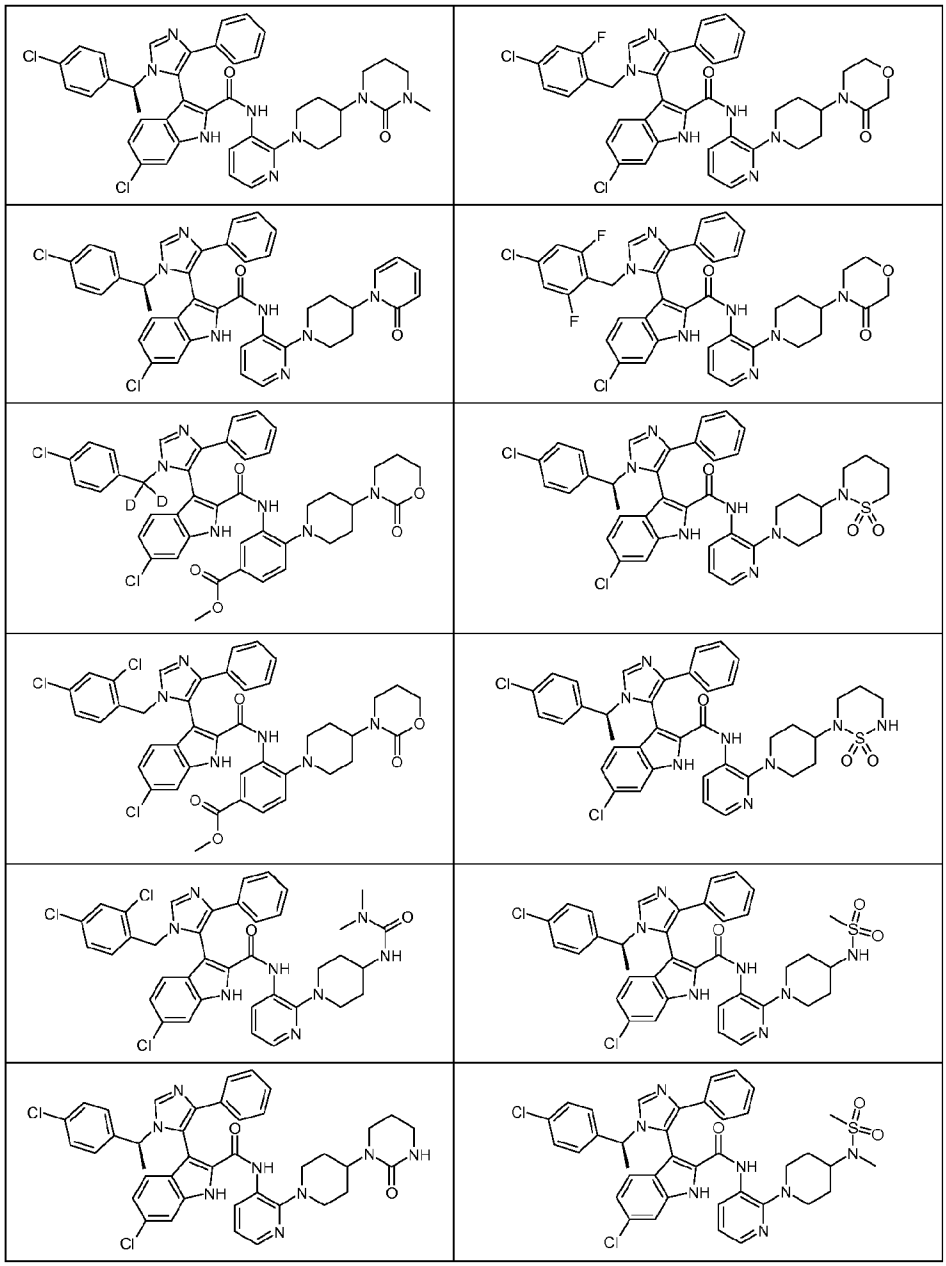




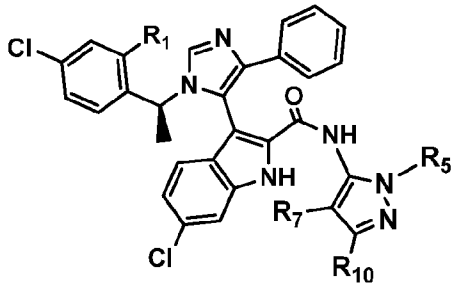








[0055] In another embodiment, with respect to compounds of formula I, are compounds of formula Ib:

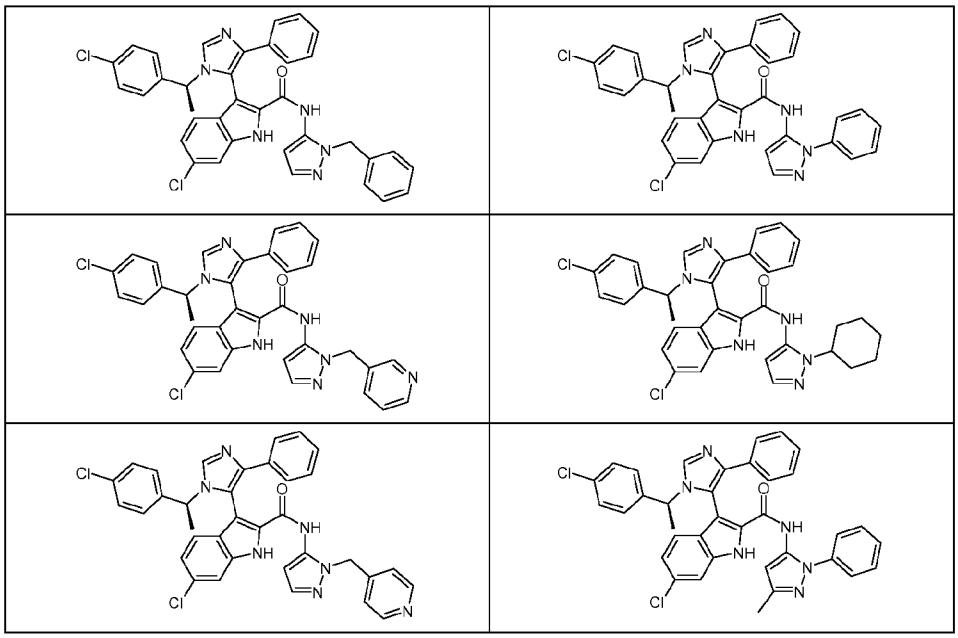


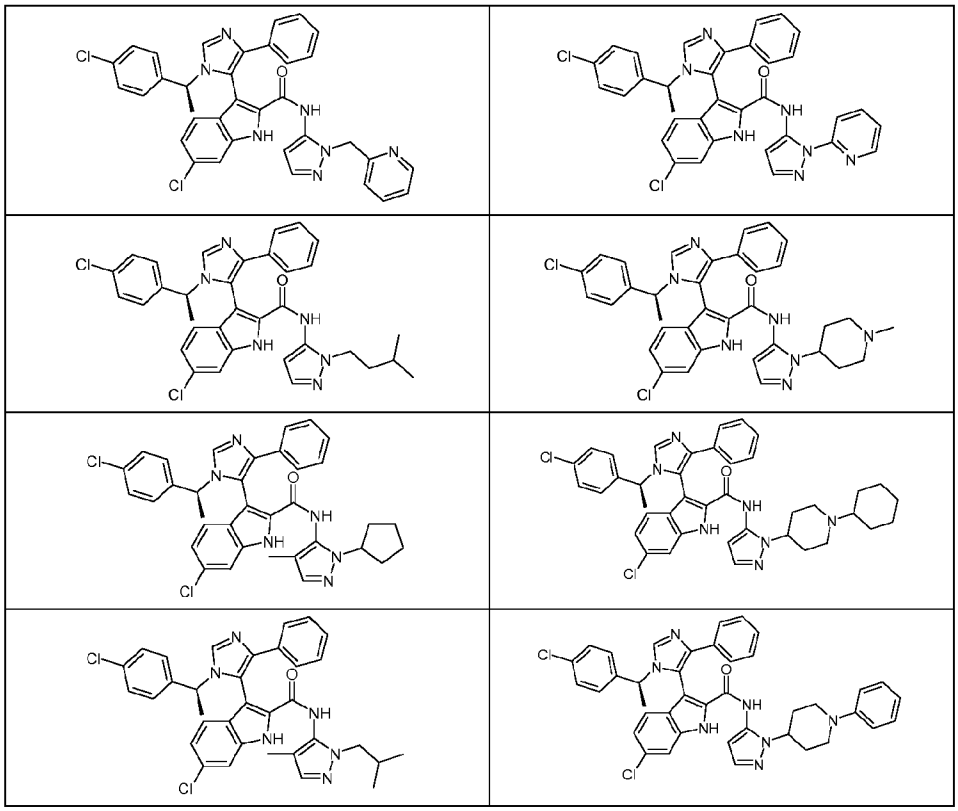
Ib

[0056] in which: R_1 is selected from hydrogen and chloro; R_5 is selected from benzyl, pyridinyl-methyl, cyclohexyl-methyl, cyclopentyl, phenyl, piperidinyl, isobutyl and isopentyl; wherein said piperidinyl is substituted with phenyl, cyclohexyl and methyl; R_7 is selected from hydrogen, C_{1-4}alkyl and C_{1-4}alkoxy; and R_{10} is selected from hydrogen and C_{1-4}alkyl.

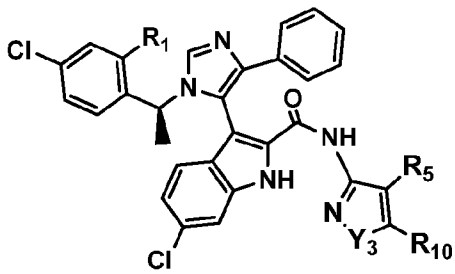
[0057] In a further embodiment, R_7 is selected from hydrogen, methyl and methoxy; and R_{10} is selected from hydrogen and methyl.

[0058] In a further embodiment are compounds (and the pharmaceutically acceptable salts thereof) selected from:





[0059] Inanother embodiment, with respect to compounds of formula I, are compounds of formula Ic:

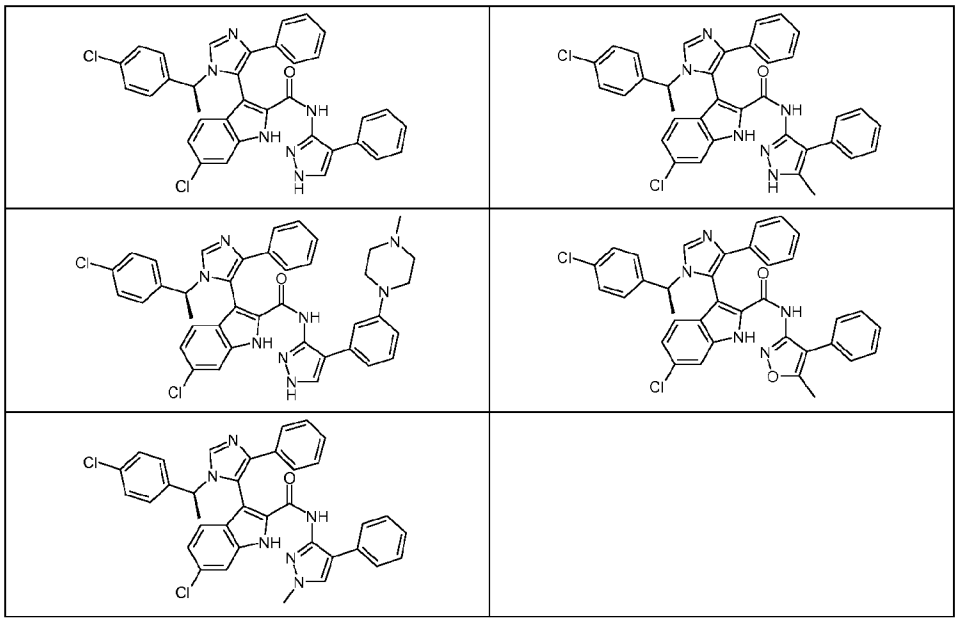


Ic

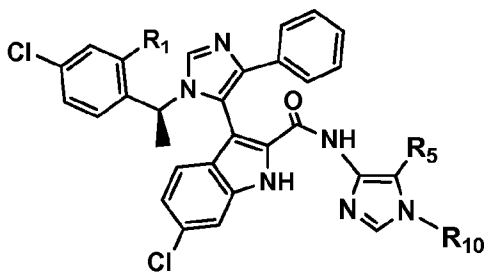
[0060] in which: R_1 is selected from hydrogen and chloro; R_5 is selected from phenyl; wherein said phenyl is substituted with piperazinyl; wherein said piperazinyl substituent of R_5 is optionally further substituted with methyl; R_{10} is selected from hydrogen and methyl; Y_3 is

selected from NR_{11} and O; and R_{11} is selected from hydrogen and methyl; or the pharmaceutically acceptable salts thereof.

[0061] In a further embodiment are compounds (and the pharmaceutically acceptable salts thereof) selected from:



[0062] In another embodiment, with respect to compounds of formula I, are compounds of formula Id:

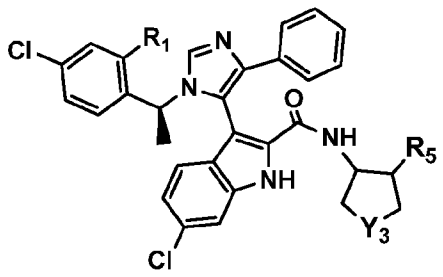


Id

[0063] in which: R_1 is selected from hydrogen and chloro; R_5 is piperidinyl substituted with 2-oxoimidazolidin-1-yl; and R_{10} is selected from hydrogen and methyl; or the pharmaceutically acceptable salts thereof.

[0064] In a further embodiment is the compound 6-chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {1-methyl-5-[4-(2-oxo-imidazolidin-1-yl)-piperidin-1-yl]-1H-imidazol-4-yl}-amide, or the pharmaceutically acceptable salts thereof.

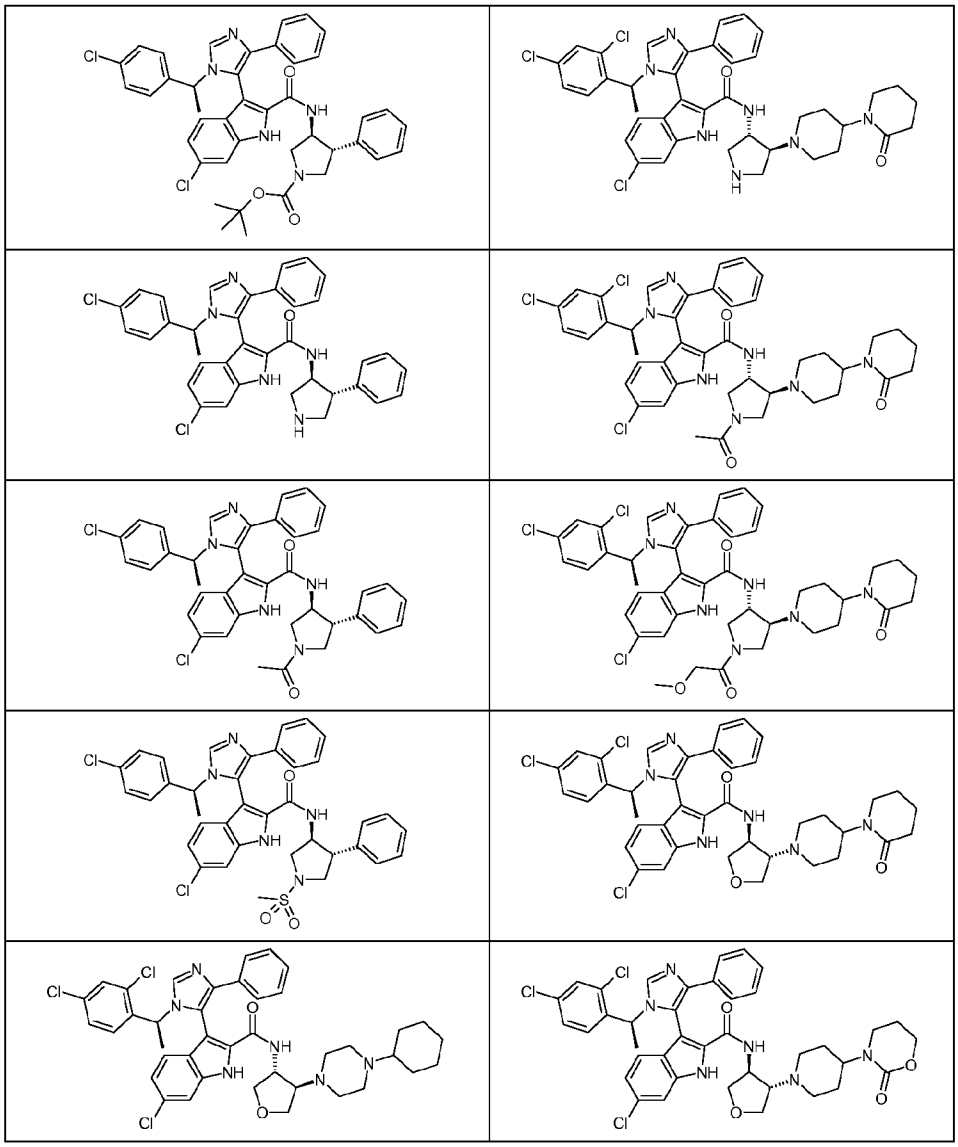
[0065] In another embodiment, with respect to compounds of formula I, are compounds of formula Ie:



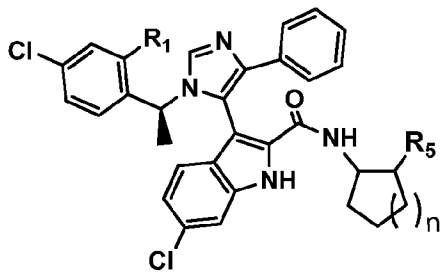
Ie

[0066] in which: R_1 is selected from hydrogen and chloro; R_5 is phenyl, piperidinyl and piperazinyl; wherein said phenyl, piperidinyl or piperazinyl is optionally substituted with a group selected from cyclohexyl, 2-oxo-1,3-oxazinan-3-yl and 2-oxopiperidin-1-yl; Y_3 is selected from O and NR_{11}; and R_{11} is selected from hydrogen, C_{1-4}alkyl, $-S(O)_{0-2}R_{12}$, $-C(O)X_2OR_{12}$ and $-C(O)R_{12}$; wherein R_{12} is selected from isobutyl and methyl; and X_2 is methylene; or the pharmaceutically acceptable salts thereof.

[0067] In a further embodiment are compounds (and the pharmaceutically acceptable salts thereof) selected from:



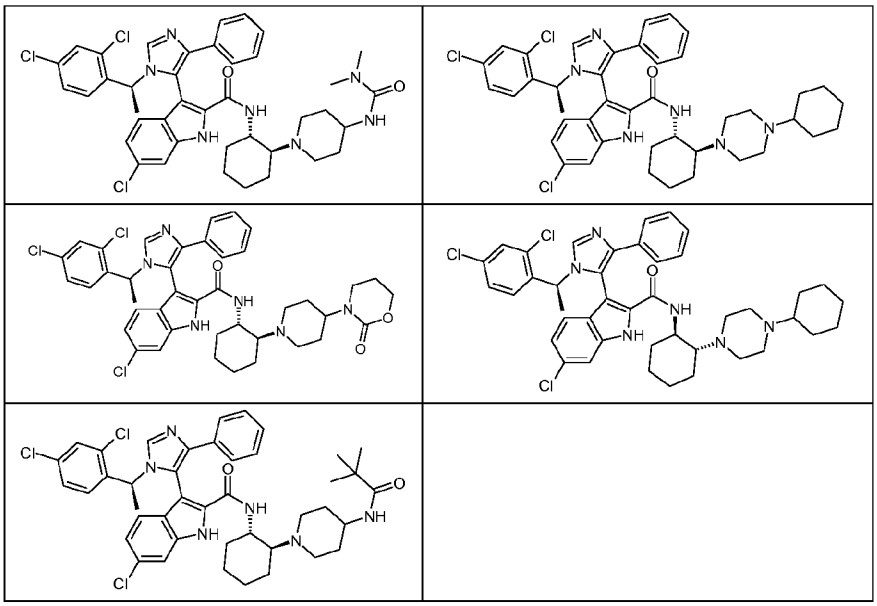
[0068] In another embodiment, with respect to compounds of formula I, are compounds of formula Ig:



Ig

[0069] in which: n is selected from 1 and 2; R_1 is selected from hydrogen and chloro; and R_5 is benzoxy, piperidinyl and piperazinyl; wherein said benzoxy, piperidinyl or piperazinyl is optionally substituted with a group selected from methoxy, cyclohexyl, 2-oxo-1,3-oxazinan-3-yl, 2-oxopiperidin-1-yl, -NHC(O)OR_{14}, -NHC(O)R_{14} and -NHC(O)$NR_{13}R_{14}$; wherein R_{13} is methyl and R_{14} at each occurrence is independently selected from methyl and t-butyl; or the pharmaceutically acceptable salts thereof.

[0070] In a further embodiment are compounds (and the pharmaceutically acceptable salts thereof) selected from:



Pharmacology and Utility

[0071] The present invention makes available methods and compounds capable of inhibiting the interaction between p53 and MDM2 and/or MDM4, especially binding to MDM2 and/or MDM4.

[0072] Protein p53 is known as a tumor suppressor protein which helps to control cellular integrity and prevents the proliferation of permanently damaged cells by initiating growth arrest or apoptosis (controlled cell death). p53 mediates its effects in that it is a transcription factor capable of regulating a number of genes that regulate cell cycle and apoptosis. Thus, p53 is an important cell cycle inhibitor. These activities are tightly controlled by MDM2, an important negative regulator of the p53 tumor supressor. "MDM2" (originally from the oncogene "murine double minute") refers both to the name of the gene as well as the protein encoded by that gene. MDM2 protein functions both as a E3 ubiquitin ligase that recognizes the N-terminal trans-activation domain (TAD) of the p53 tumor supressor and thus mediates the ubiquitin-dependent degradation of p53, and as an inhibitor of p53 transcriptional activation.

[0073] The original mouse oncogene, which codes for the MDM2 protein, was originally cloned from a transformed mouse cell line. The human homologue of this protein was later identified and is sometimes also called HDM2 (for "human double minute 2"). Further supporting the role of MDM2 as an oncogene, several human tumor and proliferative disease types have been shown to have increased levels of MDM2, including *inter alia* soft tissue sarcomas, bone cancer, e.g. osteosarcomas, breast tumors, bladder cancer, Li-Fraumeni syndrome, brain tumor, rhabdomyosarcoma and adrenocortical carcinoma and the like. Another protein belonging to the MDM2 family is MDM4, also known as MDMX.

[0074] Dysregulation of the MDM2/p53 ratio, e.g. due to mutations or molecular defects in the affected cells, can thus be found in many proliferative diseases. MDM2, in view of its mentioned effects, is capable to inhibit the activity of the tumor suppressor protein p53, thus leading to loss of p53's tumor suppressor activity and inhibiting regulatory mechanisms that impede cells from uncontrolled proliferation. As a consequence, uncontrolled proliferation can take place, leading to tumors, leukemias or other proliferative diseases.

[0075] Thus there is a need for new drugs that are capable to interfere with the interaction between p53 and MDM2 or especially oncogenic variants thereof and that thus allow p53 to exert its beneficial effect against uncontrolled tumor growth, allowing it, for example, to accumulate, to arrest the cell cycle and/or to cause apoptosis of the affected cells.

[0076] The compounds of formula I have advantageous pharmacological properties and interfere with the binding interaction between p53 and MDM2 and/or MDM4 or (especially oncogenic) variants thereof (also referred to herein as p53/MDM2 and p53/MDM4 interaction or as p53/MDM2 interaction solely).

[0077] The inhibition of p53-HDM2 interaction is measured by fluorescence polarization. Fluorescence polarization measures the rotational movement of molecules in a homogeneous suspension. For this assay, HDM2 protein (amino acids 2-185) is combined with a Cy5-labelled p53-derived peptide optimised for HDM2 binding (*J. Med. Chem.* 2000, *43*, 3205-3208). Upon excitation of the Cy5 fluorescent ligand with linearly polarized light, the peptide rotates faster and emits light which is perpendicularly polarized. If the peptide is bound by Hdm2, rotation will slow down and the perpendicular component will decrease. Disruption of the formation of the peptide-HDM2 complex due to an inhibitor molecule binding to the p53 binding site of HDM2 results in faster rotation of the peptide. The ratiometric polarization assay readout is calculated from the parallel and perpendicular components of the fluorescence light with respect to the polarization of the excitation light. See "Fluorescence Polarization Assay", below.

[0078] The inhibition of p53-HDM4 interaction is measured by time resolved fluorescence energy transfer (TR-FRET). Fluorescence energy transfer (or Foerster resonance energy transfer) describes an energy transfer between donor and acceptor fluorescent molecules. For this assay, MDM4 protein (amino acids 2-185), tagged with a C-terminal Biotin moiety, is used in combination with a Europium labeled streptavidin (Perkin Elmer, Inc., Waltham, MA, USA) serving as the donor fluorophore. The p53 derived, Cy5 labeled peptide Cy5-TFSDLWKLL (p53 aa18-26) is the energy acceptor. Upon excitation of the donor molecule at 340nm, binding interaction between MDM4 and the p53 peptide induces energy transfer and enhanced response at the acceptor emission wavelength at 665nm. Disruption of the formation of the p53-MDM4 complex due to an inhibitor molecule binding to the p53 binding site of MDM4 results in

increased donor emission at 615nm. The ratiometric FRET assay readout is calculated from the raw data of the two distinct fluorescence signals measured in time resolved mode (countrate 665nm/countrate 615nm x 1000). See "Time Resolved Fluorescence energy Transfer (TR-FRET) Assay", below.

[0079] Having regard to their inhibitory effect on p53/MDM2 and/or p53/MDM4 interaction, compounds of formula (I) in free or pharmaceutically acceptable salt form, are useful in the treatment of conditions which are mediated by the activity (including normal activity or especially overactivity) of MDM2 and/or MDM4, or variants thereof, respectively, as described, such as proliferative and/or inflammatory conditions, e.g. by activation of the P53/MDM2 interaction, and/or that are responsive (meaning especially in a therapeutically beneficial way) to inhibition of the p53/MDM2 interaction, most especially a disease or disorder as mentioned hereinbelow.

[0080] "Treatment" in accordance with the invention may be therapeutic, e.g. symptomatic, palliative and/or curative, and/or prophylactic. Preferred is the treatment of warm-blooded animals, especially humans.

[0081] In one aspect of the invention is a compound of formula I for use or the use thereof in the treatment of a disease or disorder that responds to treatment with a compound of the formula I, especially selected from disease that is based on dysregulation of cell cycle or especially apoptosis,: e.g. diseases involving the immune system, e.g. autoimmune diseases or immune diseases resulting due to transplantation (such as rheumatoid arthritis, graft-versus-host disease, systemic lupus erythematosus, Sjögren's syndrome, multiple sclerosis, Hashimoto's thyreoiditis, polymyositis), chronic inflammatory conditions, such as asthma, osteoarthritis, atherosclerosis, Morbus Crohn or inflammatory or allergic conditions of the skin, for example psoriasis, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, pemphigus, epidermolysis bullosa acquisita, or other inflammatory or allergic conditions of the skin, hyperproliferative disorders, (e.g. Li-Fraumeni syndrome, cancer or tumor diseases, such as benign or malignant tumors, sarcomas, such as rhabdomyosarcoma, bone cancer, e.g. osteosarcomas, carcinoma of the brain, e.g. soft tissue brain tumor, kidney, liver, adrenal gland,

bladder, breast, stomach, gastric tumors, ovaries, colon, rectum, prostate, pancreas, lung, vagina or thyroid, glioblastomas, multiple myeloma, gastrointestinal cancer, especially colon carcinoma or colorectal adenoma, a tumor of the neck and head, melanoma, prostate hyperplasia, a neoplasia, a neoplasia of epithelial character, a mammary carcinoma, a leukemia, such as B- or T-cell lymphomas adrenocortical carcinoma, including metastasis in other organs, respectively), viral infections (e.g. herpes, papilloma, HIV, viral hepatitis) or other diseases, for example those in which the p53/MDM2 and/or p53/MDM4 interaction is dysregulated and/or that are responsive to inhibition of the p53/MDM2 interaction and/or p53/MDM4.

[0082] The invention especially relates to the use of a compound of the formula I (or a pharmaceutical formulation comprising a compound of the formula I) in the treatment of one or more of the diseases mentioned above and below where the disease(s) respond or responds (in a beneficial way, e.g. by partial or complete removal of one or more of its symptoms up to complete cure or remission) to an inhibition of the p53/MDM2 interaction, especially where the involved MDM2 or MDM4 and/or variant shows (e.g.in the context of other regulatory mechanisms, due to overexpression, to mutation or the like) inadequately high or more higher than normal activity.

[0083] Whereever the term "use" or "used" or especially use is mentioned, this is intended to include a compound of the formula I for use in the prophylactic and/or therapeutic treatment of a disease of a warm-blooded animal, especially a human, preferably of one or more diseases mentioned above or below, a method of use or a method of treatment comprising administering a compound of the formula I to a person in need of such treatment in an effective amount for the prophylactic and/or therapeutic treatment of a disease as mentioned above and below, the preparation or a method for the preparation of a pharmaceutical formulation for use in the prophylactic and therapeutic treatment of a disease or disorder mentioned above and below, especially involving combining a compound of the formula I (as therapeutically active ingredient) with at least one pharmaceutically acceptable carrier material, preferably including making it ready for use in such treatment (e.g. adding an instruction insert (e.g. package leaflet or the like), formulation, appropriate preparation, adaptation for specific uses, customizing and the like), and/or the use of a compound of the formula I for such preparation, and/or all other prophylactic or therapeutic uses mentioned hereinbefore or below. The invention can also relate to the use of a

compound of the formula I to induce cell cycle deceleration or preferably arrest and/or apoptosis in cells containing p53 or variants thereof that are still functional, for sensitizing cells to one or more additional pharmaceutically active agents, such as inducers of apoptosis and/or of cell cycle deceleration or arrest, and to chemoprotection of normal cells through the inductoin of cell cycle deceleration or arrest prior to treatment with one or more other chemotherapeutic agents, to the use in rendering normal cells resistant to chemotherapeutic agents and/or treatments, and/or the use in protecting cells from toxic side effects of chemotherapeutic agens or treatments, such as side effects resulting in mucositis, stomatitis, xerostomia, gastrointestinal disorders and/or alopecia.

[0084] There are also experiments that can demonstrate the antitumor activity of compounds of the formula (I) *in vivo*. For example, female Harlan (Indianapolis, Indiana, USA) athymic nu/nu mice with s.c. transplanted human osteosarcoma SJSA-1 tumors can be used to determine the anti-tumor activity of p53/MDM2 interaction inhibitors. On day 0, with the animals under peroral Forene® (1-chloro-2,2,2-trifluoroethyldifluormethylether, Abbot, Wiesbaden, Germany) narcosis, 3x106 cells are injected under the skin on the animals' left flank. When tumors reach a volume of 100 mm^3, the mice are divided at random into groups of 6-8 animals and treatment commences. The treatment is carried out for a 2-3 weeks period with peroral, intravenous or intra-peritoneal administration once daily (or less frequently) of a compound of formula (I) in a suitable vehicle at defined doses. The tumors are measured twice a week with a slide gauge and the volume of the tumors is calculated.

[0085] As an alternative to cell line SJSA-1, other cell lines may also be used in the same manner, for example: the HCT116 colon carcinoma cell line (ATCC No. CCL-247); the LNCaP clone FGC prostate carcinoma cell line (ATCC No. CRL-1740); the RKO colon carcinoma cell line (ATCC No.CRL-2577); the HT1080 fibrosarcoma cell line (ATCC No. CCL-121); the A375 malignant melanoma cell line (ATCC No. CRL-1619); and the NCI-H460 large cell lung carcinoma cell line (ATCC No. HTB-177).

[0086] A compound of formula (I) can also be used in combination with other anti-proliferative compounds. Such antiproliferative compounds include, but are not limited to aromatase inhibitors; antiestrogens; topoisomerase I inhibitors; topoisomerase II inhibitors;

microtubule active compounds; alkylating compounds; histone deacetylase inhibitors; compounds which induce cell differentiation processes; cyclooxygenase inhibitors; MMP inhibittors; mTOR inhibitors,such as RAD001; antineoplastic antimetabolites; platin compounds; compounds targeting/decreasing a protein or lipid kinase activity and further anti-angiogenic compounds; compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase; gonadorelin agonists; anti-androgens; methionine aminopeptidase inhibitors; bisphosphonates; biological response modifiers; antiproliferative antibodies, such as HCD122; heparanase inhibitors; inhibitors of Ras oncogenic isoforms; telomerase inhibitors; proteasome inhibitors; compounds used in the treatment of hematologic malignancies, such as FLUDARABINE; compounds which target, decrease or inhibit the activity of Flt-3, such as PKC412; Hsp90 inhibitors such as 17-AAG (17-allylaminogeldanamycin, NSC330507), 17-DMAG (17-dimethylaminoethylamino-17-demethoxy-geldanamycin, NSC707545), IPI-504, CNF1010, CNF2024, CNF1010 from Conforma Therapeutics and AUY922; temozolomide (TEMODAL®); kinesin spindle protein inhibitors, such as SB715992 or SB743921 from GlaxoSmithKline, or pentamidine/chlorpromazine from CombinatoRx; PI3K inhibitors, such as BEZ235; RAF inhibitors, such as LGX818 or RAF265; MEK inhibitors such as ARRY142886 from Array PioPharma, AZD6244 from AstraZeneca, PD181461 from Pfizer, leucovorin, EDG binders, antileukemia compounds, ribonucleotide reductase inhibittors, S-adenosylmethionine decarboxylase inhibitors, antiproliferative antibodies or other chemotherapeutic compounds. Further, alternatively or in addition they may be used in combination with other tumor treatment approaches, including surgery, ionizing radiation, photodynamic therapy, implants, e.g. with corticosteroids, hormones, or they may be used as radiosensitizers. Also, in anti-inflammatory and/or antiproliferative treatment, combination with anti-inflammatory drugs is included. Combination is also possible with antihistamine drug substances, bronchodilatatory drugs, NSAID or antagonists of chemokine receptors.

[0087] The term "aromatase inhibitor" as used herein relates to a compound which inhibits the estrogen production, i.e. the conversion of the substrates androstenedione and testosterone to estrone and estradiol, respectively. The term includes, but is not limited to steroids, especially atamestane, exemestane and formestane and, in particular, non-steroids, especially

aminoglutethimide, roglethimide, pyridoglutethimide, trilostane, testolactone, ketokonazole, vorozole, fadrozole, anastrozole and letrozole. Exemestane can be administered, e.g., in the form as it is marketed, e.g. under the trademark AROMASIN. Formestane can be administered, e.g., in the form as it is marketed, e.g. under the trademark LENTARON. Fadrozole can be administered, e.g., in the form as it is marketed, e.g. under the trademark AFEMA. Anastrozole can be administered, e.g., in the form as it is marketed, e.g. under the trademark ARIMIDEX. Letrozole can be administered, e.g., in the form as it is marketed, e.g. under the trademark FEMARA or FEMAR. Aminoglutethimide can be administered, e.g., in the form as it is marketed, e.g. under the trademark ORIMETEN. A combination of the invention comprising a chemotherapeutic agent which is an aromatase inhibitor is particularly useful for the treatment of hormone receptor positive tumors, e.g. breast tumors.

[0088] The term "antiestrogen" as used herein relates to a compound which antagonizes the effect of estrogens at the estrogen receptor level. The term includes, but is not limited to tamoxifen, fulvestrant, raloxifene and raloxifene hydrochloride. Tamoxifen can be administered, e.g., in the form as it is marketed, e.g. under the trademark NOLVADEX. Raloxifene hydrochloride can be administered, e.g., in the form as it is marketed, e.g. under the trademark EVISTA. Fulvestrant can be formulated as disclosed in US 4,659,516 or it can be administered, e.g., in the form as it is marketed, e.g. under the trademark FASLODEX. A combination of the invention comprising a chemotherapeutic agent which is an antiestrogen is particularly useful for the treatment of estrogen receptor positive tumors, e.g. breast tumors.

[0089] The term "anti-androgen" as used herein relates to any substance which is capable of inhibiting the biological effects of androgenic hormones and includes, but is not limited to, bicalutamide (CASODEX), which can be formulated, e.g. as disclosed in US 4,636,505.

[0090] The term "gonadorelin agonist" as used herein includes, but is not limited to abarelix, goserelin and goserelin acetate. Goserelin is disclosed in US 4,100,274 and can be administered, e.g., in the form as it is marketed, e.g. under the trademark ZOLADEX. Abarelix can be formulated, e.g. as disclosed in US 5,843,901.

[0091] The term "topoisomerase I inhibitor" as used herein includes, but is not limited to topotecan, gimatecan, irinotecan, camptothecian and its analogues, 9-nitrocamptothecin and the macromolecular camptothecin conjugate PNU-166148 (compound A1 in WO99/ 17804). Irinotecan can be administered, e.g. in the form as it is marketed, e.g. under the trademark CAMPTOSAR. Topotecan can be administered, e.g., in the form as it is marketed, e.g. under the trademark HYCAMTIN.

[0092] The term "topoisomerase II inhibitor" as used herein includes, but is not limited to the anthracyclines such as doxorubicin (including liposomal formulation, e.g. CAELYX), daunorubicin, epirubicin, idarubicin and nemorubicin, the anthraquinones mitoxantrone and losoxantrone, and the podophillotoxines etoposide and teniposide. Etoposide can be administered, e.g. in the form as it is marketed, e.g. under the trademark ETOPOPHOS. Teniposide can be administered, e.g. in the form as it is marketed, e.g. under the trademark VM 26-BRISTOL. Doxorubicin can be administered, e.g. in the form as it is marketed, e.g. under the trademark ADRIBLASTIN or ADRIAMYCIN. Epirubicin can be administered, e.g. in the form as it is marketed, e.g. under the trademark FARMORUBICIN. Idarubicin can be administered, e.g. in the form as it is marketed, e.g. under the trademark ZAVEDOS. Mitoxantrone can be administered, e.g. in the form as it is marketed, e.g. under the trademark NOVANTRON.

[0093] The term "microtubule active compound" relates to microtubule stabilizing, microtubule destabilizing compounds and microtublin polymerization inhibitors including, but not limited to taxanes, e.g. paclitaxel and docetaxel, vinca alkaloids, e.g., vinblastine, especially vinblastine sulfate, vincristine especially vincristine sulfate, and vinorelbine, discodermolides, cochicine and epothilones and derivatives thereof, e.g. epothilone B or D or derivatives thereof. Paclitaxel may be administered e.g. in the form as it is marketed, e.g. TAXOL. Docetaxel can be administered, e.g., in the form as it is marketed, e.g. under the trademark TAXOTERE. Vinblastine sulfate can be administered, e.g., in the form as it is marketed, e.g. under the trademark VINBLASTIN R.P.. Vincristine sulfate can be administered, e.g., in the form as it is marketed, e.g. under the trademark FARMISTIN. Discodermolide can be obtained, e.g., as disclosed in US 5,010,099. Also included are Epothilone derivatives which are disclosed in

WO 98/10121, US 6,194,181, WO 98/25929, WO 98/08849, WO 99/43653, WO 98/22461 and WO 00/31247. Especially preferred are Epothilone A and/or B.

[0094] The term "alkylating compound" as used herein includes, but is not limited to, cyclophosphamide, ifosfamide, melphalan or nitrosourea (BCNU or Gliadel). Cyclophosphamide can be administered, e.g., in the form as it is marketed, e.g. under the trademark CYCLOSTIN. Ifosfamide can be administered, e.g., in the form as it is marketed, e.g. under the trademark HOLOXAN.

[0095] The term "histone deacetylase inhibitors" or "HDAC inhibitors" relates to compounds which inhibit the histone deacetylase and which possess antiproliferative activity. This includes compounds such as LDH589 disclosed in WO 02/22577, especially N-hydroxy-3-[4-[[(2-hydroxyethyl)[2-(1H-indol-3-yl)ethyl]-amino]methyl]phenyl]-2E-2-propenamide, N-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide and pharmaceutically acceptable salts thereof. It further especially includes Suberoylanilide hydroxamic acid (SAHA).

[0096] The term "antineoplastic antimetabolite" includes, but is not limited to, 5-Fluorouracil or 5-FU, capecitabine, gemcitabine, DNA demethylating compounds, such as 5-azacytidine and decitabine, methotrexate and edatrexate, and folic acid antagonists such as pemetrexed. Capecitabine can be administered, e.g., in the form as it is marketed, e.g. under the trademark XELODA. Gemcitabine can be administered, e.g., in the form as it is marketed, e.g. under the trademark GEMZAR.

[0097] The term "platin compound" as used herein includes, but is not limited to, carboplatin, cis-platin, cisplatinum and oxaliplatin. Carboplatin can be administered, e.g., in the form as it is marketed, e.g. under the trademark CARBOPLAT. Oxaliplatin can be administered, e.g., in the form as it is marketed, e.g. under the trademark ELOXATIN.

[0098] The term "compounds targeting/decreasing a protein or lipid kinase activity"; or a "protein or lipid phosphatase activity"; or "further anti-angiogenic compounds" as used herein includes, but is not limited to, protein tyrosine kinase and/or serine and/or threonine kinase inhibitors or lipid kinase inhibitors, for example:

[0099] a) compounds targeting, decreasing or inhibiting the activity of the platelet-derived growth factor-receptors (PDGFR), such as compounds which target, decrease or inhibit the activity of PDGFR, especially compounds which inhibit the PDGF receptor, e.g. a N-phenyl-2-pyrimidine-amine derivative, e.g. imatinib, SU101, SU6668 and GFB-111;

[00100] b) compounds targeting, decreasing or inhibiting the activity of the fibroblast growth factor-receptors (FGFR);

[00101] c) compounds targeting, decreasing or inhibiting the activity of the insulin-like growth factor receptor I (IGF-IR), such as compounds which target, decrease or inhibit the activity of IGF-IR, especially compounds which inhibit the kinase activity of IGF-I receptor, such as those compounds disclosed in WO 02/092599, or antibodies that target the extracellular domain of IGF-I receptor or its growth factors;

[00102] d) compounds targeting, decreasing or inhibiting the activity of the Trk receptor tyrosine kinase family, or ephrin B4 inhibitors;

[00103] e) compounds targeting, decreasing or inhibiting the activity of the Axl receptor tyrosine kinase family;

[00104] f) compounds targeting, decreasing or inhibiting the activity of the Ret receptor tyrosine kinase;

[00105] g) compounds targeting, decreasing or inhibiting the activity of the Kit/SCFR receptor tyrosine kinase, i.e C-kit receptor tyrosine kinases - (part of the PDGFR family), such as compounds which target, decrease or inhibit the activity of the c-Kit receptor tyrosine kinase family, especially compounds which inhibit the c-Kit receptor, e.g. imatinib;

[00106] h) compounds targeting, decreasing or inhibiting the activity of members of the c-Abl family, their gene-fusion products (e.g. BCR-Abl kinase) and mutants, such as compounds which target decrease or inhibit the activity of c-AbI family members and their gene fusion products, e.g. a N-phenyl-2-pyrimidine-amine derivative, e.g. imatinib or nilotinib (AMN107); PD180970; AG957; NSC 680410; PD173955 from ParkeDavis; or dasatinib (BMS-354825)

[00107] i) compounds targeting, decreasing or inhibiting the activity of members of the protein kinase C (PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC,

JAK, FAK, PDK1, PKB/Akt, and Ras/MAPK family members, and/or members of the cyclin-dependent kinase family (CDK) and are especially those staurosporine derivatives disclosed in US 5,093,330, e.g. midostaurin; examples of further compounds include e.g. UCN-01, safingol, BAY 43-9006, Bryostatin 1, Perifosine; Ilmofosine; RO 318220 and RO 320432; GO 6976; Isis 3521; LY333531/LY379196; isochinoline compounds such as those disclosed in WO 00/09495; FTIs; BEZ235 (a P13K inhibitor) or AT7519 (CDK inhibitor);

[00108] j) compounds targeting, decreasing or inhibiting the activity of protein-tyrosine kinase inhibitors, such as compounds which target, decrease or inhibit the activity of protein-tyrosine kinase inhibitors include imatinib mesylate (GLEEVEC) or tyrphostin. A tyrphostin is preferably a low molecular weight (Mr < 1500) compound, or a pharmaceutically acceptable salt thereof, especially a compound selected from the benzylidenemalonitrile class or the S-arylbenzenemalonirile or bisubstrate quinoline class of compounds, more especially any compound selected from the group consisting of Tyrphostin A23/RG-50810; AG 99; Tyrphostin AG 213; Tyrphostin AG 1748; Tyrphostin AG 490; Tyrphostin B44; Tyrphostin B44 (+) enantiomer; Tyrphostin AG 555; AG 494; Tyrphostin AG 556, AG957 and adaphostin (4-{[(2,5-dihydroxyphenyl)methyl]amino}-benzoic acid adamantyl ester; NSC 680410, adaphostin);

[00109] k) compounds targeting, decreasing or inhibiting the activity of the epidermal growth factor family of receptor tyrosine kinases (EGFR, ErbB2, ErbB3, ErbB4 as homo- or heterodimers) and their mutants, such as compounds which target, decrease or inhibit the activity of the epidermal growth factor receptor family are especially compounds, proteins or antibodies which inhibit members of the EGF receptor tyrosine kinase family, e.g. EGF receptor, ErbB2, ErbB3 and ErbB4 or bind to EGF or EGF related ligands, and are in particular those compounds, proteins or monoclonal antibodies generically and specifically disclosed in WO 97/02266, e.g. the compound of ex. 39, or in EP 0 564 409, WO 99/03854, EP 0520722, EP 0 566 226, EP 0 787 722, EP 0 837 063, US 5,747,498, WO 98/10767, WO 97/30034, WO 97/49688, WO 97/38983 and, especially, WO 96/30347 (e.g. compound known as CP 358774), WO 96/33980 (e.g. compound ZD 1839) and WO 95/03283 (e.g. compound ZM105180); e.g. trastuzumab (Herceptin™), cetuximab (Erbitux™), Iressa, Tarceva, OSI-774, CI-1033, EKB-569, GW-2016,

E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 or E7.6.3, and 7H-pyrrolo-[2,3-d]pyrimidine derivatives which are disclosed in WO 03/013541; and

[00110] l) compounds targeting, decreasing or inhibiting the activity of the c-Met receptor, such as compounds which target, decrease or inhibit the activity of c-Met, especially compounds which inhibit the kinase activity of c-Met receptor, or antibodies that target the extracellular domain of c-Met or bind to HGF.

[00111] Further anti-angiogenic compounds include compounds having another mechanism for their activity, e.g. unrelated to protein or lipid kinase inhibition e.g. thalidomide (THALOMID) and TNP-470.

[00112] Compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase are e.g. inhibitors of phosphatase 1, phosphatase 2A, or CDC25, e.g. okadaic acid or a derivative thereof.

[00113] Compounds which induce cell differentiation processes are e.g. retinoic acid, α- γ- or δ-tocopherol or α- γ- or δ-tocotrienol.

[00114] The term cyclooxygenase inhibitor as used herein includes, but is not limited to, e.g. Cox-2 inhibitors, 5-alkyl substituted 2-arylaminophenylacetic acid and derivatives, such as celecoxib (CELEBREX), rofecoxib (VIOXX), etoricoxib, valdecoxib or a 5-alkyl-2-arylaminophenylacetic acid, e.g. 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenyl acetic acid, lumiracoxib.

[00115] The term "bisphosphonates" as used herein includes, but is not limited to, etridonic, clodronic, tiludronic, pamidronic, alendronic, ibandronic, risedronic and zoledronic acid. "Etridonic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark DIDRONEL. "Clodronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark BONEFOS. "Tiludronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark SKELID. "Pamidronic acid" can be administered, e.g. in the form as it is marketed, e.g. under the trademark AREDIA™. "Alendronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark FOSAMAX. "Ibandronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark BONDRANAT. "Risedronic acid" can be administered, e.g., in the form as it is marketed, e.g.

under the trademark ACTONEL. "Zoledronic acid" can be administered, e.g. in the form as it is marketed, e.g. under the trademark ZOMETA.

[00116] The term "mTOR inhibitors" relates to compounds which inhibit the mammalian target of rapamycin (mTOR) and which possess antiproliferative activity such as sirolimus (Rapamune®), everolimus (Certican™), CCI-779 and ABT578.

[00117] The term "heparanase inhibitor" as used herein refers to compounds which target, decrease or inhibit heparin sulfate degradation. The term includes, but is not limited to, PI-88.

[00118] The term " biological response modifier" as used herein refers to a lymphokine or interferons, e.g. interferon γ.

[00119] The term "inhibitor of Ras oncogenic isoforms", e.g. H-Ras, K-Ras, or N-Ras, as used herein refers to compounds which target, decrease or inhibit the oncogenic activity of Ras e.g. a "farnesyl transferase inhibitor" e.g. L-744832, DK8G557 or R115777 (Zarnestra).

[00120] The term "telomerase inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of telomerase. Compounds which target, decrease or inhibit the activity of telomerase are especially compounds which inhibit the telomerase receptor, e.g. telomestatin.

[00121] The term "methionine aminopeptidase inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of methionine aminopeptidase. Compounds which target, decrease or inhibit the activity of methionine aminopeptidase are e.g. bengamide or a derivative thereof.

[00122] The term "proteasome inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of the proteasome. Compounds which target, decrease or inhibit the activity of the proteasome include e.g. Bortezomid (Velcade™)and MLN 341.

[00123] The term "matrix metalloproteinase inhibitor" or ("MMP" inhibitor) as used herein includes, but is not limited to, collagen peptidomimetic and nonpeptidomimetic inhibitors, tetracycline derivatives, e.g. hydroxamate peptidomimetic inhibitor batimastat and its orally bioavailable analogue marimastat (BB-2516), prinomastat (AG3340), metastat (NSC 683551) BMS-279251, BAY 12-9566, TAA211, MMI270B or AAJ996.

[00124] The term "compounds used in the treatment of hematologic malignancies" as used herein includes, but is not limited to, FMS-like tyrosine kinase inhibitors e.g. compounds targeting, decreasing or inhibiting the activity of FMS-like tyrosine kinase receptors (Flt-3R); interferon, 1-b-D-arabinofuransylcytosine (ara-c) and bisulfan; and ALK inhibitors e.g. compounds which target, decrease or inhibit anaplastic lymphoma kinase.

[00125] Compounds which target, decrease or inhibit the activity of FMS-like tyrosine kinase receptors (Flt-3R) are especially compounds, proteins or antibodies which inhibit members of the Flt-3R receptor kinase family, e.g. PKC412, TKI258, midostaurin, a staurosporine derivative, SU11248 and MLN518.

[00126] The term "HSP90 inhibitors" as used herein includes, but is not limited to, compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90; degrading, targeting, decreasing or inhibiting the HSP90 client proteins via the ubiquitin proteosome pathway. Compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90 are especially compounds, proteins or antibodies which inhibit the ATPase activity of HSP90 e.g., 17-allylamino,17-demethoxygeldanamycin (17AAG), a geldanamycin derivative; other geldanamycin related compounds; radicicol and HDAC inhibitors. An example HSP90 inhibitor is AUY922.

[00127] The term "antiproliferative antibodies" as used herein includes, but is not limited to, trastuzumab (Herceptin™), Trastuzumab-DM1,erbitux, bevacizumab (Avastin™), rituximab (Rituxan®), PRO64553 (anti-CD40), 2C4 Antibody and HCD122 antibody (anti-CD40). By antibodies is meant e.g. intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies formed from at least 2 intact antibodies, and antibodies fragments so long as they exhibit the desired biological activity.

[00128] For the treatment of acute myeloid leukemia (AML), compounds of formula (I) can be used in combination with standard leukemia therapies, especially in combination with therapies used for the treatment of AML. In particular, compounds of formula (I) can be administered in combination with, e.g., farnesyl transferase inhibitors and/or other drugs useful for the treatment of AML, such as Daunorubicin, Adriamycin, Ara-C, VP-16, Teniposide, Mitoxantrone, Idarubicin, Carboplatinum and PKC412.

[00129] The term "antileukemic compounds" includes, for example, Ara-C, a pyrimidine analog, which is the 2′-alpha-hydroxy ribose (arabinoside) derivative of deoxycytidine. Also included is the purine analog of hypoxanthine, 6-mercaptopurine (6-MP) and fludarabine phosphate.

[00130] Compounds which target, decrease or inhibit activity of histone deacetylase (HDAC) inhibitors such as sodium butyrate and suberoylanilide hydroxamic acid (SAHA) inhibit the activity of the enzymes known as histone deacetylases. Specific HDAC inhibitors include MS275, SAHA, FK228 (formerly FR901228), Trichostatin A and compounds disclosed in US 6,552,065, in particular, *N*-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino]-methyl]phenyl]-2*E*-2-propenamide, or a pharmaceutically acceptable salt thereof and *N*-hydroxy-3-[4-[(2-hydroxyethyl){2-(1*H*-indol-3-yl)ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide, or a pharmaceutically acceptable salt thereof, especially the lactate salt.

[00131] Somatostatin receptor antagonists as used herein refers to compounds which target, treat or inhibit the somatostatin receptor such as octreotide, and SOM230 (pasireotide).

[00132] Tumor cell damaging approaches refer to approaches such as ionizing radiation. The term "ionizing radiation" referred to above and hereinafter means ionizing radiation that occurs as either electromagnetic rays (such as X-rays and gamma rays) or particles (such as alpha and beta particles). Ionizing radiation is provided in, but not limited to, radiation therapy and is known in the art. See Hellman, Principles of Radiation Therapy, Cancer, in *Principles and Practice of Oncology*, Devita et al., Eds., 4th Edition, Vol. 1, pp. 248-275 (1993).

[00133] The term "EDG binders" as used herein refers a class of immunosuppressants that modulates lymphocyte recirculation, such as FTY720.

[00134] The term "ribonucleotide reductase inhibitors" refers to pyrimidine or purine nucleoside analogs including, but not limited to, fludarabine and/or cytosine arabinoside (ara-C), 6-thioguanine, 5-fluorouracil, cladribine, 6-mercaptopurine (especially in combination with ara-C against ALL) and/or pentostatin. Ribonucleotide reductase inhibitors are especially hydroxyurea or 2-hydroxy-1*H*-isoindole-1,3-dione derivatives, such as PL-1, PL-2, PL-3, PL-4, PL-5, PL-6, PL-7 or PL-8 mentioned in Nandy et al., *Acta Oncologica*, Vol. 33, No. 8, pp. 953-961 (1994).

[00135] The term "*S*-adenosylmethionine decarboxylase inhibitors" as used herein includes, but is not limited to the compounds disclosed in US 5,461,076.

[00136] Also included are in particular those compounds, proteins or monoclonal antibodies of VEGF disclosed in WO 98/35958, e.g. 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof, e.g. the succinate, or in WO 00/09495, WO 00/27820, WO 00/59509, WO 98/11223, WO 00/27819 and EP 0 769 947; those as described by Prewett et al, *Cancer Res*, Vol. 59, pp. 5209-5218 (1999); Yuan et al., *Proc Natl Acad Sci U S A*, Vol. 93, pp. 14765-14770 (1996); Zhu et al., *Cancer Res*, Vol. 58, pp. 3209-3214 (1998); and Mordenti et al., *Toxicol Pathol*, Vol. 27, No. 1, pp. 14-21 (1999); in WO 00/37502 and WO 94/10202; ANGIOSTATIN, described by O'Reilly et al., *Cell*, Vol. 79, pp. 315-328 (1994); ENDOSTATIN, described by O'Reilly et al., *Cell*, Vol. 88, pp. 277-285 (1997); anthranilic acid amides; ZD4190; ZD6474; SU5416; SU6668; bevacizumab; or anti-VEGF antibodies or anti-VEGF receptor antibodies, e.g. rhuMAb and RHUFab, VEGF aptamer e.g. Macugon; FLT-4 inhibitors, FLT-3 inhibitors, VEGFR-2 IgG1 antibody, Angiozyme (RPI 4610) and Bevacizumab (Avastin™).

[00137] Photodynamic therapy as used herein refers to therapy which uses certain chemicals known as photosensitizing compounds to treat or prevent cancers. Examples of photodynamic therapy includes treatment with compounds, such as e.g. VISUDYNE and porfimer sodium.

[00138] Angiostatic steroids as used herein refers to compounds which block or inhibit angiogenesis, such as, e.g., anecortave, triamcinolone. hydrocortisone, 11-α-epihydrocotisol, cortexolone, 17α-hydroxyprogesterone, corticosterone, desoxycorticosterone, testosterone, estrone and dexamethasone.

[00139] Implants containing corticosteroids refers to compounds, such as e.g. fluocinolone, dexamethasone.

[00140] "Other chemotherapeutic compounds" include, but are not limited to, plant alkaloids, hormonal compounds and antagonists; biological response modifiers, preferably lymphokines or interferons; antisense oligonucleotides or oligonucleotide derivatives; shRNA or siRNA; or miscellaneous compounds or compounds with other or unknown mechanism of action.

[00141] The structure of the active compounds identified by code nos., generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications).

[00142] None of the quotations of references made within the present disclosure is to be understood as an admission that the references cited are prior art that would negatively affect the patentability of the present invention.

Pharmaceutical formulations, uses and methods

[00143] The above-mentioned compounds, which can be used in combination with a compound of the formula I, can be prepared and administered as described in the art, such as in the documents cited above.

[00144] By "combination", there is meant either a fixed combination in one dosage unit form, or a kit of parts for the combined administration where a compound of the formula I and a combination partner may be administered independently at the same time or separately within time intervals that especially allow that the combination partners show a cooperative, e.g. synergistic effect.

[00145] The invention also provides a pharmaceutical preparation, comprising a compound of formula I as defined herein, and/or an N-oxide or a tautomer thereof, and/oror a pharmaceutically acceptable salt of such a compound, or a hydrate or solvate thereof (all referred to often as "a compound of the formula I" merely herein), and at least one pharmaceutically acceptable carrier.

[00146] A compound of formula I can be administered alone or in combination with one or more other therapeutic compounds, possible combination therapy taking the form of fixed combinations or the administration of a compound of the invention and one or more other therapeutic (including prophylactic) compounds being staggered or given independently of one another, or the combined administration of fixed combinations and one or more other therapeutic compounds. A compound of formula I can besides or in addition be administered especially for tumor therapy in combination with chemotherapy, radiotherapy, immunotherapy, phototherapy, surgical intervention, or a combination of these. Long-term therapy is equally possible as is

adjuvant therapy in the context of other treatment strategies, as described above. Other possible treatments are therapy to maintain the patient's status after tumor regression, or even chemopreventive therapy, for example in patients at risk.

[00147] The dosage of the active ingredient depends upon a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound employed. A physician, clinician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition. Optimal precision in achieving concentration of drug within the range that yields efficacy requires a regimen based on the kinetics of the drug's availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of a drug.

[00148] The dose of a compound of the formula I or a pharmaceutically acceptable salt thereof to be administered to warm-blooded animals, for example humans of approximately 70 kg body weight, is preferably from approximately 3 mg to approximately 15 g, more preferably from approximately 10 mg to approximately 3 g, yet more preferably from approximately 50 mg to 1.5 g per person per day, undivided in 1 dose or divided preferably into 2 to 4, e.g. 2 or 3, single doses which may, for example, be of the same size. Usually, children receive half of the adult dose.

[00149] The compounds of the formula I may be administered by any conventional route, in particular parenterally, for example in the form of injectable solutions or suspensions, enterally, e.g. orally, for example in the form of tablets or capsules, topically, e.g. in the form of lotions, gels, ointments or creams, or in a nasal or a suppository form. Topical administration is e.g. to the skin. A further form of topical administration is to the eye. Pharmaceutical compositions comprising a compound of the invention in association with at least one pharmaceutical acceptable carrier or diluent may be manufactured in conventional manner by mixing with a pharmaceutically acceptable carrier or diluent.

[00150] The invention relates also to pharmaceutical compositions comprising an effective amount, especially an amount effective in the treatment of one of the above-mentioned disorders, of a compound of formula I and/or an N-oxide or a tautomer thereof, and/or a

pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable carriers that are suitable for topical, enteral, for example oral or rectal, or parenteral administration and that may be inorganic or organic, solid or liquid. There can be used for oral administration especially tablets or gelatin capsules that comprise the active ingredient together with diluents, for example lactose, dextrose, mannitol, and/or glycerol, and/or lubricants and/or polyethylene glycol. Tablets may also comprise binders, for example magnesium aluminum silicate, starches, such as corn, wheat or rice starch, gelatin, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and, if desired, disintegrators, for example starches, agar, alginic acid or a salt thereof, such as sodium alginate, and/or effervescent mixtures, or adsorbents, dyes, flavorings and sweeteners. It is also possible to use the pharmacologically active compounds of the present invention in the form of parenterally administrable compositions or in the form of infusion solutions. The pharmaceutical compositions may be sterilized and/or may comprise excipients, for example preservatives, stabilisers, wetting compounds and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers. The present pharmaceutical compositions, which may, if desired, comprise other pharmacologically active substances are prepared in a manner known per se, for example by means of conventional mixing, granulating, confectionning, dissolving or lyophilising processes, and comprise approximately from 1% to 99%, especially from approximately 1% to approximately 20%, active ingredient(s).

[00151] Additionally, the present invention provides a compound of formula I, and/ or an N-oxide or a tautomer thereof, and/or a pharmaceutically acceptable salt thereof, for use in a method for the treatment of the human or animal body, especially for the treatment of a disease mentioned herein, most especially in a patient requiring such treatment..

[00152] The present invention also relates to the use of a compound of formula I and/or an N-oxide or a tautomer thereof, andor a pharmaceutically acceptable salt of such a compound, for the preparation of a medicament for the treatment especially of a proliferative disease.

[00153] Furthermore, the invention relates to a method for the treatment of a proliferative disease which responds to an inhibition p53/MDM2 interaction, which comprises administering a compound of formula I, and/or an N-oxide or a tautomer thereof, and/or a pharmaceutically acceptable salt thereof, wherein the radicals and symbols have the meanings as

defined above, to a warm-blooded animal requiring such treatment, especially in a quantity effective against said disease and/or capable of inhibiting the p53/MDM2 interaction in said warm-blooded animal.

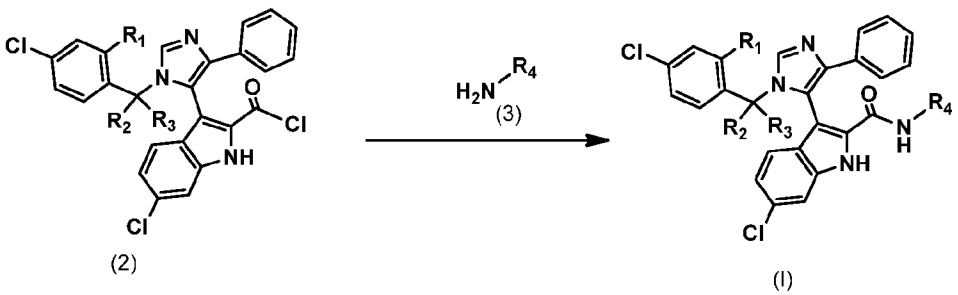
[00154] Furthermore, the invention relates to a pharmaceutical composition for treatment of solid or liquid tumours in warm-blooded animals, including humans, comprising an antiproliferativly effective dose of a compound of the formula I as described above or a pharmaceutically acceptable salt of such a compound together with a pharmaceutical carrier.

Processes for Making Compounds of the Invention

[00155] The present invention also includes processes for the preparation of compounds of the invention. In the reactions described, it can be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups can be used in accordance with standard practice, for example, see T.W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry", John Wiley and Sons, 1991.

[00156] Compounds of Formula I can be prepared by proceeding as in the following Reaction Scheme I:

Reaction Scheme I:

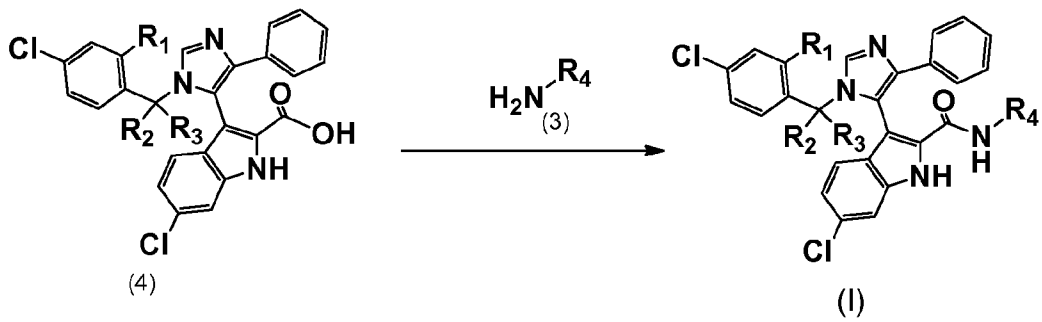


[00157] in which R_1, R_2, R_3 and R_4 are as defined for Formula I in the Summary of the Invention. A compound of Formula I can be prepared by reacting a compound of (2) with

a compound of formula (3) in the presence of a Lewis acid as an activator (such as dimethylaluminumchloride, or the like) and a suitable solvent (such as DCM, and the like). The reaction takes place at about room temperature and can take up to about 4 hours to complete.

[00158] Compounds of Formula I can be prepared by proceeding as in the following Reaction Scheme II:

Reaction Scheme II:



[00159] in which R_1, R_2, R_3 and R_4 are as defined for Formula I in the Summary of the Invention. A compound of Formula I can be prepared by reacting a compound of (4) with a compound of formula (3) in the presence of a coupling agent (such as HATU, or the like), optionally a suitable base (such as N-methylmorpholine, or the like) and a suitable solvent (such as DMF, and the like). The reaction takes place up to about 60°C and can take up to about 4 hours to complete.

[00160] Detailed examples of the synthesis of compounds of Formula I can be found in the Examples, *infra*.

Additional Processes for Making Compounds of the Invention

[00161] A compound of the invention can be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically

acceptable base addition salt of a compound of the invention can be prepared by reacting the free acid form of the compound with a pharmaceutically acceptable inorganic or organic base.

[00162] Compounds of the formula I can also be modified by appending appropriate functionalities to enhance selective biological properties. Modifications of this kind are known in the art and include those that increase penetration into a given biological system (e.g. blood, lymphatic system, central nervous system, testis), increase bioavailability, increase solubility to allow parenteral administration (e.g. injection, infusion), alter metabolism and/or alter the rate of secretion. Examples of this type of modifications include but are not limited to esterification, e.g. with polyethylene glycols, derivatisation with pivaloyloxy or fatty acid substituents, conversion to carbamates, hydroxylation of aromatic rings and heteroatom substitution in aromatic rings. Whereever compounds of the formula I, and/or N-oxides, tautomers and/or (preferably pharmaceutically acceptable) salts thereof are mentioned, this comprises such modified formulae, while preferably the molecules of the formula I, their N-oxides, their tautomers and/or their salts are meant.

[00163] Alternatively, the salt forms of the compounds of the invention can be prepared using salts of the starting materials or intermediates. In view of the close relationship between the novel compounds of the formula I in free form and those in the form of their salts, including those salts that can be used as intermediates, for example in the purification or identification of the novel compounds, any reference to the compounds or a compound of the formula I hereinbefore and hereinafter is to be understood as referring to the compound in free form and/or also to one or more salts thereof, as appropriate and expedient, as well as to one or more solvates, e.g. hydrates.

[00164] Salts are formed, for example, as acid addition salts, preferably with organic or inorganic acids, from compounds of formula I with a basic nitrogen atom, especially the pharmaceutically acceptable salts. Suitable inorganic acids are, for example, halogen acids, such as hydrochloric acid, sulfuric acid, or phosphoric acid. Suitable organic acids are, for example, carboxylic, phosphonic, sulfonic or sulfamic acids, for example acetic acid, propionic acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, fumaric acid, succinic acid, malonic acid, adipic acid, pimelic acid, suberic acid, azelaic acid, malic acid, tartaric acid,

citric acid, amino acids, such as glutamic acid or aspartic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, cyclohexanecarboxylic acid, adamantanecarboxylic acid, benzoic acid, salicylic acid, 4-aminosalicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid, methane- or ethane-sulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 4-toluenesulfonic acid, 2-naphthalenesulfonic acid, 1,5-naphthalene-disulfonic acid, 2- or 3-methylbenzenesulfonic acid, methylsulfuric acid, ethylsulfuric acid, dodecylsulfuric acid, N-cyclohexylsulfamic acid, N-methyl-, N-ethyl- or N-propyl-sulfamic acid, or other organic protonic acids, such as ascorbic acid.

[00165] For isolation or purification purposes it is also possible to use pharmaceutically unacceptable salts, for example picrates or perchlorates. For therapeutic use, only pharmaceutically acceptable salts or free compounds are employed (where applicable in the form of pharmaceutical preparations), and these are therefore preferred.

[00166] The free acid or free base forms of the compounds of the invention can be prepared from the corresponding base addition salt or acid addition salt from, respectively. For example a compound of the invention in an acid addition salt form can be converted to the corresponding free base by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, and the like). A compound of the invention in a base addition salt form can be converted to the corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc.).

[00167] Compounds of the invention in unoxidized form can be prepared from N-oxides of compounds of the invention by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like) in a suitable inert organic solvent (e.g. acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80°C.

[00168] Prodrug derivatives of the compounds of the invention can be prepared by methods known to those of ordinary skill in the art (e.g., for further details see Saulnier et al., (1994), Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985). For example, appropriate prodrugs can be prepared by reacting a non-derivatized compound of the

invention with a suitable carbamylating agent (e.g., 1,1-acyloxyalkylcarbanochloridate, para-nitrophenyl carbonate, or the like).

[00169] Protected derivatives of the compounds of the invention can be made by means known to those of ordinary skill in the art. A detailed description of techniques applicable to the creation of protecting groups and their removal can be found in T. W. Greene, "Protecting Groups in Organic Chemistry", 3rd edition, John Wiley and Sons, Inc., 1999.

[00170] Compounds of the present invention can be conveniently prepared, or formed during the process of the invention, as solvates (e.g., hydrates). Hydrates of compounds of the present invention can be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

[00171] Compounds of the invention can be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. While resolution of enantiomers can be carried out using covalent diastereomeric derivatives of the compounds of the invention, dissociable complexes are preferred (e.g., crystalline diastereomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981.

[00172] In summary, the compounds of Formula I can be made by a process, which involves:

(a) those of reaction schemes I & II; and

(b) optionally converting a compound of the invention into a pharmaceutically acceptable salt;

(c) optionally converting a salt form of a compound of the invention to a non-salt form;

(d) optionally converting an unoxidized form of a compound of the invention into a pharmaceutically acceptable N-oxide;

(e) optionally converting an N-oxide form of a compound of the invention to its unoxidized form;

(f) optionally resolving an individual isomer of a compound of the invention from a mixture of isomers;

(g) optionally converting a non-derivatized compound of the invention into a pharmaceutically acceptable prodrug derivative; and

(h) optionally converting a prodrug derivative of a compound of the invention to its non-derivatized form.

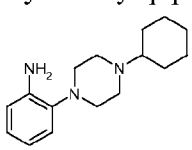
Insofar as the production of the starting materials is not particularly described, the compounds are known or can be prepared analogously to methods known in the art or as disclosed in the Examples hereinafter.

[00173] One of skill in the art will appreciate that the above transformations are only representative of methods for preparation of the compounds of the present invention, and that other well known methods can similarly be used.

Examples

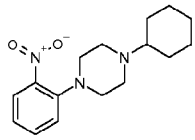
[00174] The following examples serve to illustrate the invention without limiting the scope thereof. Note that in some cases compounds are mentioned as intermediates.

[00175] Intermediate 4.1: 2-(4-Cyclohexyl-piperazin-1-yl)-phenylamine.



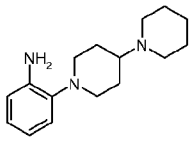
[00176] The title Intermediate 4.1 (0.99 g, 3.78 mmol, 99%) was obtained as a beige solid from Intermediate 4.2 (1.1 g, 3.80 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.07 min; LC-MS: m/z 260.4 $[M+H]^+$.

[00177] Intermediate 4.2: 1-Cyclohexyl-4-(2-nitro-phenyl)-piperazine.



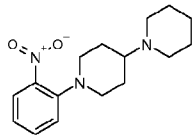
[00178] To a solution of 2-fluoro-nitrobenzene (600 mg, 4.25 mmol) in acetonitrile (20 mL) was added successively K_2CO_3 (1.76 g, 12.76 mmol) and 1-cyclohexyl-piperazine (787 mg, 4.68 mmol) at 0 °C. The ice bath was removed and the orange suspension was stirred over night at RT, the inorganic salts were filtered off and washed several times with THF. The filtrate was concentrated *in vacuo* and silica gel column chromatography (eluting with gradient DCM:EtOAc = 100:0 to 0:100) of the residue (eluting with a gradient of DCM:EtOAc = 100:0 to 0:100) afforded the title compound (1.1 g, 3.73 mmol, 88%) as an orange oil analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.16 min; LC-MS: m/z 290.2 $[M+H]^+$.

[00179] Intermediate 5.1: 2-[1,4']Bipiperidinyl-1'-yl-phenylamine.



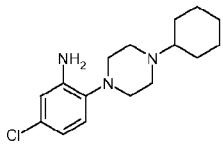
[00180] The title Intermediate 5.1 (1.62 g, 5.93 mmol, 96%) was obtained as a beige solid from Intermediate 5.2 (1.79 g, 6.12 mmol) in analogy to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 2.97 min; LC-MS: m/z 260.2 $[M+H]^+$.

[00181] Intermediate 5.2: 1'-(2-Nitro-phenyl)-[1,4']bipiperidinyl.



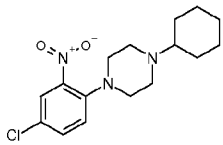
[00182] The title Intermediate 5.2 (1.79 g, 6.12 mmol, 81%) was obtained as a yellow solid from 2-fluoro-nitrobenzene (0.8 mL, 7.6 mmol) and [1,4']bipiperidinyl (1.4 g, 8.36 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.02 min.

[00183] Intermediate 6.1: 5-Chloro-2-(4-cyclohexyl-piperazin-1-yl)-phenylamine.



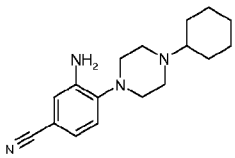
[00184] A mixture of Intermediate 6.2 (2.78 g, 8.59 mmol) and PtO_2 (260 mg) in MeOH (70 mL) was shaken under H_2 gas atmosphere at RT for 1.5 h. The catalyst was filtered off under a N_2 gas stream and washed with MeOH and THF. The filtrate was concentrated *in vacuo* and dried under high vacuum, which gave the title Intermediate 6.1 (2.27 g, 7.73 mmol, 90%) as a white solid.HPLC: $^{A}t_{Ret}$ = 4.06 min; LC-MS: m/z 294.4 $[M+H]^+$.

[00185] Intermediate 6.2: 1-(4-Chloro-2-nitro-phenyl)-4-cyclohexyl-piperazine.



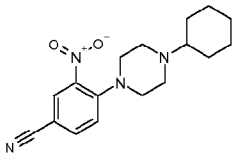
[00186] The title Intermediate 6.2 (2.8 g, 8.21 mmol, 95%) was obtained as an orange semi solid from 5-chloro-2-fluoro-nitrobenzene (1.52 g, 8.66 mmol) and 1-cyclohexyl-piperazine (1.60 g, 9.52 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.48 min; LC-MS: m/z 324.2 $[M+H]^+$.

[00187] Intermediate 7.1: 3-Amino-4-(4-cyclohexyl-piperazin-1-yl)-benzonitrile.



[00188] The title Intermediate 7.1 (2.38 g, 8.37 mmol, 98%) was obtained as a white solid from Intermediate 7.2 (2.69 g, 8.56 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.85 min; LC-MS: m/z 285.2 $[M+H]^+$.

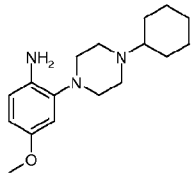
[00189] Intermediate 7.2: 4-(4-Cyclohexyl-piperazin-1-yl)-3-nitro-benzonitrile.



[00190] The title Intermediate 7.2 (2.8 g, 8.21 mmol, 95%) was obtained as an orange solid from 4-fluoro-3-nitro-benzonitrile (1.50 g, 9.03 mmol) and 1-cyclohexyl-piperazine (1.67 g,

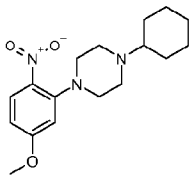
9.93 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.08 min; LC-MS: m/z 315.3 $[M+H]^+$.

[00191] Intermediate 8.1: 2-(4-Cyclohexyl-piperazin-1-yl)-4-methoxy-phenylamine.



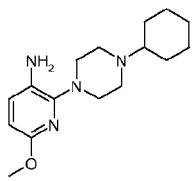
[00192] The title Intermediate 8.1 (1.72 g, 5.65 mmol, 96%) was obtained as a purple solid from Intermediate 8.2 (1.87 g, 5.56 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.04 min; LC-MS: m/z 290.4 $[M+H]^+$.

[00193] Intermediate 8.2: 1-Cyclohexyl-4-(5-methoxy-2-nitro-phenyl)-piperazine.



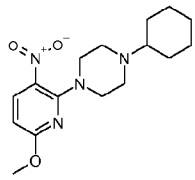
[00194] The title Intermediate 8.2 (1.87 g, 5.56 mmol, quantitative) was obtained as a yellow oil from 2-chloro-4-methoxy-nitrobenzene (1.0 g, 5.33 mmol) and 1-cyclohexyl-piperazine (0.987 g, 5.86 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.28 min; LC-MS: m/z 320.3 $[M+H]^+$.

[00195] Intermediate 9.1: 2-(4-Cyclohexyl-piperazin-1-yl)-6-methoxy-pyridin-3-ylamine.



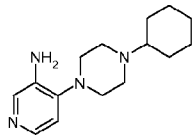
[00196] The title Intermediate 9.1 (1.34 g, 4.48 mmol, 85%) was obtained as a dark gray solid from Intermediate 9.2 (1.68 g, 5.14 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.29 min; LC-MS: m/z 291.4 $[M+H]^+$.

[00197] Intermediate 9.2: 1-Cyclohexyl-4-(6-methoxy-3-nitro-pyridin-2-yl)-piperazine.



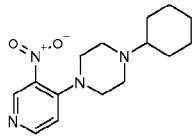
[00198] The title Intermediate 9.2 (1.68 g, 5.14 mmol, 97%) was obtained as a yellow oil from 2-chloro-6-methoxy-3-nitro-pyridine (1.0 g, 5.30 mmol) and 1-cyclohexyl-piperazine (0.982 g, 5.83 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.24 min; LC-MS: m/z 321.3 $[M+H]^+$.

[00199] Intermediate 10.1: 4-(4-Cyclohexyl-piperazin-1-yl)-pyridin-3-ylamine.



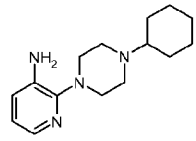
[00200] The title Intermediate 10.1 (914 mg, 3.42 mmol, quantitative) was obtained as a beige solid from Intermediate 10.2 (993 mg, 3.42 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 2.90 min; LC-MS: m/z 261.2 $[M+H]^+$.

[00201] Intermediate 10.2: 1-Cyclohexyl-4-(3-nitro-pyridin-4-yl)-piperazine.



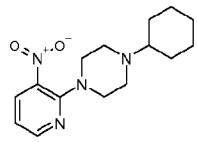
[00202] The title Intermediate 10.2 (993 mg, 3.39 mmol, 53.9%) was obtained as a yellow oil from 4-chloro-3-nitro-pyridine (996 mg, 6.28 mmol) and 1-cyclohexyl-piperazine (1.58 g, 9.42 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 3.01 min; LC-MS: m/z 291.2 $[M+H]^+$.

[00203] Intermediate 11.1: 2-(4-Cyclohexyl-piperazin-1-yl)-pyridin-3-ylamine.



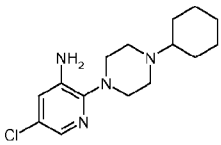
[00204] The title Intermediate 11.1 (3.03 g, 11.52 mmol, 93%) was obtained as a pink solid from Intermediate 11.2 (3.61 g, 12.43 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 2.93 min; LC-MS: m/z 261.3 $[M+H]^+$.

[00205] Intermediate 11.2: 1-Cyclohexyl-4-(3-nitro-pyridin-2-yl)-piperazine.



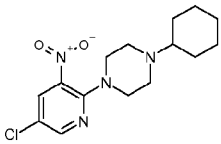
[00206] The title Intermediate 11.2 (3.61 g, 12.31 mmol, 96%) was obtained as a brown semi solid from 2-chloro-3-nitro-pyridine (2.09 g, 12.81 mmol) and 1-cyclohexyl-piperazine (3.30 g, 19.21 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 3.90 min; LC-MS: m/z 291.2 $[M+H]^+$.

[00207] Intermediate 12.1: 5-Chloro-2-(4-cyclohexyl-piperazin-1-yl)-pyridin-3-ylamine.



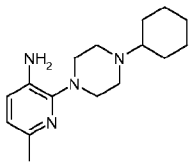
[00208] The title Intermediate 12.1 (3.03 g, 11.52 mmol, 93%) was obtained as a pink solid from Intermediate 12.2 (3.61 g, 12.43 mmol), analogously to Intermediate 6.1. HPLC: $^{A}t_{Ret}$ = 3.95 min; LC-MS: m/z 295.0 $[M+H]^+$.

[00209] Intermediate 12.2: 1-(5-Chloro-3-nitro-pyridin-2-yl)-4-cyclohexyl-piperazine.



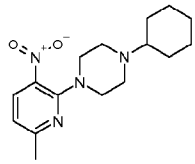
[00210] The title Intermediate 12.2 (1.54 g, 4.50 mmol, 87%) was obtained as a brown semi solid from 2,5-dichloro-3-nitro-pyridine (1.0 g, 5.18 mmol) and 1-cyclohexyl-piperazine (0.96 g, 5.70 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.28 min; LC-MS: m/z 325.3 $[M+H]^+$.

[00211] Intermediate 13.1: 2-(4-Cyclohexyl-piperazin-1-yl)-6-methyl-pyridin-3-ylamine.



[00212] The title Intermediate 13.1 (1.6 g, 5.54 mmol, 97%) was obtained as a white solid from Intermediate 13.2 (1.73 g, 5.68 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.02 min; LC-MS: m/z 275.4 $[M+H]^+$.

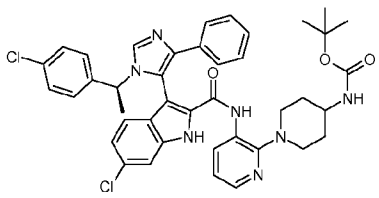
[00213] Intermediate 13.2: 1-Cyclohexyl-4-(6-methyl-3-nitro-pyridin-2-yl)-piperazine.



[00214] The title Intermediate 13.2 (1.73 g, 5.57 mmol, 96%) was obtained as a yellow oil from 2-chloro-6-methyl-3-nitro-pyridine (1.0 g, 5.79 mmol) and 1-cyclohexyl-piperazine (1.07 g, 6.37 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.19 min; LC-MS: m/z 305.3 $[M+H]^+$.

Example 1

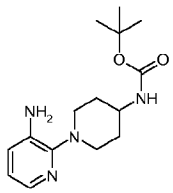
{3'-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl}-carbamic acid tert-butyl ester



[00215] To a solution of Intermediate 1.1 (808 mg, 2.76 mmol) in DCM (24 mL) was added drop wise a 1 M hexane solution of Me_2AlCl (4.61 mL, 4.61 mmol) at 0 °C. The clear dark blue solution was stirred at 0 °C for 25 min and at RT for 30 min. Intermediate 1.3 (1.2 g, 2.30 mmol) was added to the reaction mixture at RT. After 1.5 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ at 0 °C, then poured into vigourously stirring H_2O and immdediately diluted with EtOAc and THF. Large excess Rochelle's salt was added and the mixture was stirred at RT for 1 h. The organic phase was separated, the aqueous phase was extracted twice with a mixture of EtOAc and THF (70:30), washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel column chromatography (eluting with a gradient of DCM:EtOAc = 90:10 to 0:100, then MeOH:EtOAc = 0:100 to 20:80) of the residue afforded the

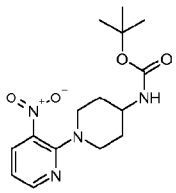
title compound 1 (1.17 g, 1.56 mmol, 67.8%) as a white solid. HPLC: $^{A}t_{Ret}$ = 4.994 min; LC-MS: m/z 750 $[M+H]^+$.

Intermediate 1.1: (3'-Amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-carbamic acid tert-butyl ester.



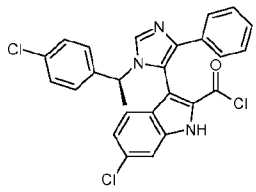
[00216] A mixture of Intermediate 1.2 (5.0 g, 15.5 mmol) and 10% Pd/C (0.9 g) in MeOH (120 mL) was shaken under H_2 gas atmosphere at RT for 2 h. The catalyst was filtered off under N_2 gas stream and washed with MeOH and THF. The filtrate was concentrated *in vacuo* and dried under high vacuum, which gave the title intermediate 1.1 (4.42 g, 15.1 mmol, 97%) as a red solid. HPLC: $^{A}t_{Ret}$ = 3.75 min; LC-MS: m/z 293.2 $[M+H]^+$.

Intermediate 1.2: (3'-Nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-carbamic acid tert-butyl ester.



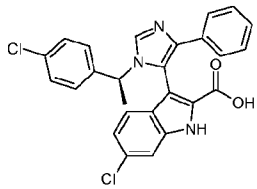
[00217] To a solution of 2-chloro-3-nitro-pyridine (5.0 g, 31.5 mmol) in acetonitrile (150 mL) was added successively K_2CO_3 (10.9 g, 79.0 mmol) and piperidin-4-yl-carbamic acid tert-butyl ester (7.24 g, 34.7 mmol) at 0 °C. The ice bath was removed and the orange suspension was stirred at RT. After 1 h, 80 mL of THF was added to the reaction mixture in order to ease the stirring. After stirring for 18 h, the inorganic salts were filtered off and washed several times with THF. The filtrate was concentrated *in vacuo* and silica gel column chromatography (eluting with a gradient of DCM:EtOAc = 100:0 to 0:100) of the residue afforded the title intermediate 1.2 (10.0 g, 31.1 mmol, 99%) as a yellow solid.

Intermediate 1.3: 6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl chloride.



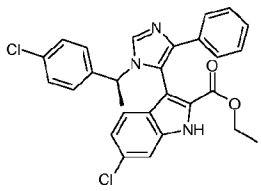
[00218] To a suspension of Intermediate 1.4 (2.03 g, 4.26 mmol) in dry DCM (30 mL) was added drop wise (COCl)2 (5.60 mL, 63.9 mmol) at RT. The reaction mixture was heated to 50 °C. After a period of 1.5 h an aliquote was quenched with MeOH and analyzed by HPLC. Only traces of starting material were detected. The mixture was allowed to cool to RT and evaporated to dryness followed by sonication in DCM (8 mL) and evaporation of solvent (2 times). The residue was dried under high vacuum at 50 °C which gave the title intermediate 1.3 (1.88 g, 3.42 mmol, 80%) as a slightly yellow solid. HPLC: $^{A}t_{Ret}$ = 5.06 min (methyl ester of 1.3); LC-MS: m/z 490.2 [methyl ester of 1.3 + H] $^{+}$.

Intermediate 1.4: 6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid.



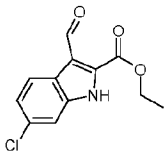
[00219] To a mixture of Intermediate 1.5 (45.0 g, 89.0 mmol) in EtOH (450 mL) was added 2 M aqueous solution of NaOH (450 mL, 900 mmol) at RT, the mixture was then heated to reflux for 1 h. The reaction mixture was cooled to RT and concentrated *in vacuo* to half of the volume. The resulting mixture was slowly acidified with conc. HCl (100 mL) at 0 °C, the aqueous phase was extracted with EtOAc (twice), the organic phases were combined and washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* which initiated crystallization. The resulting suspension was stirred at RT for 30 min, filtered and washed with EtOAc. The remaining crystally were dried at 100 °C in an oven yielding the title intermediate 1.4 (21.0 g, 44.1 mmol, 49.5%) as a white solid. HPLC: $^{B}t_{Ret}$ = 6.27 min; LC-MS: m/z 478.1 $[M+H]^{+}$.

Intermediate 1.5: 6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid ethyl ester.



[00220] A mixture of Intermediate 1.6 (25.0 g, 99.0 mmol), (S)-4-chloro-phenylethyl-amine (17.0 g, 109 mmol), Et_3N (41.5 mL, 298 mmol) and 1-(isocyano-phenyl-methanesulfonyl)-4-methyl-benzene (32.3 g, 119 mmol) in EtOH (540 mL) was heated at 65 °C. After stirring for 20 h, the reaction mixture was concentrated *in vacuo*, poured into aqueous $NaHCO_3$ and was extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel column chromatography (eluting with hexane:EtOAc = 50:50) of the crude product afforded the title intermediate 1.5 (41.0 g, 81.0 mmol, 82%) as a light yellow form. HPLC: $^{B}t_{Ret}$ = 6.69 min; LC-MS: m/z 504.0 $[M+H]^+$.

Intermediate 1.6: 6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid ethyl ester.

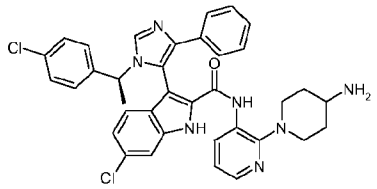


[00221] The title compound was prepared according to a published literature procedure (see J. Med. Chem. 2005, 48, 995-1018.) A solution of 6-chloro-1H-indole-2-carboxylic acid ethyl ester (60.0 g, 268 mmol) (commercially available from 3D Medical Systems Inc.) and $POCl_3$ (30.0 mL, 322 mmol) in DMF (600 mL) is heated at 50 °C. After 20 h, $POCl_3$ (15 mL) was added to the reaction mixture and heating at 50 °C was continued for 46 h. After completion, the reaction mixture was slowly poured into crashed ice and H_2O (3 L), the resulting suspension was stirred at RT for 5 h, filtered and washed several times with H_2O. The wet filter cake was transfered to a flask, acetonitrile was added and the resulting suspension was stirred for 1 h. Filtration of the suspension, washing of the residue with acetonitrile and drying at 40 °C in an

oven gave the title intermediate 1.6 (55.95 g, 222 mmol, 83%) as a white solid. HPLC: $^{B}t_{Ret}$ = 6.89 min; LC-MS: m/z 252.1 $[M+H]^+$.

Example 2

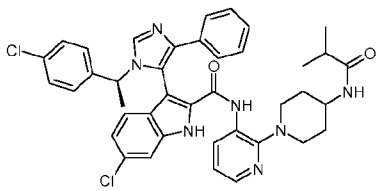
6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (4-amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl)-amide 2 HCl salt.



[00222] To a solution of Example 1 (3.48 g, 4.64 mmol) in EtOH (18 mL) was added drop wise 4 M dioxane solution of HCl (17.4 mL, 69.6 mmol) at 0 °C. The reaction mixture was stirred at RT for 1.5 h. The reaction mixture was evaporated *in vacuo*, dissolved in DCM and concentrated *in vacuo* (2 times), which gave the title compound 2 (3.77 g, 4.90 mmol, quantitative) as a white solid. HPLC: $^{A}t_{Ret}$ = 4.292 min; LC-MS: m/z 649.9 $[M+H]^+$.

Example 3

6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (4-isobutyryl-amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl)-amide.

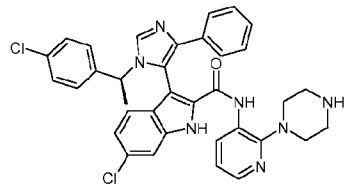


[00223] To a suspension of Example 2 (90 mg, 0.124 mmol) in DCM (2 mL) was added drop wise Et_3N (0.078 mL, 0.56 mmol) at 0 °C, then Isobutyryl chloride (0.019 mL, 0.187 mmol) was added. The reaction mixture was stirred at RT for 1 h and then diluted with DCM and H_2O.

The aqueous phase was extracted with DCM (3 times), the combined organic phases were washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel column chromatography (eluting with a gradient of DCM:MeOH = 100:0 to 80:20) of the residue afforded the title compound (62 mg, 0.086 mmol, 69.2%) as a white solid. HPLC: $^{A}t_{Ret}$ = 4.691 min; LC-MS: m/z 721.7 $[M+H]^+$.

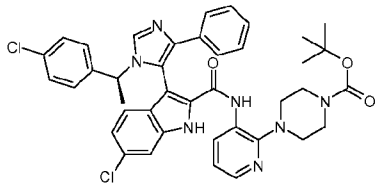
Example 14

6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (2-piperazin-1-yl-pyridin-3-yl)-amide.



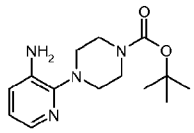
[00224] The title compound (1.77 g, 2.40 mmol, quantitative) was obtained as a yellow solid from Intermediate 14.1 (1.75 g, 2.40 mmol) analogously to Example 2. HPLC: $^{A}t_{Ret}$ = 4.44 min; LC-MS: m/z 635.9 $[M+H]^+$.

[00225] Intermediate 14.1: 4-{3-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-pyridin-2-yl}-piperazine-1-carboxylic acid tert-butyl ester.



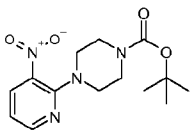
[00226] The title compound (1.75 g, 2.40 mmol, 52.7%) was obtained as a yellow foam from Intermediate 14.2 (1.38 g, 4.96 mmol) and Intermediate 1.3 (2.4 g, 4.51 mmol), analogously to Example 1. HPLC: $^{A}t_{Ret}$ = 5.14 min; LC-MS: m/z 736.2 $[M+H]^+$.

[00227] Intermediate 14.2: 4-(3-Amino-pyridin-2-yl)-piperazine-1-carboxylic acid tert-butyl ester.



[00228] The title Intermediate 14.2 (3.26 g, 11.59 mmol, 93%) was obtained as a white solid from Intermediate 14.3 (3.83 g, 12.42 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.75 min; MS: m/z 279.2 $[M+H]^+$.

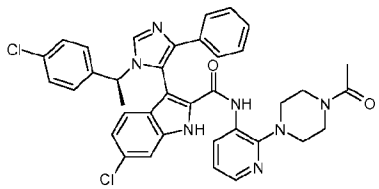
[00229] Intermediate 14.3: 4-(3-Nitro-pyridin-2-yl)-piperazine-1-carboxylic acid tert-butyl ester.



[00230] The title Intermediate 14.3 (3.83 g, 12.3 mmol, 97%) was obtained as a yellow oil from 2-chloro-3-nitro-pyridine (2.0 g, 12.61 mmol) and Piperazine-1-carboxylic acid tert-butyl ester (2.58 g, 13.88 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 5.31 min; MS: m/z 309.1 $[M+H]^+$.

Example 15

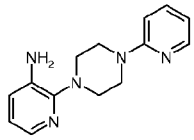
6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-acetyl-piperazin-1-yl)-pyridin-3-yl]-amide.



[00231] To a suspension of Example 2 (102 mg, 0.142 mmol) in DCM (1 mL) was added drop wise Et_3N (0.079 mL, 0.57 mmol) at 0 °C, then acetic anhydride (0.02 mL, 0.213 mmol) was added. The reaction mixture was stirred at RT for 30 min and then diluted with DCM and H_2O. The aqueous phase was extracted with DCM (multiple times), the organic phase was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel column chromatography (eluting with DCM:MeOH = 90:10) of the residue afforded the title compound

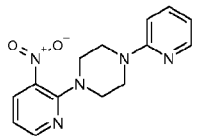
15 (90 mg, 0.133 mmol, 93%) as a white solid. HPLC: $^{A}t_{Ret}$ = 4.63 min; LC-MS: m/z 678.1 $[M+H]^+$.

[00232] Intermediate 16.1: 2-(4-Pyridin-2-yl-piperazin-1-yl)-pyridin-3-ylamine.



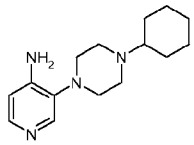
[00233] The title Intermediate 16.1 (1.25 g, 4.85 mmol, 96%) was obtained as a purple solid from Intermediate 16.2 (1.44 g, 5.05 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 2.69 min; LC-MS: m/z 256.2 $[M+H]^+$.

[00234] Intermediate 16.2: 1-(3-Nitro-pyridin-2-yl)-4-pyridin-2-yl-piperazine.



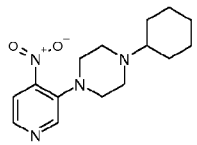
[00235] The title Intermediate 16.2 (1.44 g, 5.0 mmol, 78%) was obtained as an orange oil from 2-chloro-3-nitro-pyridine (1.01 g, 6.41 mmol) and 1-pyridin-2-yl-piperazine (1.57 g, 9.61 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 3.68 min; LC-MS: m/z 286.1 $[M+H]^+$.

[00236] Intermediate 17.1: 3-(4-Cyclohexyl-piperazin-1-yl)-pyridin-4-ylamine.



[00237] The title Intermediate 17.1 (176 mg, 0.676 mmol, 99%) was obtained as a white solid from Intermediate 17.2 (208 mg, 0.681 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 2.95 min; LC-MS: m/z 261.2 $[M+H]^+$.

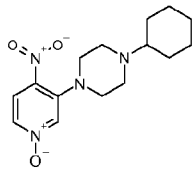
[00238] Intermediate 17.2: 1-Cyclohexyl-4-(4-nitro-pyridin-3-yl)-piperazine.



[00239] To a solution of Intermediate 17.3 (500 mg, 1.61 mmol) and triphenylphosphine (509 mg, 1.94 mmol) in DCM (20 mL) was added trichlorooxobis(triphenyl-

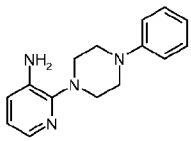
phosphine)rhenium(V) (81 mg, 0.097 mmol) and the mixture was heated to 45 °C. After 4 h, the reaction mixture was cooled down to RT and concentrated *in vacuo*. Silica gel column chromatography (eluting with a gradient of DCM:MeOH = 100:0 to 80:20) of the residue afforded the title Intermediate 17.2 (212 mg, 0.694 mmol, 42.9%) as a red oil. HPLC: $^{A}t_{Ret}$ = 3.72 min; LC-MS: m/z 291.2 $[M+H]^+$.

[00240] Intermediate 17.3: 1-Cyclohexyl-4-(4-nitro-1-oxy-pyridin-3-yl)-piperazine.



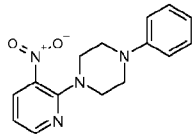
[00241] To a solution of 3-bromo-4-nitro-pyridine-1-oxide (2.0 g, 9.13 mmol) in dry THF (120 mL) was added successively Et_3N (8.86 mL, 63.9 mmol) and 1-cyclohexyl-piperazine (1.61 g, 9.59 mmol) at 0 °C. After 30 min, the reaction mixture was heated to 70 °C. After 15 h, the reaction mixture was cooled down to RT and diluted with DCM (200 mL). The organic phase was washed with H_2O and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Silica gel column chromatography (eluting with EtOAc) of the residue afforded the title Intermediate 17.3 (2.67 g, 8.63 mmol, 94%) as a red solid. HPLC: $^{A}t_{Ret}$ = 3.38 min; LC-MS: m/z 307.2 $[M+H]^+$.

[00242] Intermediate 18.1: 2-(4-Phenyl-piperazin-1-yl)-pyridin-3-ylamine.



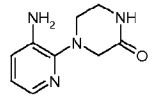
[00243] The title Intermediate 18.1 (441 mg, 1.71 mmol, 27.4%) was obtained as a beige solid from Intermediate 18.2 (1.78 g, 6.26 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.45 min; LC-MS: m/z 255.2 $[M+H]^+$.

[00244] Intermediate 18.2: 1-(3-Nitro-pyridin-2-yl)-4-phenyl-piperazine.



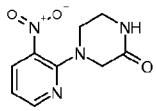
[00245] The title Intermediate 18.2 (1.79 g, 6.23 mmol, 93%) was obtained as a orange oil from 2-chloro-3-nitro-pyridine (1.09 g, 6.69 mmol) and 1-phenyl-piperazine (1.63 g, 10.0 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.65 min; LC-MS: m/z 285.1 $[M+H]^+$.

[00246] Intermediate 19.1: 4-(3-Amino-pyridin-2-yl)-piperazin-2-one.



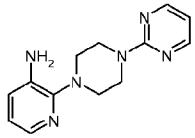
[00247] The title Intermediate 19.1 (880 mg, 4.49 mmol, quantitative) was obtained as a white solid from Intermediate 19.2 (1.0 g, 4.5 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 2.15 min; MS: m/z 193.1 $[M+H]^+$.

[00248] Intermediate 19.2: 4-(3-Nitro-pyridin-2-yl)-piperazin-2-one.



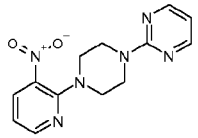
[00249] The title Intermediate 19.2 (2.29 g, 10.2 mmol, 81%) was obtained as a yellow solid from 2-chloro-3-nitro-pyridine (2.0 g, 12.61 mmol) and piperazin-2-one (1.39 g, 13.88 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 3.55 min; MS: m/z 223.1 $[M+H]^+$.

[00250] Intermediate 20.1: 2-(4-Pyrimidin-2-yl-piperazin-1-yl)-pyridin-3-ylamine



[00251] The title Intermediate 20.1 (790 mg, 3.02 mmol, 97%) was obtained as a white solid from Intermediate 20.2 (900 mg, 3.11 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.07 min.

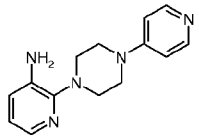
[00252] Intermediate 20.2: 2-[4-(3-Nitro-pyridin-2-yl)-piperazin-1-yl]-pyrimidine.



[00253] The title Intermediate 20.2 (900 mg, 3.11 mmol, 99%) was obtained as a yellow solid from 2-chloro-3-nitro-pyridine (500 mg, 3.15 mmol) and 2-piperazin-1-yl-pyrimidine

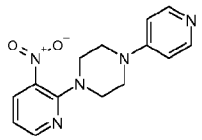
(570 mg, 3.47 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.27 min; MS: m/z 287.1 $[M+H]^+$.

[00254] Intermediate 21.1: 2-(4-Pyridin-4-yl-piperazin-1-yl)-pyridin-3-ylamine.



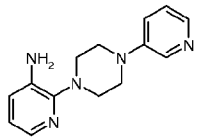
[00255] The title Intermediate 21.1 (998 mg, 3.87 mmol, 85%) was obtained as a gray solid from Intermediate 21.2 (1.3 g, 4.56 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 2.68 min; LC-MS: m/z 256.1 $[M+H]^+$.

[00256] Intermediate 21.2: 1-(3-Nitro-pyridin-2-yl)-4-pyridin-4-yl-piperazine.



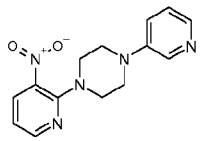
[00257] The title Intermediate 21.2 (1.3 g, 4.51 mmol, 72.4%) was obtained as an orange oil from 2-chloro-3-nitro-pyridine (1.02 g, 6.23 mmol) and 1-pyridin-4-yl-piperazine (1.57 g, 9.34 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 3.75 min; LC-MS: m/z 286.1 $[M+H]^+$.

[00258] Intermediate 22.1: 2-(4-Pyridin-3-yl-piperazin-1-yl)-pyridin-3-ylamine.



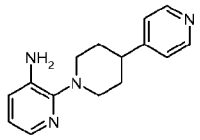
[00259] The title Intermediate 22.1 (1.24 g, 4.57 mmol, 94%) was obtained as a brown solid from Intermediate 22.2 (1.38 g, 4.84 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 2.70 min; LC-MS: m/z 256.2 $[M+H]^+$.

[00260] Intermediate 22.2: 1-(3-Nitro-pyridin-2-yl)-4-pyridin-3-yl-piperazine.



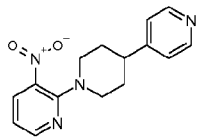
[00261] The title Intermediate 22.2 (1.38 g, 4.79 mmol, 75%) was obtained as a orange oil from 2-chloro-3-nitro-pyridine (1.01 g, 6.35 mmol) and 1-pyridin-3-yl-piperazine (1.55 g, 9.53 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 3.76 min; LC-MS: m/z 286.1 $[M+H]^+$.

[00262] Intermediate 23.1: 2 3',4',5',6'-Tetrahydro-2'H-[2,1';4',4"]terpyridin-3-ylamine.



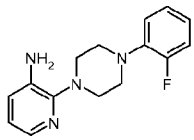
[00263] The title Intermediate 23.1 (740 mg, 2.76 mmol, 91%) was obtained as a white solid from Intermediate 23.2 (860 mg, 2.96 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 2.74 min; MS: m/z 255.2 $[M+H]^+$.

[00264] Intermediate 23.2: 3-Nitro-3',4',5',6'-tetrahydro-2'H-[2,1';4',4"]terpyridine.



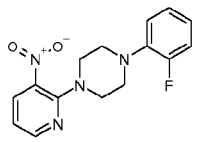
[00265] The title Intermediate 23.2 (860 mg, 2.96 mmol, 94%) was obtained as a yellow foam from 2-chloro-3-nitro-pyridine (500 mg, 3.15 mmol) and 1,2,3,4,5,6-Hexahydro-[4,4']bipyridinyl (563 mg, 3.47 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 3.79 min; MS: m/z 285.1 $[M+H]^+$.

[00266] Intermediate 24.1: 2-[4-(2-Fluoro-phenyl)-piperazin-1-yl]-pyridin-3-ylamine.



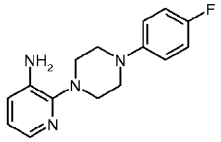
[00267] The title Intermediate 24.1 (810 mg, 2.94 mmol, 97%) was obtained as a yellow solid from Intermediate 24.2 (920 mg, 3.04 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.94 min; MS: m/z 273.1 $[M+H]^+$.

[00268] Intermediate 24.2: 1-(2-Fluoro-phenyl)-4-(3-nitro-pyridin-2-yl)-piperazine.



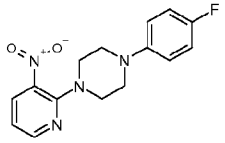
[00269] The title Intermediate 24.2 (920 mg, 3.0 mmol, 96%) was obtained as a orange oil from 2-chloro-3-nitro-pyridine (500 mg, 3.15 mmol) and 1-(2-fluorophenyl)piperazine (752 mg, 3.47 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 5.53 min; MS: m/z 303.1 $[M+H]^+$.

[00270] Intermediate 25.1: 2-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-pyridin-3-ylamine.



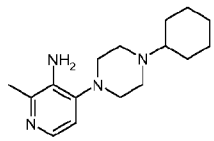
[00271] The title Intermediate 25.1 (774 mg, 2.81 mmol, 95%) was obtained as a white solid from Intermediate 25.2 (900 mg, 2.95 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.68 min; MS: m/z 273.2 $[M+H]^+$.

[00272] Intermediate 25.2: 1-(4-Fluoro-phenyl)-4-(3-nitro-pyridin-2-yl)-piperazine.



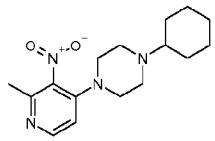
[00273] The title Intermediate 25.2 (900 mg, 2.95 mmol, 93%) was obtained as a orange oil from 2-chloro-3-nitro-pyridine (500 mg, 3.15 mmol) and 1-(4-fluorophenyl)piperazine (625 mg, 3.47 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.92 min; LC-MS: m/z 303.1 $[M+H]^+$.

[00274] Intermediate 26.1: 4-(4-Cyclohexyl-piperazin-1-yl)-2-methyl-pyridin-3-ylamine.



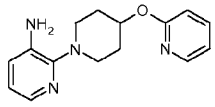
[00275] The title Intermediate 26.1 (172 mg, 0.58 mmol, 80%) was obtained as a brown solid from Intermediate 26.2 (222 mg, 0.722 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 2.96 min; LC-MS: m/z 275.3 $[M+H]^+$.

[00276] Intermediate 26.2: 1-Cyclohexyl-4-(2-methyl-3-nitro-pyridin-4-yl)-piperazine.



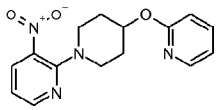
[00277] The title Intermediate 26.2 (227 mg, 0.738 mmol, 86%) was obtained as a white solid from 4-chloro-2-methyl-3-nitro-pyridine (186 mg, 0.862 mmol) and 1-cyclohexyl-piperazine (218 mg, 1.29 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 3.10 min; LC-MS: m/z 305.2 $[M+H]^+$.

[00278] Intermediate 27.1: 4-(Pyridin-2-yloxy)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-ylamine.



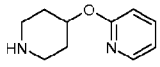
[00279] The title Intermediate 27.1 (286 mg, 1.06 mmol, 62.5%) was obtained as a white solid from Intermediate 27.2 (508 mg, 1.69 mmol), analogously to Intermediate 1.1. HPLC: $^{B}t_{Ret}$ = 3.90 min; LC-MS: m/z 271.0 $[M+H]^+$.

[00280] Intermediate 27.2: 3'-Nitro-4-(pyridin-2-yloxy)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl.



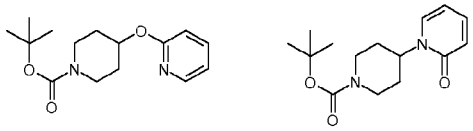
[00281] The title Intermediate 27.2 (508 mg, 1.69 mmol, 93%) was obtained as a solid from 2-chloro-3-nitro-pyridine (290 mg, 1.81 mmol) and Intermediate 27.3 (500 mg, 1.99 mmol), analogously to Intermediate 1.2. HPLC: $^{B}t_{Ret}$ = 6.08 min; LC-MS: m/z 301.1 $[M+H]^+$.

[00282] Intermediate 27.3: 2-(Piperidin-4-yloxy)-pyridine 2HCl salt.



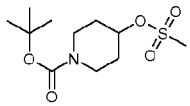
[00283] The title Intermediate 27.3 (1.45 g, 5.77 mmol, 96%) was obtained as a white solid from Intermediate 27.4 (1.68 g, 6.04 mmol), analogously to Example 2. HPLC: $^{A}t_{Ret}$ = 0.97 min; LC-MS: m/z 179.1 $[M+H]^+$.

[00284] Intermediate 27.4 and 27.5: 4-(Pyridin-2-yloxy)-piperidine-1-carboxylic acid tert-butyl ester and 2-Oxo-3',4',5',6'-tetrahydro-2H,2'H-[1,4']bipyridinyl-1'-carboxylic acid tert-butyl ester.



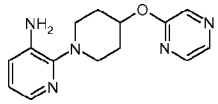
[00285] A mixture of Intermediate 27.6 (3.5 g, 12.53 mmol), 2-hydroxypyridine (1.31 g, 13.78 mmol) and $CsCO_3$ (9.57 g, 26.3 mmol) in DMF (70 mL) was heated to 100 °C for 2 h. After cooling down, the inorganic salt was filtered off and the filtrate was concentrated *in vacuo*. Silica gel column chromatography (eluting with a gradient of DCM:MeOH:NH3 = 95:5:0.5 to 90:10:0.1) of the residue afforded Intermediate 27.4 (1.68 g, 6.04 mmol, 48.2%) as a white solid and Intermediate 27.5 (361 mg, 1.29 mmol, 10.3%) as a white solid. Intermediate 27.4: HPLC: $^{B}t_{Ret}$ = 6.186 min; LC-MS: m/z 279.2 $[M+H]^+$. Intermediate 27.5: HPLC: $^{B}t_{Ret}$ = 5.66 min; LC-MS: m/z 279.2 $[M+H]^+$.

[00286] Intermediate 27.6: 4-Methanesulfonyloxy-piperidine-1-carboxylic acid tert-butyl ester.



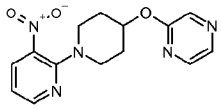
[00287] To a mixture of tert-butyl-4-hydroxy-1-piperidinecarboxylate (5.0 g, 24.1 mmol) and Et_3N (3.69 mL, 26.5 mmol) in DCM (40 mL) was added methanesulfonyl chloride (2.1 ml, 26.5 mmol) at 0 °C. After stirring for 1.5 h at RT, the reaction mixture was diluted with DCM, washed with H_2O, dried over Na_2SO_4 and concentrated *in vacuo*, which gave the title Intermediate 27.6 (7.08 g, 24.0 mmol, quantitative) as a beige crude solid. LC-MS: m/z 280.0 $[M+H]^+$. ^1H NMR (600 MHz, DMSO-d_6) δ ppm 1.40 (s, 9 H) 1.55 - 1.65 (m, *J*=12.94, 8.72, 8.72, 3.94 Hz, 2 H) 1.86 - 1.94 (m, 2 H) 3.17 (br. s., 2 H) 3.20 (s, 3 H) 3.55 - 3.65 (m, 2 H) 4.78 - 4.86 (m, 1 H).

[00288] Intermediate 28.1: 4-(Pyrazin-2-yloxy)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-ylamine.



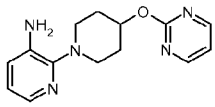
[00289] The title Intermediate 28.1 (600 mg, 2.19 mmol, 85%) was obtained as a white solid from Intermediate 28.2 (780 mg, 2.59 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.10 min; LC-MS: m/z 305.2 $[M+H]^+$.

[00290] Intermediate 28.2: 3'-Nitro-4-(pyrazin-2-yloxy)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl.



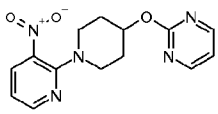
[00291] The title Intermediate 28.2 (780 mg, 2.56 mmol, 81%) was obtained as a solid from 2-chloro-3-nitro-pyridine (290 mg, 1.81 mmol) and 2-(piperidin-4-yloxy)pyrazine HCl salt (748 mg, 3.47 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 5.17 min; MS: m/z 302.1 $[M+H]^+$.

[00292] Intermediate 29.1: 4-(Pyrimidin-2-yloxy)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-ylamine.



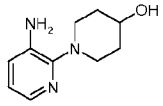
[00293] The title Intermediate 29.1 (500 mg, 1.82 mmol, 69.6%) was obtained as a white solid from Intermediate 29.2 (790 mg, 2.62 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.31 min; MS: m/z 272.2 $[M+H]^+$.

[00294] Intermediate 29.2: 3'-Nitro-4-(pyridin-2-yloxy)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl.



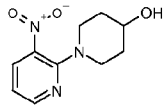
[00295] The title Intermediate 29.2 (790 mg, 2.60 mmol, 82%) was obtained as a solid from 2-chloro-3-nitro-pyridine (500 mg, 3.15 mmol) and 2-(piperidin-4-yloxy)pyrimidine (622 mg, 3.47 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.79 min; MS: m/z 302.1 $[M+H]^+$.

[00296] Intermediate 30.1: 3'-Amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-ol.



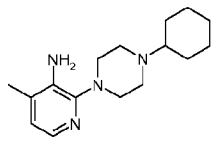
[00297] The title Intermediate 30.1 (2.92 g, 14.3 mmol, 93%) was obtained as a purple solid from Intermediate 30.2 (3.49 g, 15.48 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 2.63 min; LC-MS: m/z 194.1 $[M+H]^+$.

[00298] Intermediate 30.2: 3'-Nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-ol.



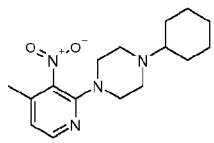
[00299] The title Intermediate 30.2 (3.49 g, 15.63 mmol, 99%) was obtained as an orange oil from 2-chloro-3-nitro-pyridine (2.5 g, 15.77 mmol) and 4-hydroxy-piperidine (1.75 g, 17.35 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 3.88 min; LC-MS: m/z 224.1 $[M+H]^+$.

[00300] Intermediate 31.1: 2-(4-Cyclohexyl-piperazin-1-yl)-4-methyl-pyridin-3-ylamine.



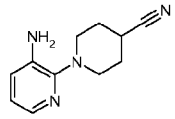
[00301] The title Intermediate 31.1 (1.81 g, 6.60 mmol, 56.6%) was obtained as a beige solid from Intermediate 31.2 (3.55 g, 11.08 mmol), analogously to Intermediate 1.1. HPLC: $^{B}t_{Ret}$ = 3.71 min; LC-MS: m/z 275.3 $[M+H]^+$.

[00302] Intermediate 31.2: 1-Cyclohexyl-4-(4-methyl-3-nitro-pyridin-2-yl)-piperazine.



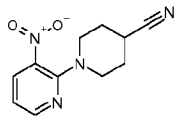
[00303] The title Intermediate 31.2 (3.55 g, 11.08 mmol, 99%) was obtained as a gray solid from 2-chloro-4-methyl-3-nitro-pyridine (2.0 g, 11.24 mmol) and 1-cyclohexyl-piperazine (2.90 g, 16.86 mmol), analogously to Intermediate 1.2. HPLC: $^{B}t_{Ret}$ = 5.17 min; LC-MS: m/z 305.3 $[M+H]^+$.

[00304] Intermediate 32.1: 3'-Amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carbonitrile.



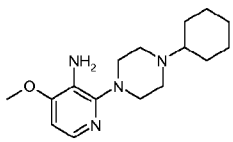
[00305] The title Intermediate 32.1 (3.64 g, 17.83 mmol, quantitative) was obtained as a yellow solid from Intermediate 32.2 (4.14 g, 17.83 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 2.92 min; LC-MS: m/z 203.2 $[M+H]^+$.

[00306] Intermediate 32.2: 3'-Nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carbonitrile.



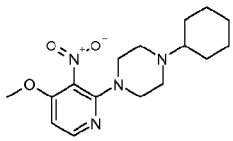
[00307] The title Intermediate 32.2 (4.15 g, 17.87 mmol, 94%) was obtained as a yellow solid from 2-chloro-3-nitro-pyridine (3.0 g, 18.92 mmol) and piperidine-4-carbonitrile (2.29 g, 20.81 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.55 min; LC-MS: m/z 233.1 $[M+H]^+$.

[00308] Intermediate 33.1: 2-(4-Cyclohexyl-piperazin-1-yl)-4-methoxy-pyridin-3-ylamine.



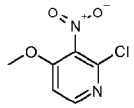
[00309] The title Intermediate 33.1 (897 mg, 2.93 mmol, 91%) was obtained as a purple solid from Intermediate 33.2 (1.03 g, 3.21 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.05 min; LC-MS: m/z 291.2 $[M+H]^+$.

[00310] Intermediate 33.2: 1-Cyclohexyl-4-(4-methoxy-3-nitro-pyridin-2-yl)-piperazine.



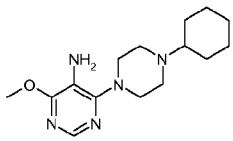
[00311] The title Intermediate 33.2 (1.04 g, 3.21 mmol, 59.6%) was obtained as a yellow solid from Intermediate 33.3 (1.08 g, 5.39 mmol) and 1-cyclohexyl-piperazine (1.39 g, 8.08 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.02 min; LC-MS: m/z 321.2 $[M+H]^+$.

[00312] Intermediate 33.3: 2-Chloro-4-methoxy-3-nitro-pyridine.



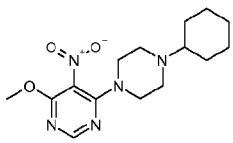
[00313] To a solution of 2,4-dichloro-3-nitro-pyridine which was prepared according to a published literature procedure (*J.Med.Chem*, 2000, 43(22), 4308.) (2.23 g, 11.21 mmol) in MeOH (58 mL) was added NaOMe (0.91 g, 16.81 mmol) portion wise at 0 °C. After stirring for 2 h at RT, further NaOMe (182 mg, 3.36 mmol) was added and the reaction mixture was stirred for 4 h. The mixture was concentrated *in vacuo*, diluted with DCM, washed with saturated aqueous NH_4Cl, then with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*, which gave the crude title Intermediate 33.3 (2.12 g, 10.51 mmol, 93%) as a beige solid. HPLC: $^{A}t_{Ret}$ = 4.53 min; LC-MS: m/z 187.0 $[M-H]^+$.

[00314] Intermediate 34.1: 4-(4-Cyclohexyl-piperazin-1-yl)-6-methoxy-pyrimidin-5-ylamine.



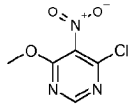
[00315] The title Intermediate 34.1 (739 mg, 2.54 mmol, 94%) was obtained as a beige solid from Intermediate 34.2 (871 mg, 2.71 mmol), analogously to Intermediate 1.1. HPLC: $^{B}t_{Ret}$ = 4.23 min; LC-MS: m/z 292.0 $[M+H]^+$.

[00316] Intermediate 34.2: 4-(4-Cyclohexyl-piperazin-1-yl)-6-methoxy-5-nitro-pyrimidine.



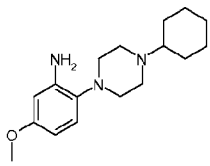
[00317] The title Intermediate 34.2 (875 mg, 2.72 mmol, 88%) was obtained as a yellow oil from Intermediate 34.3 (665 mg, 3.09 mmol) and 1-cyclohexyl-piperazine (795 mg, 4.62 mmol), analogously to Intermediate 1.2. HPLC: $^{B}t_{Ret}$ = 4.97 min; LC-MS: m/z 322.0 $[M+H]^+$.

[00318] Intermediate 34.3: 4-Chloro-6-methoxy-5-nitro-pyrimidine.



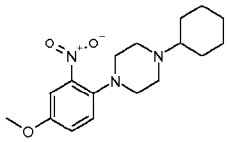
[00319] To a solution of 4,6-dichloro-5-nitro-pyridine (2.0 g, 10.0 mmol) in MeOH (36 mL) was added NaOMe freshly prepared with Na (230 mg, 10.0 mmol) in MeOH (16 ml) at 0 °C. After stirring for 80 min, the mixture was concentrated *in vacuo*, then recrystallization in ether gave the title Intermediate 34.3 (2.01 g, 10.0 mmol, quantitative) as a yellow solid. HPLC: $^{B}t_{Ret}$ = 6.20 min; GC-MS: m/z 189.0 $[M+H]^+$.

[00320] Intermediate 35.1: 2-(4-Cyclohexyl-piperazin-1-yl)-5-methoxy-phenylamine.



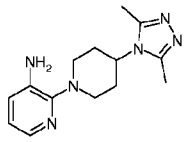
[00321] The title Intermediate 35.1 (131 mg, 1.03 mmol, 36%) was obtained as a beige solid from Intermediate 35.2 (914 mg, 2.86 mmol), analogously to Intermediate 1.1. HPLC: $^{B}t_{Ret}$ = 3.27 min; LC-MS: m/z 290.4 $[M+H]^+$.

[00322] Intermediate 35.2: 4-(4-Cyclohexyl-piperazin-1-yl)-6-methoxy-5-nitro-pyrimidine.



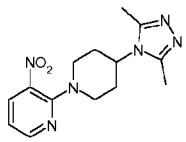
[00323] The title Intermediate 35.2 (914 mg, 2.58 mmol, 32%, 90% purity) was obtained as a brown solid from 1-chloro-4-methoxy-2-nitrobenzene (1.50 g, 8.00 mmol) and 1-cyclohexyl-piperazine (2.02 g, 11.99 mmol), analogously to Intermediate 1.2. HPLC: $^{B}t_{Ret}$ = 4.32 min; LC-MS: m/z 320.3 $[M+H]^+$.

[00324] Intermediate 36.1: 4-(3,5-Dimethyl-[1,2,4]triazol-4-yl)-3,4,5,6-tetrahydro-2H-[1,2'] bipyridinyl-3'-ylamine.



[00325] The title Intermediate 36.1 (640 mg, 2.326 mmol, 79%) was obtained as a beige solid from Intermediate 36.2 (885 mg, 2.93 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 2.64 min; LC-MS: m/z 273.2 $[M+H]^+$.

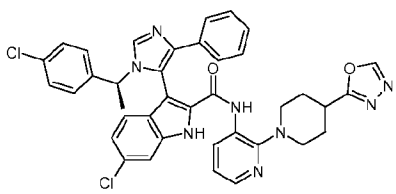
[00326] Intermediate 36.2: 4-(3,5-Dimethyl-[1,2,4]triazol-4-yl)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl.



[00327] The title Intermediate 36.2 (885 mg, 2.90 mmol, 92%) was obtained as a yellow solid from 2-chloro-3-nitropyridine (500 mg, 3.15 mmol) and 4-(3,5-Dimethyl-[1,2,4]triazol-4-yl)-piperidine (853 mg, 4.73 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 3.67 min; LC-MS: m/z 303.2 $[M+H]^+$.

Example 37

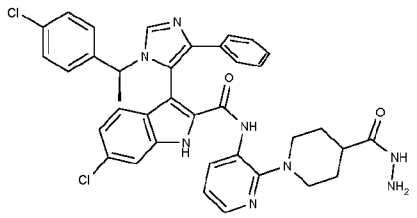
6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (4-[1,3,4]oxadiazol-2-yl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl)-amide.



[00328] A solution of Intermediate 37.1 (140 mg, 0.202 mmol) in triethoxymethane (598 mg, 4.04 mmol) was refluxed for 2 h. The reaction mixture was cooled, diluted with water and a saturated solution of sodium bicarbonate, followed by multiple extractions with ethyl acetate. The organic layers were combined, dried using $MgSO_4$, filtered and concentrated in

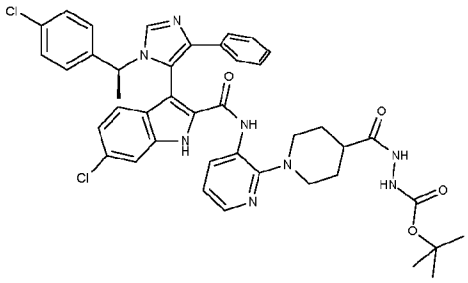
vacuo: The crude product was purified by reversed phase prep-HPLC (gradient elution, MeCN/water + 0.1% TFA). Fractions containing pure material were combined, concentrated and the resulting aqueous mixture was neutralized with a saturated solution of $NaHCO_3$ followed by extraction with DCM. The organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness to yield the title Intermediate 37.1 (50 mg, 0.07 mmol, 34%) as a colourless solid. HPLC: $^{C}t_{Ret}$ = 4.07 min; LC-MS: m/z 703.2

[00329] Intermediate 37.1: 6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (4-hydrazinocarbonyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl)-amide.



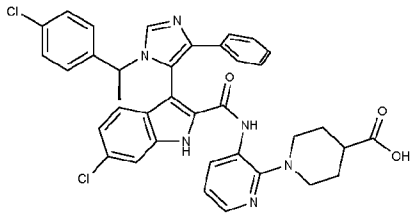
[00330] To a solution of Intermediate 37.2 (702 mg, 0.88 mmol) in EtOH (5 mL) was added drop wise 4 M dioxane solution of HCl (3.32 mL, 13.27 mmol) at RT. The reaction mixture was stirred at RT for 2 h and evaporated to dryness. The residue was suspended in DCM and evaporated several times. The resulting crude product was purified by silica gel column chromatography (eluting with a gradient of DCM + 0.5%NH3:MeOH = 100:0 to 80:20) yielding Intermediate 37.1 (440 mg, 0.63 mmol, 71%) as a colourless solid. HPLC: $^{A}t_{Ret}$ = 4.23 min; LC-MS: m/z 694.4 $[M+H]^+$.

[00331] Intermediate 37.2: N'-{3'-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carbonyl}-hydrazinecarboxylic acid tert-butyl ester.



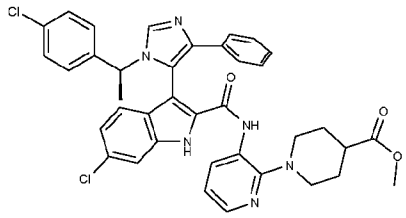
[00332] To a solution of Intermediate 37.3 (605 mg, 0.89 mmol) in DMF (7 mL) was added tert-butyl hydrazinecarboxylate (141 mg, 1.07 mmol), HATU (508 mg, 1.34 mmol) and 4-methylmorpholine (450 mg, 0.49 mL, 4.45 mmol) and the solution was stirred at RT for 1 h. The reaction mixture was diluted with EtOAc, washed with a saturated solution of $NaHCO_3$ and brine, dried using $MgSO_4$, filtered and concentrated. The resulting crude product was purified by silica gel column chromatography (eluting with a gradient of DCM:MeOH = 100:0 to 80:20) yielding Intermediate 37.2 (702 mg, 0.80 mmol, 89%) as a yellowish solid. HPLC: $^{A}t_{Ret}$ = 4.74 min; LC-MS: m/z 794.8 $[M+H]^+$.

[00333] Intermediate 37.3: 3'-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid



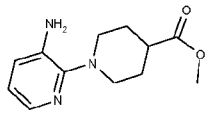
[00334] To a solution of Intermediate 37.4 (917 mg, 1.32 mmol) in THF (8 mL) was added a solution of aqueous NaOH 4M (0.66 mL, 2.64 mmol) and the reaction mixture was stirred for 1 h. Additional NaOH 4M (2.64 mL, 10.56 mmol) was added and stirring was continued for 1 h. EtOH (8 mL) and additional NaOH 4M (3.3 mL) were added and stirring was continued for 2 h. Solvents were concentrated, water was added to the mixture and the pH was adjusted to pH 5 using 2N HCl. The resulting suspension was filtered, washed with water and dried to yield Intermediate 37.3 (898 mg, 1.32 mmol, 100%) as a colourless solid. HPLC: $^{A}t_{Ret}$ = 4.49 min; LC-MS: m/z 678.9 $[M+H]^+$.

[00335] Intermediate 37.4: 3'-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid methyl ester.



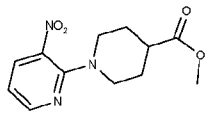
[00336] The title Intermediate 37.4 (917 mg, 1.32 mmol, 47%) was obtained as a yellowish solid from Intermediate 1.3 (1.40 g, 2.83 mmol) and Intermediate 37.5 (0.70 g, 2.97 mmol) analogously to Example 1. HPLC: $^{A}t_{Ret}$ = 4.77 min; LC-MS: m/z 292.9 $[M+H]^+$.

[00337] Intermediate 37.5: 3'-Amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid methyl ester.



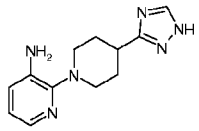
[00338] The title Intermediate 37.5 (2.34 g, 9.85 mmol, 96%) was obtained as a colourless solid from Intermediate 37.6 (2.73 g, 10.29 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.14 min; MS: m/z 236.2 $[M+H]^+$.

[00339] Intermediate 37.6: 3'-Nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid methyl ester.



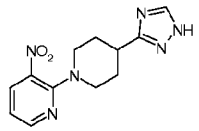
[00340] The title Intermediate 37.6 (2.73 g, 10.19 mmol, 81%) was obtained from 2-chloro-3-nitropyridine (2.00 g, 12.61 mmol) and methyl piperidine-4-carboxylate (1.99 g, 13.88 mmol) analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.85 min; MS: m/z 266.1 $[M+H]^+$.

[00341] Intermediate 38.1: 4-(1H-[1,2,4]Triazol-3-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-ylamine.



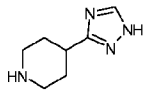
[00342] The title Intermediate 38.1 (464 mg, 1.90 mmol, 89%) was obtained as a brownish solid from Intermediate 38.2 (586 mg, 2.14 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 2.72 min + tautomer; LC-MS: m/z 245.2 $[M+H]^+$.

[00343] Intermediate 38.2: 3'-Nitro-4-(1H-[1,2,4]triazol-3-yl)-3,4,5,6-tetrahydro-2H-[1,2'] bipyridinyl.



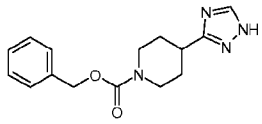
[00344] The title Intermediate 38.2 (589 mg, 2.15 mmol, 83%) was obtained from 2-chloro-3-nitropyridine (409 mg, 2.58 mmol) and Intermediate 38.3 (412 mg, 2.71 mmol) analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 3.63 min; LC-MS: m/z 275.1 $[M+H]^+$.

[00345] Intermediate 38.3: 4-(1H-[1,2,4]Triazol-3-yl)-piperidine.



[00346] A suspension of Intermediate 38.4 (1.57 g, 5.48 mmol) and Pd/C 10% (0.25 g. 0.24 mmol) in EtOH (20 mL) was shaken for 3 h at RT under an atmosphere of hydrogen. The suspension was filtered and the solid was washed with EtOH. The filtrate was concentrated and the remaining solid was dried in vacuo to yield the title Intermediate 38.3 (830 mg, 5.18 mmol, 94%) as a solid residue. LC-MS: m/z 153.1 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) ppm 1.52 (qd, *J*=12.08, 3.53 Hz, 2 H), 1.78 (d, *J*=12.31 Hz, 2 H), 2.51 (t, *J*=11.91 Hz, 2 H), 2.75 (ddt, *J*=11.55, 7.82, 3.83, 3.83 Hz, 1 H), 2.93 (d, *J*=12.11 Hz, 2 H), 7.97 (s, 1 H).

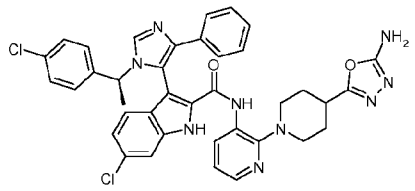
[00347] Intermediate 38.4: 4-(1H-[1,2,4]Triazol-3-yl)-piperidine-1-carboxylic acid benzyl ester.



[00348] The title Intermediate 38.4 (1.57 g, 5.48 mmol) was synthesized from 4-cyano-piperidine-1-carboxylic acid benzyl ester (5.00 g, 20.47 mmol) and formic acid hydrazide (1.23 g, 20.47 mmol) according to literature procedure (US2005/044294). HPLC: $^{C}t_{Ret}$ = 4.93 min; LC-MS: m/z 287.3 $[M+H]^+$.

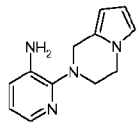
Example 39

6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(5-amino-[1,3,4]oxadiazol-2-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide.



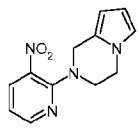
[00349] To a solution of Intermediate 37.1 (140 mg, 0.202 mmol) in MeOH (2 mL) was added cyanogen bromide (32 mg, 0.30 mmol) and the reaction mixture was stirred at RT for 2 h. A saturated solution of NaHCO3 was added upon which precipitation of a solid occured. The precipitate was filtered and washed with water and dried to yield the title Example 39 (140 mg, 0.19 mmol, 96%) as a colourless solid. HPLC: $^{A}t_{Ret}$ = 4.40 min; LC-MS: m/z 718.3

[00350] Intermediate 40.1: 2-(3,4-Dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-pyridin-3-ylamine.



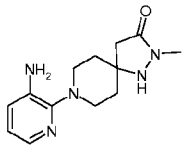
[00351] The title Intermediate 40.1 (679 mg, 2.95 mmol, 93%) was obtained as a colourless solid from Intermediate 40.2 (778 mg, 3.19 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.35 min; LC-MS: m/z 216.1 $[M+H]^+$.

[00352] Intermediate 40.2: 2-(3-Nitro-pyridin-2-yl)-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine.



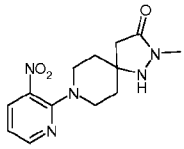
[00353] The title Intermediate 40.2 (778 mg, 3.19 mmol, 84%) was obtained from 2-chloro-3-nitropyridine (600 mg, 3.78 mmol) and 1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine (485 mg, 3.97 mmol) analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 5.06 min; LC-MS: m/z 245.2 $[M+H]^+$.

[00354] Intermediate 41.1: 8-(3-Amino-pyridin-2-yl)-2-methyl-1,2,8-triaza-spiro[4.5]decan-3-one.



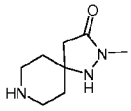
[00355] The title Intermediate 41.1 (837 mg, 3.04 mmol, 99%) was obtained as a pinkish solid from Intermediate 41.2 (896 mg, 3.08 mmol), analogously to Intermediate 1.1. HPLC: $^{B}t_{Ret}$ = 3.30 min; LC-MS: m/z 262.3 $[M+H]^+$.

[00356] Intermediate 41.2: 2-Methyl-8-(3-nitro-pyridin-2-yl)-1,2,8-triaza-spiro[4.5]decan-3-one.



[00357] The title Intermediate 41.2 (896 mg, 3.08 mmol, 100%) was obtained from 2-chloro-3-nitropyridine (490 mg, 3.09 mmol) and Intermediate 41.3 (823 mg, 3.40 mmol) analogously to Intermediate 1.2. HPLC: $^{B}t_{Ret}$ = 4.85 min; LC-MS: m/z 292.2 $[M+H]^+$.

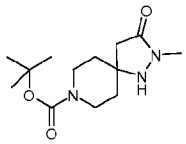
[00358] Intermediate 41.3: 2-Methyl-1,2,8-triaza-spiro[4.5]decan-3-one.



[00359] To a solution of Intermediate 41.4 (0.91 g, 3.38 mmol) in dioxane (11.37 mL) was added 4N HCl in dioxane (11.37 mL, 3.38 mmol) and the suspension was stirred at RT for 1 h. The reaction mixture was evaporated to dryness, suspended in dioxane and evaporated again (2

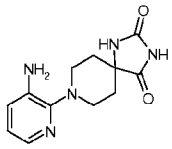
times). The solid residue was dried in a vacum oven to yield the title Intermediate 41.3 (810 mg, 3.18 mmol, 94%) as a colourless solid. LC-MS: m/z 170.0 $[M+H]^+$.

[00360] Intermediate 41.4: 2-Methyl-3-oxo-1,2,8-triaza-spiro[4.5]decane-8-carboxylic acid tert-butyl ester.



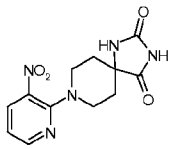
[00361] To a solution of tert-butyl 4-(2-methoxy-2-oxoethylidene)piperidine-1-carboxylate in toluene (5 mL) was added methyl hydrazin (0.92 g, 1.05 mmol) and the solution was heated to 100 °C for 22 h. The reaction mixture was evaporated and dried using high vacuum to yield the title Intermediate 41.4 (925 mg, 3.43 mmol, 88 %) as a colourless oil. HPLC: $^{B}t_{Ret}$ = 4.94 min; LC-MS: m/z 270.3 $[M+H]^+$.

[00362] Intermediate 42.1: 8-(3-Amino-pyridin-2-yl)-1,3,8-triaza-spiro[4.5] decane-2,4-dione.



[00363] The title Intermediate 42.1 (185 mg, 0.71 mmol, 69%) was obtained as a clourless solid from Intermediate 41.2 (300 mg, 1.03 mmol), analogously to Intermediate 1.1. HPLC: $^{B}t_{Ret}$ = 3.27 min; LC-MS: m/z 262.2 $[M+H]^+$.

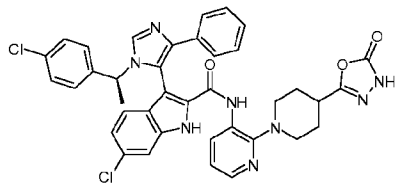
[00364] Intermediate 42.2: 8-(3-Nitro-pyridin-2-yl)-1,3,8-triaza-spiro[4.5]decane-2,4-dione.



[00365] The title Intermediate 42.2 (305 mg, 1.05 mmol, 24%) was obtained from 2-chloro-3-nitropyridine (700 mg, 4.42 mmol) and 1,3,8-triazaspiro[4.5]decane-2,4-dione (999 mg, 4.86 mmol) analogously to Intermediate 1.2. HPLC: $^{B}t_{Ret}$ = 4.80 min; LC-MS: m/z 292.2 $[M+H]^+$.

Example 43

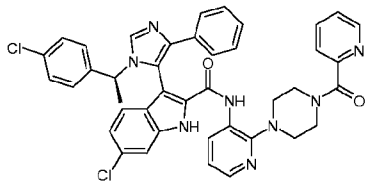
6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(5-oxo-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide.



[00366] To a solution of Intermediate 37.1 (140 mg, 0.202 mmol) in THF/DMF (1/1, 2 mL) was added N,N'-carbonyldiimidazole (49.1 mg, 0.30 mmol) and triethylamine (56 L, 40.80 mg, 0.40 mmol) and the resulting solution was stirred at 55 °C for 2 h. The reaction was quenched by water and extracted with EtOAc. The combined organic layers were washed with brine, dried using $MgSO_4$, filtered and concentrated. The residue was purified by silica gel column chromatography (eluting with a gradient of DCM:MeOH = 100:0 to 80:20) yielding the Example 43 (68 mg, 0.09 mmol, 46%) as a colourless solid. LC-MS: m/z 719.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) ppm 1.13 - 1.37 (m, 2 H) 1.56 (d, *J*=7.03 Hz, 3 H) 2.72 - 2.90 (m, 4 H) 2.98 - 3.09 (m, 2 H) 5.03 (q, *J*=6.38 Hz, 1 H) 6.67 (d, *J*=8.59 Hz, 1 H) 6.73 (d, *J*=8.59 Hz, 2 H) 6.83 (dd, *J*=8.59, 1.95 Hz, 1 H) 6.98 (t, 1 H) 7.05 (t, 3 H) 7.13 (dd, *J*=7.81, 4.69 Hz, 1 H) 7.45 (d, *J*=7.42 Hz, 2 H) 7.51 (d, 1 H) 8.03 - 8.09 (m, 1 H) 8.28 (s, 2 H) 8.33 - 8.44 (m, 1 H) 12.33 - 12.58 (m, 1 H).

Example 44

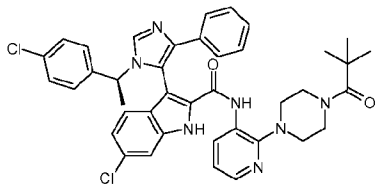
6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {2-[4-(pyridine-2-carbonyl)-piperazin-1-yl]-pyridin-3-yl}-amide.



[00367] To a solution of Example 14 (80 mg, 0.113 mmol) in DMF (1 mL) was added 2-picolinic acid (15.27 mg, 0.124 mmol), N-methylmorphline (57.0 mg, 62 L, 0.564 mmol) and HATU (64.3 mg, 0.169 mmol) and the resulting solution was stirred at RT for 1.5 h. The reaction was diluted with EtOAc, washed with a saturated solution of $NaHCO_3$ and brine, dried using MgSO4, filtered and evaporated to dryness. The residue was purified by silica gel column chromatography (eluting with a gradient of DCM:MeOH = 100:0 to 80:20) yielding Example 44 (71 mg, 0.096 mmol, 85%) as a colourless solid. HPLC: $^{A}t_{Ret}$ = 4.76 min; LC-MS: m/z 740.9 $[M+H]^+$.

Example 45

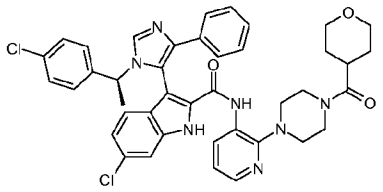
6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {2-[4-(2,2-dimethyl-propionyl)-piperazin-1-yl]-pyridin-3-yl}-amide.



[00368] The title Example 45 (57 mg, 0.079 mmol, 67%) was obtained from Example 14 (84 mg, 0.118 mmol) and pivaloyl chloride (21.41 mg, 0.022 mL, 0.178 mmol), analogously to Example 3. HPLC: $^{A}t_{Ret}$ = 5.01 min; LC-MS: m/z 719.9 $[M+H]^+$.

Example 46

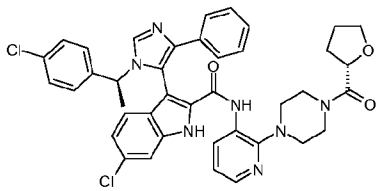
6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {2-[4-(tetrahydro-pyran-4-carbonyl)-piperazin-1-yl]-pyridin-3-yl}-amide.



[00369] The title Example 46 (77 mg, 0.103 mmol, 91%) was obtained from Example 14 (80 mg, 0.113 mmol) and tetrahydro-2H-pyran-4-carboxylic acid (16.14 mg, 0.124 mmol), analogously to Example 44. HPLC: $^{A}t_{Ret}$ = 4.70 min; LC-MS: m/z 748.3 $[M+H]^+$.

Example 47

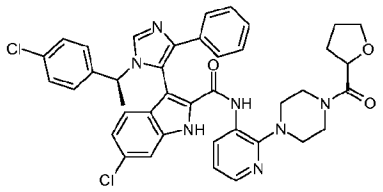
6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {2-[4-((S)-tetrahydro-furan-2-carbonyl)-piperazin-1-yl]-pyridin-3-yl}-amide.



[00370] The title Example 47 (91 mg, 0.123 mmol, 72%) was obtained from Example 14 (120 mg, 0.169 mmol) and (R)-tetrahydrofuran-2-carboxylic acid (26.30 mg, 0.011 mL, 0.226 mmol), analogously to Example 44. HPLC: $^{A}t_{Ret}$ = 4.74 min; LC-MS: m/z 734 $[M+H]^+$.

Example 48

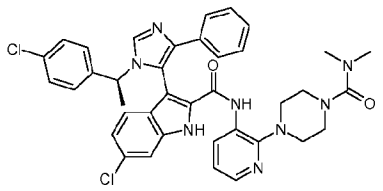
6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {2-[4-((R)-tetrahydro-furan-2-carbonyl)-piperazin-1-yl]-pyridin-3-yl}-amide.



[00371] The title Example 48 (99 mg, 0.133 mmol, 79%) was obtained from Example 14 (120 mg, 0.169 mmol) and (S)-tetrahydrofuran-2-carboxylic acid (21.60 mg, 0.018 mL, 0.186 mmol), analogously to Example 44. HPLC: $^{A}t_{Ret}$ = 4.73 min; LC-MS: m/z 733.7 $[M+H]^+$.

Example 49

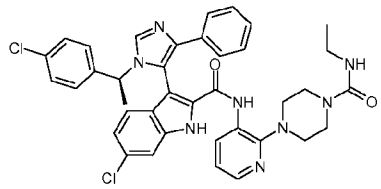
6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-dimethyl-carbamoyl-piperazin-1-yl)-pyridin-3-yl]-amide.



[00372] The title Example 49 (60 mg, 0.084 mmol) was obtained by a standard coupling procedure from Example 14 (103 mg, 0.145 mmol), sodium hydride (29.0 mg, 0.726 mmol) and dimethylcarbamic chloride (31.2 mg, 0.027 mL, 0.290 mmol) in THF. HPLC: $^{A}t_{Ret}$ = 4.74 min; LC-MS: m/z 706.9 $[M+H]^+$.

Example 50

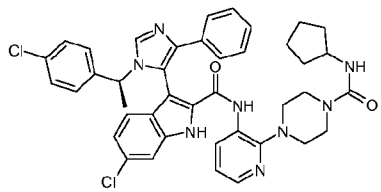
6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-ethyl-carbamoyl-piperazin-1-yl)-pyridin-3-yl]-amide.



[00373] To a solution of Example 14 (90.4 mg, 0.127 mmol) and NEt_3 (27.1 mg, 0.037 mL, 0.268 mmol) in DCM (1 mL) was added isocyanatoethane (10.87 mg, 0.012 mL, 0.153 mmol) and the reaction mixture was stirred at RT for 1 h. Further isocyanatoethane (0.010 mL) were added and stirring was continued for 30 min. The reaction was diluted with DCM and water, phases were separated and the water pahse was re-extracted with DCM. The combined organic phases were washed with brine, dried using MgSO4, filtered and evaporated to dryness. The residue was purified by silica gel column chromatography (eluting with a gradient of DCM:MeOH = 100:0 to 80:20) yielding Example 50 (49 mg, 0.069 mmol, 54%) as a colourless solid. HPLC: ${}^{A}t_{Ret}$ = 4.64 min; LC-MS: m/z 706.9 $[M+H]^+$.

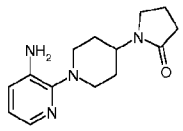
Example 51

6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-cyclopentyl-carbamoyl-piperazin-1-yl)-pyridin-3-yl]-amide.



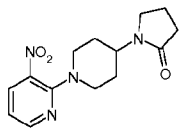
[00374] The title Example 51 (46 mg, 0.062 mmol) was obtained from Example 14 (80 mg, 0.113 mmol), and isocyanatocyclopentan (22.56 mg, 0.023 mL, 0.203 mmol), analogously to Example 50. HPLC: ${}^{A}t_{Ret}$ = 4.93; LC-MS: m/z 747.2 $[M+H]^+$.

[00375] Intermediate 52.1: 1-(3'-Amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-pyrrolidin-2-one.



[00376] The title Intermediate 52.1 (714 mg, 2.72 mmol, 96%) was obtained as a pinkish solid from Intermediate 52.2 (820 mg, 2.82 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.08 min; LC-MS: m/z 261.2 $[M+H]^+$.

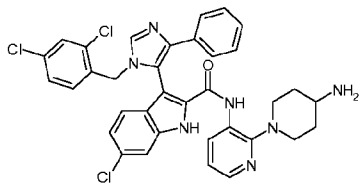
[00377] Intermediate 52.2: 1-(3'-Nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-pyrrolidin-2-one.



[00378] The title Intermediate 52.2 (820 mg, 2.80 mmol, 88%) was obtained as a yellowsh solid from 2-chloro-3-nitro-pyridine (502 mg, 3.17 mmol) and 1-(piperidin-4-yl)pyrrolidin-2-one analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.46 min; LC-MS: m/z 291.1 $[M+H]^+$.

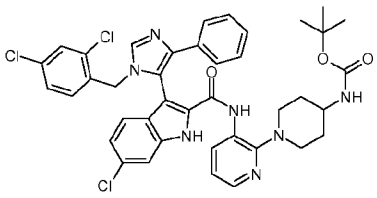
Example 53

6-Chloro-3-[3-(2,4-dichloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid (4-amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl)-amide 2HCl salt.



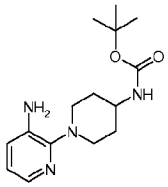
[00379] The title compound (563 mg, 0.749 mmol, 99%) was obtained as a yellowish solid from Intermediate 53.1 (586 mg, 0.760 mmol) analogously to Example 2. HPLC: $^{A}t_{Ret}$ = 4.30 min; LC-MS: m/z 672.0 $[M+H]^+$.

[00380] Intermediate 53.1: [3'-({6-Chloro-3-[3-(2,4-dichloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carbonyl}-amino)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]-carbamic acid tert-butyl ester.



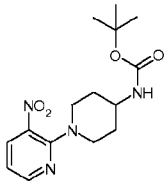
[00381] The title Intermediate (607 mg, 0.764 mmol, 44%) was obtained as a yellowish solid from Intermediate 53.4 (900 mg, 1.747 mmol) and Intermediate 53.2 (562 mg, 1.922 mmol), analogously to Example 1. HPLC: $^{A}t_{Ret}$ = 5.02 min; LC-MS: m/z 769.8 $[M+H]^+$.

[00382] Intermediate 53.2: (3'-Amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-carbamic acid tert-butyl ester.



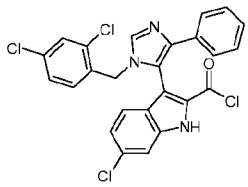
[00383] The title intermediate (3.07 g, 10.40 mmol, 100%) was obtained as a redish solid from Intermediate 53.3 (3.04 g, 10.40 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.75 min; LC-MS: m/z 293.2 $[M+H]^+$.

[00384] Intermediate 53.3: (3'-Nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-carbamic acid tert-butyl ester.



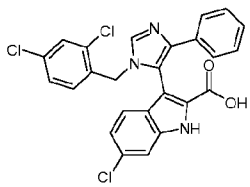
[00385] The title Intermediate 53.3 (3.42 g, 10.50 mmol, 98%) was obtained from 2-chloro-3-nitro-pyridine (1.7 g, 10.72 mmol) and piperidin-4-yl-carbamic acid tert-butyl ester (2.362, 11.79 mmol) analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 5.13 min; MS: m/z 323.1 $[M+H]^+$.

[00386] Intermediate 53.4: 6-Chloro-3-[3-(2,4-dichloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carbonyl chloride.



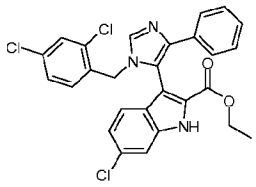
[00387] To a suspension of Intermediate 53.5 (1.5 g, 3.02 mmol) in dry DCM (10 mL) was added drop wise $(COCl)_2$ (3.96 mL, 45.3 mmol) at RT. The suspension was heated to 50 °C. After a period of 1 h an the mixture was allowed to cool to RT, was evaporated to dryness followed by sonication in DCM and evaporation of solvent (2 times). The residue was dried under high vacuum at 50 °C yielding the title Intermediate 53.4 (1.43 g, 2.78 mmol, 92%) as a yellow solid. HPLC: $^{A}t_{Ret}$ = 5.05 min (methyl ester of 53.4); LC-MS: m/z 511.9 [methyl ester of 53.4 + H] $^{+}$.

[00388] Intermediate 53.5: 6-Chloro-3-[3-(2,4-dichloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid.



[00389] To a mixture of Intermediate 53.6 (3.09.0 g, 5.89 mmol) in EtOH (50 mL) was added 2 M aqueous solution of NaOH (40 mL, 80 mmol) at RT and the reaction mixture was heated to 60 °C for 1 h. The reaction mixture was cooled, slowly acidified using 4M HCl (20 mL)and concentrated to form a suspension. EtOAc (100 mL) was added, the suspension was filtered and the solid residue was washed with water and EtOAc. The filtrate was washed water and with brine, dried using Na_2SO_4 and evaporated *in vacuo* which initiated crystallization. The resulting suspension was filtered and washed with EtOAc and the combined crystalls were dried at 70 °C in a vacuum oven yielding the title Intermediate 53.5 (2.3 g, 4.63 mmol, 79%) as a colourless solid. HPLC: $^{C}t_{Ret}$ = 6.24 min; LC-MS: m/z 498.2 $[M+H]^{+}$.

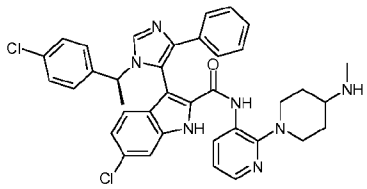
[00390] Intermediate 53.6: 6-Chloro-3-[3-(2,4-dichloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid ethyl ester.



[00391] A mixture of Intermediate 1.6 (2.0 g, 7.95 mmol), 2,4-dichloro-benzylamine (1.587 g, 8.74 mmol), Et_3N (3.32 mL, 23.84 mmol) and 1-(isocyano-phenyl-methanesulfonyl)-4-methyl-benzene (2.59 g, 9.54 mmol) in EtOH (45 mL) were heated at 65 °C. After stirring for 20 h, the reaction mixture was concentrated *in vacuo*, poured into aqueous $NaHCO_3$ and was extracted with EtOAc. The organic phase was washed with brine, dried using Na_2SO_4 and evaporated *in vacuo*. Crystallization of the crude product in TBME afforded the title Intermediate 53.6 (3.21 g, 6.12 mmol, 77%) as a colourless solid. HPLC: ${}^{B}t_{Ret}$ = 6.61 min; LC-MS: m/z 526.3 $[M+H]^+$.

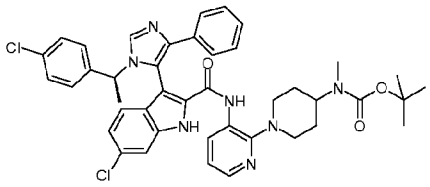
Example 54

6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (4-methylamino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl)-amide.



[00392] The title compound (350 mg, 0.475 mmol, 102%) was obtained as a yellowish solid from Intermediate 54.1 (355 mg, 0.464 mmol) analogously to Example 2. HPLC: ${}^{A}t_{Ret}$ = 4.37 min; LC-MS: m/z 663.9 $[M+H]^+$.

[00393] Intermediate 54.1: 3'-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl}-methyl-carbamic acid tert-butyl ester.

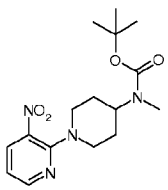


[00394] The title Intermediate 54.1 (378 mg, 0.494 mmol, 47%) was obtained as a slightly yellow solid from Intermediate 1.3 (565 mg, 1.062 mmol) and Intermediate 54.2 (360 mg, 1.115 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 6.70 min; LC-MS: m/z 763.9 $[M+H]^+$.

[00395] Intermediate 54.2: (3'-Amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-methyl-carbamic acid tert-butyl ester.

[00396] The title Intermediate 54.2 (751 mg, 2.328 mmol, 97%) was obtained as a pinkish solid from Intermediate 54.3 (851 mg, 2.403 mmol) analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 4.06 min; LC-MS: m/z 307.1 $[M+H]^+$.

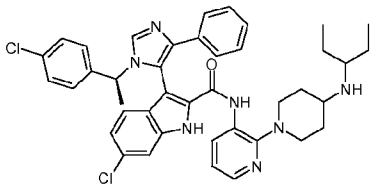
[00397] Intermediate 54.3: Methyl-(3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-carbamic acid tert-butyl ester.



[00398] The title Intermediate 54.3 (854 mg, 2.412 mmol, 92%) was obtained as an orange oil from 2-chloro-3-nitro-pyridine (417 mg, 2.63 mmol) and methyl-piperidin-4-yl-carbamic acid tert-butyl ester (592 mg, 2.76 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 5.53 min; LC-MS: m/z 337.1 $[M+H]^+$.

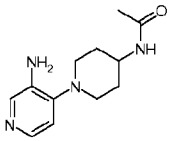
Example 55

6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(1-ethyl-propylamino)-3,4,5,6-tetrahydro-2H-[1,2'] bipyridinyl-3'-yl]-amide.



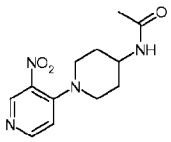
[00399] Example 2 (63 mg, 0.087 mmol), pentan-3-one (8.25 mg, 0.096), sodium acetate (10.00 mg, 0.122 mmol) and acetic acid (8.89 mg, 8.47 L, 0.148 mmol) were suspended in THF (1 mL) and stirred at RT for 3 h followed by addition of sodium triacetoxyborohydride (36.9 mg, 0.174 mmol). After a period of 18 h further sodium triacetoxyborohydride (36.9 mg, 0.174 mmol) was added and the reaction mixture was continued to stirr at RT for 4 h. The reaction mixture was quenched with $NaHCO_3$ and extracted with DCM. The combined organic layers were washed with brine, dried using $MgSO_4$, filtered and concentrated. The crude product was purified by reversed phase prep-HPLC (gradient elution, MeCN/water + 0.1% TFA). Fractions containing pure material were combined, concentrated and the resulting aqueous mixture was neutralized with a saturated solution of $NaHCO_3$, followed by extraction with DCM. The organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness to yield the title Example 55 (9 mg, 0.012 mmol, 14%) as a colourless solid. HPLC: $^{A}t_{Ret}$ = 4.66 min; LC-MS: m/z 719.9 $[M+H]^+$.

[00400] Intermediate 56.1: N-(3'-Amino-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-acetamide.



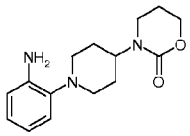
[00401] The title Intermediate 56.1 (650 mg, 2.75 mmol, 94%) was obtained as a colourless solid from Intermediate 56.2 (770 mg, 2.91 mmol) analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 2.82 min; MS: m/z 235.2 $[M+H]^+$.

[00402] Intermediate 56.2: N-(3'-Nitro-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-acetamide.



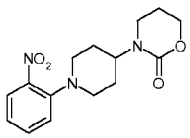
[00403] The title Intermediate 56.2 (770 mg, 2.86 mmol, 91%) was obtained as a yellow foam from 4-chloro-3-nitropyridine (500 mg, 3.15 mmol) and N-(piperidin-4-yl)acetamide (493 mg, 3.47 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 2.79 min; MS: m/z 265.1 $[M+H]^+$.

[00404] Intermediate 57.1: 3-[1-(2-Amino-phenyl)-piperidin-4-yl]-[1,3]oxazinan-2-one.



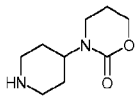
[00405] The title Intermediate 57.1 (950 mg, 3.45 mmol, 89%) was obtained as a colourless solid from Intermediate 57.2 (1.19 g, 3.90 mmol) analogously to Intermediate 1.1. HPLC: $^{B}t_{Ret}$ = 3.99 min; LC-MS: m/z 276.2 $[M+H]^+$.

[00406] Intermediate 57.2: N-(3'-Nitro-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-acetamide.



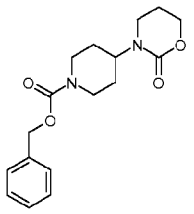
[00407] The title Intermediate 57.2 (1.20 g, 3.93 mmol, 79%) was obtained as a yellow solid from 2-fluoro-nitrobenzene (0.72 g, 4.95 mmol) and Intermediate 57.3 (1.00 g, 5.44 mmol), analogously to Intermediate 1.2. HPLC: $^{B}t_{Ret}$ = 3.99 min; LC-MS: m/z 276.2 $[M+H]^+$.

[00408] Intermediate 57.3: 3-Piperidin-4-yl-[1,3]oxazinan-2-one.



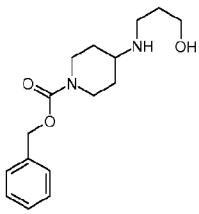
[00409] The title Intermediate 57.3 (740 mg, 4.02 mmol, 87%) was obtained as a colourless solid by hydrogenation reaction of Intermediate 57.4 (1.465 g, 4.60 mmol) with H_2 gas and Pd/C (0.3 g, 0.282 mmol) in MeOH (30 mL) at RT for 90 h. HPLC: $^{B}t_{Ret}$ = not visible; LC-MS: m/z 185.1 $[M+H]^+$.

[00410] Intermediate 57.4: 4-(2-Oxo-[1,3]oxazinan-3-yl)-piperidine-1-carboxylic acid benzyl ester.



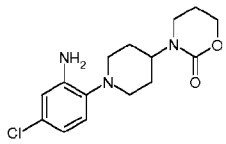
[00411] To a solution of Intermediate 57.5 (3.03 g, 10.36 mmol) in DCM (60 mL) at 0 °C was added CDI (2.52 g, 15.55 mmol) and triethylamine (1.15 g, 1.59 mL, 11.4 mmol). The reaction was allowed to warm to RT and was stirred for 23 h. The reaction mixture was then cooled to 0 °C and water (60 mL) and HCl conc (6 mL) were added dropwise. The organic phase was washed with brine, dried using Na_2SO_4 filtered and concentrated to dryness to yield the title Intermediate 57.4 (1.467 g, 4.61 mmol) as a colourless oil. HPLC: $^{B}t_{Ret}$ = 5.75 min; LC-MS: m/z 319.2 $[M+H]^+$.

[00412] Intermediate 57.5: 4-(3-Hydroxy-propylamino)-piperidine-1-carboxylic acid benzyl ester.



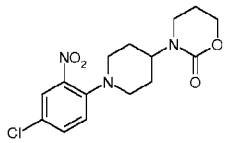
[00413] To a solution of benzyl 4-oxo-piperidine-1-carboxylate (5.00 g, 21.22 mmol) in EtOH (25 mL) was added 3-amino-propanol (3.57 g, 3.62 mL, 46.00 mmol) at RT and the reaction mixture was stirred for 2 h. The reaction mixture was then cooled to 0 °C, 4N HCl in dioxane (5.86 mL, 23.40 mmol) and sodium cyanoborohydride (1.334 g, 21.22 mmol) were added and the reaction was continued to stirr at RT for 23 h. Water was added and the mixture was extracted with EtOAc. The organic phase was washed with water, dried using Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (eluting with DCM:MeOH = 90:10) yielding Intermediate 57.5 (3.03 g, 10.36 mmol, 49%) as a colourless oil. HPLC: $^{B}t_{Ret}$ = 4.61 min; LC-MS: m/z 293.2 $[M+H]^+$.

[00414] Intermediate 58.1: 3-[1-(2-Amino-4-chloro-phenyl)-piperidin-4-yl]-[1,3]oxazinan-2-one.



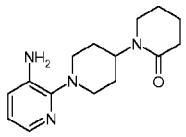
[00415] The title Intermediate 58.1 (1.31 g, 3.81 mmol, 71%) was obtained as a slighly purple solid from Intermediate 58.2 (1.81 g, 5.36 mmol) analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.98 min; LC-MS: m/z 310.3 $[M+H]^+$.

[00416] Intermediate 58.2: 3-[1-(4-Chloro-2-nitro-phenyl)-piperidin-4-yl]-[1,3]oxazinan-2-one.



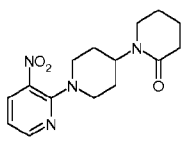
[00417] The title Intermediate 58.2 (1.82 g, 5.09 mmol, 89%) was obtained as an orange solid from 4-chloro-1-fluoro-2-nitro-benzene (1.00 g, 5.70 mmol) and Intermediate 57.3 (1.154 g, 11.39 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 5.07 min; LC-MS: m/z 340.1 $[M+H]^+$.

[00418] Intermediate 59.1: 3''-Amino-3,4,5,6,3',4',5',6'-octahydro-2'H-[1,4';1',2'']terpyridin-2-one.



[00419] The title Intermediate 59.1 (340 mg, 1.139 mmol, 41%) was obtained as a colourless solid from Intermediate 59.2 (925 mg, 3.04 mmol) analogously to Intermediate 1.1. HPLC: $^{B}t_{Ret}$ = 3.87 min; LC-MS: m/z 275.3 $[M+H]^+$.

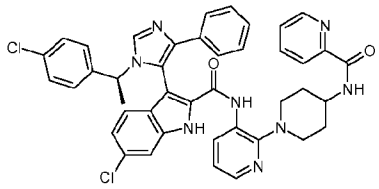
[00420] Intermediate 59.2: 3''-Nitro-3,4,5,6,3',4',5',6'-octahydro-2'H-[1,4';1',2'']terpyridin-2-one.



[00421] The title Intermediate 59.2 (930 mg, 3.06 mmol, 99%) was obtained as a yellow solid from 2-chloro-3-nitro-pyridine (500 mg, 3.09 mmol) and [1,4'-bipiperidin]-2-one (620 mg, 3.40 mmol), analogously to Intermediate 1.2. HPLC: $^{B}t_{Ret}$ = 5.82 min; LC-MS: m/z 305.1 $[M+H]^+$.

Example 60

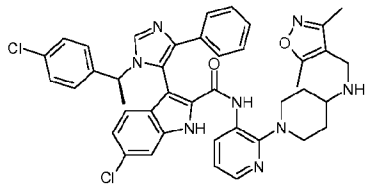
6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {4-[(pyridine-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl}-amide.



[00422] To a solution of Example 2 (93 mg, 0.129 mmol) in DMF (1 mL) was added 2-picolinic acid (17.41 mg, 0.141 mmol), N-methylmorphline (65.0 mg, 71 L, 0.643 mmol) and HATU (73.3 mg, 0.193 mmol) and the resulting suspension was stirred at RT for 1 h. The reaction was diluted with EtOAc, washed with a saturated solution of $NaHCO_3$ and brine, dried using $MgSO_4$, filtered and evaporated to dryness. The residue was purified by silica gel column chromatography (eluting with a gradient of DCM:MeOH = 100:0 to 80:20) yielding Example 60 (75 mg, 0.099 mmol, 77%) as a colourless solid. HPLC: $^{A}t_{Ret}$ = 4.77 min; LC-MS: m/z 755.5 $[M+H]^+$.

Example 61

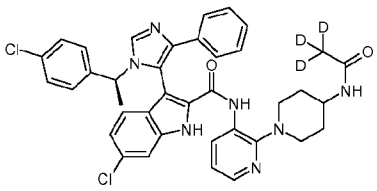
6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {4-[(3,5-dimethyl-isoxazol-4-ylmethyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl}-amide.



[00423] Example 2 (62 mg, 0.086 mmol), 3,5-dimethyl-1,2-oxazole-4-carbaldehyde (10.72 mg, 0.086), sodium acetate (21.79 mg, 0.266 mmol) and acetic acid (18.01 mg, 17 L, 0.300 mmol) were suspended in THF (1 mL) and stirred at RT for 3 h followed by addition of sodium triacetoxyborohydride (74.5 mg, 0.357 mmol). After a period of 16 h the reaction mixture was quenched with $NaHCO_3$ and extracted with DCM. The combined organic layers were washed with brine, dried using $MgSO_4$, filtered and concentrated. The crude product was purified by reversed phase prep-HPLC (gradient elution, MeCN/water + 0.1% TFA). Fractions containing pure material were combined, concentrated and the resulting aqueous mixture was neutralized with a saturated solution of $NaHCO_3$, followed by extraction with DCM. The organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness to yield the title Example 61 (14 mg, 0.018 mmol, 22%) as a solid. HPLC: $^{A}t_{Rei}$ = 4.60 min; LC-MS: m/z 758.9 $[M+H]^+$.

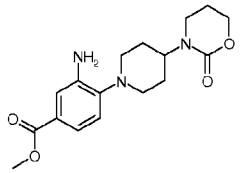
Example 62

6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(d_3-methyl-carbonyl-amino)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide.



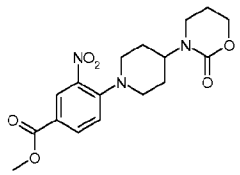
[00424] The title Example 62 (83 mg, 0.119 mmol, 78%) was obtained as a yellowish solid from Example 2 (110 mg, 0.152 mmol) and tetradeutero acetic acid (17.54 mg, 0.016 mL, 0.274 mmol), analogously to Example 60. HPLC: $^{A}t_{Ret}$ = 4.49 min; LC-MS: m/z 695.0 $[M+H]^+$.

[00425] Intermediate 66.1: 3-Amino-4-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-benzoic acid methyl ester.



[00426] The title Intermediate 66.1 (641 mg, 1.865 mmol, 43%) was obtained as a colourless solid from Intermediate 66.2 (1.58 g, 4.35 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.77 min; LC-MS: m/z 334.0 $[M+H]^+$.

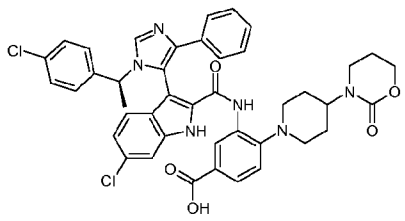
[00427] Intermediate 66.2: 3-Nitro-4-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-benzoic acid methyl ester.



[00428] The title Intermediate 66.2 (1.58 g, 4.26 mmol, 71.4%) was obtained as a yellow solid from 4-chloro-3-nitro-benzoic acid methyl ester (1.1 g, 5.97 mmol) and 3-(piperidin-4-yl)-1,3-oxazinan-2-one (1.287 g, 5.97 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.71 min; LC-MS: m/z 364.0 $[M+H]^+$.

Example 67

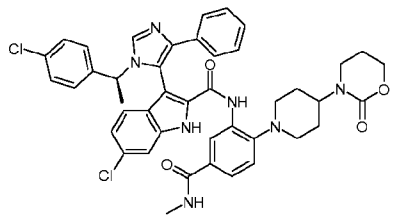
3-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-benzoic acid.



[00429] To a suspension of Example 66 (165 mg, 0.208 mmol) in MeOH:THF = 1:1 (1 mL) was added NaOH 4M (0.156 mL, 0.625 mmol) and the reaction mixture was stirred over night at RT. Solvents were evaporated, MeOH (0.5 mL) and water was added and the solution was acidified to pH3 by adding 2N HCl upon which precipitation occured. The precipitate was filtered, washed with water and dried at 50 °C using high vacuum. The solid was dissolved in a 1/1 mixture of THF/ETOAc, washed twice with brine, dried using $MgSO_4$ and evaporated. The crude product was purified by silica gel column chromatography (eluting with a gradient of DCM:MeOH = 100:0 to 80:20) yielding Example 67 (98 mg, 0.122 mmol, 59%) as a colourless solid. HPLC: $^{A}t_{Ret}$ = 4.92 min; LC-MS: m/z 777.0 $[M+H]^+$.

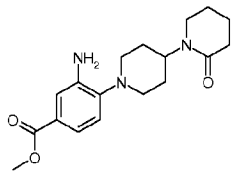
Example 68

6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {5-methylcarbamoyl-2-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-phenyl}-amide.



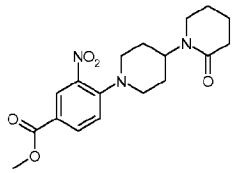
[00430] The title Example 68 (40 mg, 0.049 mmol, 72%) was obtained as a slightly yellow solid from Example 67 (53 mg, 0.068 mmol) and methylamine hydrochloride (9.20 mg, 0.136 mmol), analogously to Example 44. HPLC: $^{A}t_{Ret}$ = 4.92 min; LC-MS: m/z 790.4 $[M+H]^+$.

[00431] Intermediate 69.1: 3-Amino-4-(2-oxo-[1,4']bipiperidinyl-1'-yl)-benzoic acid methyl ester.



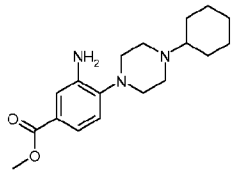
[00432] The title Intermediate 69.1 (1.2 g, 3.55 mmol, 99%) was obtained as a colourless solid from Intermediate 69.2 (1.3 g, 3.60 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.90 min; LC-MS: m/z 332.2 $[M+H]^+$.

[00433] Intermediate 69.2: 3-Nitro-4-(2-oxo-[1,4']bipiperidinyl-1'-yl)-benzoic acid methyl ester.



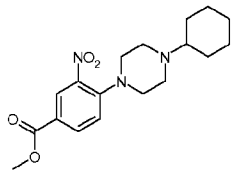
[00434] The title Intermediate 69.2 (1.3 g, 3.60 mmol, 86%) was obtained as a yellow solid from 4-chloro-3-nitro-benzoic acid methyl ester (900 mg, 4.17 mmol) and [1,4']bipiperidinyl-2-one (800 mg, 4.39 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 5.11 min; LC-MS: m/z 362.1 $[M+H]^+$.

[00435] Intermediate 70.1: 3-Amino-4-(4-cyclohexyl-piperazin-1-yl)-benzoic acid methyl ester.



[00436] The title Intermediate 70.1 (1.47 g, 4.40 mmol, 98%) was obtained as a colourless solid from Intermediate 70.2 (1.56 g, 4.49 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.75 min; LC-MS: m/z 318.2 $[M+H]^+$.

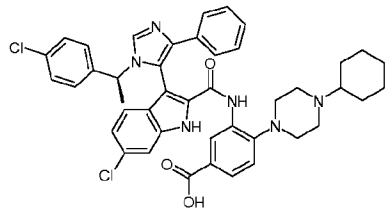
[00437] Intermediate 70.2: 4-(4-Cyclohexyl-piperazin-1-yl)-3-nitro-benzoic acid methyl ester.



[00438] The title Intermediate 70.2 (1.56 g, 4.45 mmol, 96%) was obtained from 4-chloro-3-nitro-benzoic acid methyl ester (1.00 g, 4.64 mmol) and 1-cyclohexylpiperazine (0.859 g, 5.10 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.28 min.

Example 71

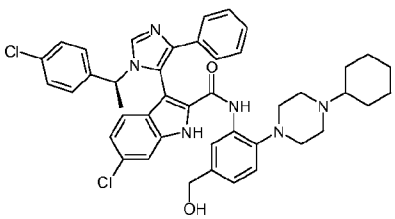
3-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-(4-cyclohexyl-piperazin-1-yl)-benzoic acid.



[00439] The title Example 71 (33 mg, 0.042 mmol, 23%) was obtained from Example 70 (147 mg, 0.189 mmol) analogously to Example 67. HPLC: $^{A}t_{Ret}$ = 4.84 min; LC-MS: m/z 761.3 $[M+H]^{+}$.

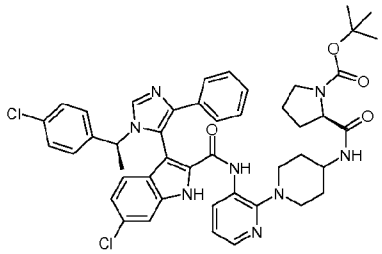
Example 72

6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-cyclohexyl-piperazin-1-yl)-5-hydroxymethyl-phenyl]-amide.



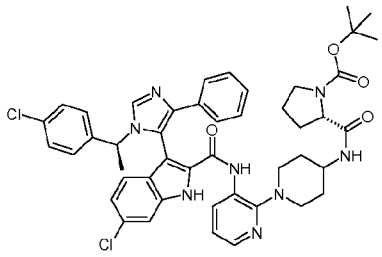
[00440] A solution of Example 71 (170 mg, 0.219 mmol) in THF (2 mL) was cooled to 0 °C and $LiAlH_4$ (16.63 mg, 0.022 mmol) was added portionwise. After 1 h at 0 °C and an additional 1 h at RT further $LiAlH_4$ (1 eq) was added and stirring was continued for 1 h. The reaction mixture was quenched with water at 0 °C and extracted with DCM. The combined organic layers were washed with brine, dried using $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel column chromatography (eluting with a gradient of DCM:MeOH = 100:0 to 80:20). Further purification was achived by reversed phase prep-HPLC (gradient elution, MeCN/water + 0.1% TFA). Fractions containing pure material were combined, concentrated and the resulting aqueous mixture was neutralized with a saturated solution of $NaHCO_3$, followed by extraction with DCM. The organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness to yield the title Example 72 (17 mg, 0.022 mmol, 10%) as a colourless solid. HPLC: $^{A}t_{Ret}$ = 4.80 min; LC-MS: m/z 747.2 $[M+H]^+$.

[00441] Intermediate 73.1: (R)-2-{3'-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl-carbamoyl}-pyrrolidine-1-carboxylic acid tert-butyl ester.



[00442] The title Intermediate 73.1 (110 mg, 0.130 mmol, 85%) was obtained as a yellow solid from Example 2 (111 mg, 0.153 mmol) and *N*-(*tert*-Butoxycarbonyl)-D-proline (39.6 mg, 0.184 mmol), analogously to Example 44. HPLC: $^{A}t_{Ret}$ = 4.89 min; LC-MS: m/z 847.4 $[M+H]^+$.

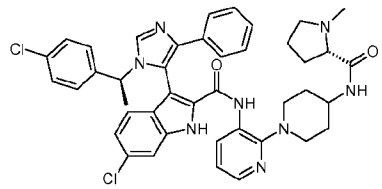
[00443] Intermediate 74.1: (S)-2-{3'-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl-carbamoyl}-pyrrolidine-1-carboxylic acid tert-butyl ester.



[00444] The title Intermediate 74.1 (98 mg, 0.116 mmol, 73%) was obtained as a yellow solid from Example 2 (111 mg, 0.158 mmol) and *N*-(*tert*-butoxycarbonyl)-L-proline (40.7 mg, 0.189 mmol), analogously to Example 44. HPLC: $^{A}t_{Ret}$ = 4.89 min; LC-MS: m/z 846.9 $[M+H]^+$.

Example 75

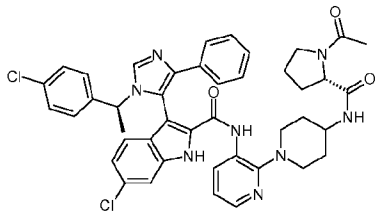
6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {4-[((S)-1-methyl-pyrrolidine-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl}-amide.



[00445] The title Example 75 (73 mg, 0.096 mmol, 69%) was obtained as a clourless solid from Example 2 (100 mg, 0.138 mmol) and *N*-methyl-L-proline (22.38 mg, 0.152 mmol), analogously to Example 44. HPLC: $^{A}t_{Ret}$ = 4.33 min; LC-MS: m/z 760.9 $[M+H]^+$.

Example 76

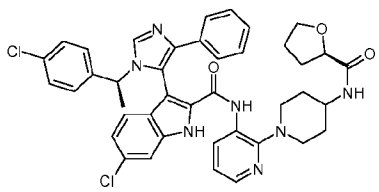
6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {4-[((S)-1-acetyl-pyrrolidine-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl}-amide.



[00446] The title Example 76 (87 mg, 0.110 mmol, 80%) was obtained as a yellow solid from Example 2 (100 mg, 0.138 mmol) and *N*-acetyl-L-proline (24.17 mg, 0.152 mmol), analogously to Example 44. HPLC: $^{A}t_{Ret}$ = 4.56 min; LC-MS: m/z 788.9 $[M+H]^+$.

Example 77

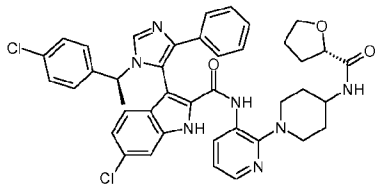
6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {4-[((R)-tetrahydro-furan-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl}-amide.



[00447] The title Example 77 (66 mg, 0.088 mmol, 56%) was obtained as a yellow solid from Example 2 (109 mg, 0.151 mmol) and (*R*)-(+)-tetrahydro-2-furoic acid (19.24 mg, 0.166 mmol), analogously to Example 44. HPLC: $^{A}t_{Ret}$ = 4.64 min; LC-MS: m/z 748.1 $[M+H]^+$.

Example 78

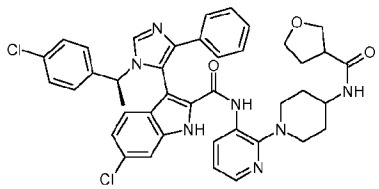
6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {4-[((S)-tetrahydro -furan-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl}-amide.



[00448] The title Example 78 (88 mg, 0.118 mmol, 74%) was obtained as a yellow solid from Example 2 (115 mg, 0.159 mmol) and (*S*)-(-)-tetrahydro-2-furoic acid (20.30 mg, 0.175 mmol), analogously to Example 44. HPLC: $^{A}t_{Ret}$ = 4.65 min; LC-MS: m/z 747.9 $[M+H]^+$.

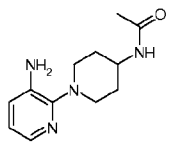
Example 79

6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {4-[(tetrahydro-furan-3-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl}-amide.



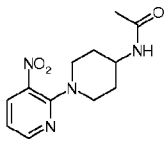
[00449] A stereoisomeric mixture of the title Example 79 (98 mg, 0.131 mmol, 81%) was obtained as a yellow solid from Example 2 (117 mg, 0.162 mmol) and tetrahydro-3-furoic acid (24.60 mg, 0.212 mmol), analogously to Example 44. HPLC: $^{A}t_{Ret}$ = 4.54 min; LC-MS: m/z 747.9 $[M+H]^+$.

[00450] Intermediate 80.1: N-(3'-Amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-acetamide.



[00451] The title Intermediate 80.1 (611 mg, 2.58 mmol, 97%) was obtained as a beige solid from Intermediate 80.2 (700 mg, 2.65 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 2.79 min; LC-MS: m/z 235.2 $[M+H]^+$.

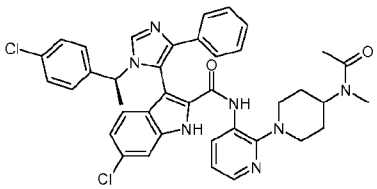
[00452] Intermediate 80.2: N-(3'-Nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-acetamide.



[00453] The title Intermediate 80.2 (700 mg, 2.62 mmol, 83%) was obtained from 2-chloro-3-nitropyridine (500 mg, 3.15 mmol) and N-(piperidin-4-yl)acetamide (673 mg, 4.73 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 3.99 min; LC-MS: m/z 265.1 $[M+H]^+$.

Example 81

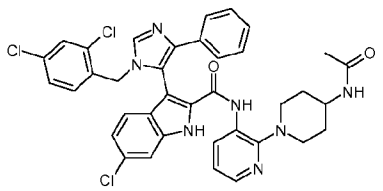
6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(acetyl-methyl-amino)-3,4,5,6-tetrahydro-2H-[1,2'] bipyridinyl-3'-yl]-amide.



[00454] To a solution of Example 54 (125 mg, 0.159 mmol) in pyridine (1.4 mL) was added acetic anhydride (48.8 mg, 0.045 mL, 0.478 mmol) at RT and the solution was stirred for 45 min. The reaction mixture was quenched with $NaHCO_3$ and extracted with DCM. The combined organic layers were washed with water, then brine, dried using $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel column chromatography (eluting with a gradient of DCM:MeOH = 100:0 to 80:20) yielding the title Example 81 (89 mg, 0.126 mmol, 79%) as a colourless solid. HPLC: $^{A}t_{Ret}$ = 4.60 min; LC-MS: m/z 705.9 $[M+H]^+$.

Example 86

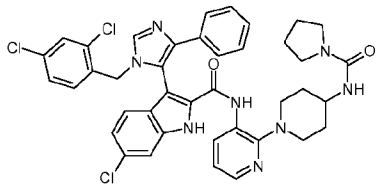
6-Chloro-3-[3-(2,4-dichloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid (4-acetylamino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl)-amide.



[00455] The title Example 86 (279 mg, 0.391 mmol, 58%) was obtained from Intermediate 53.4 (350 mg, 0.679 mmol) and Intermediate 80.1 (191 mg, 0.815 mmol), analogously to Example 1. HPLC: $^{C}t_{Ret}$ = 5.65 min; LC-MS: m/z 714.3 $[M+H]^+$.

Example 87

6-Chloro-3-[3-(2,4-dichloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid {4-[(pyrrolidine-1-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2'] bipyridinyl-3'-yl}-amide.

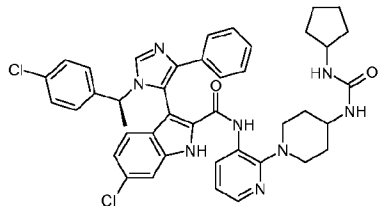


[00456] To a suspension of Example 53 (143 mg, 0.192 mmol) in DCM (2 mL) at 0 °C were added NEt_3 (58.4 mg, 0.080 mL, 0.577 mmol) and chloroformic acid 4-nitrophenyl ester (46.5 mg, 0.231 mmol) and the solution was stirred for 1 h. During a period of 2 h pyrrolidine (30.08 mg, 0.034 mL, 0.422 mmol) was added at 0 °C and the reaction mixture was stirred at RT. The reaction mixture was diluted with DCM and 1M NaOH was added. Phases were separated and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried using $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel

column chromatography (eluting with a gradient of DCM:MeOH = 100:0 to 80:20) yielding the title Example 87 (100 mg, 0.128 mmol, 66%) as a colourless solid. HPLC: $^{A}t_{Ret}$ = 4.73 min; LC-MS: m/z 769.1 $[M+H]^+$.

Example 88

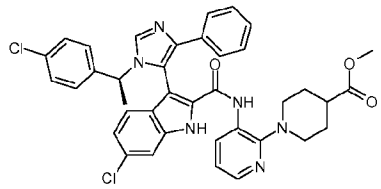
6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(3-cyclopentyl-ureido)-3,4,5,6-tetrahydro-2H-[1,2'] bipyridinyl-3'-yl]-amide.



[00457] To a suspension of Example 2 (80 mg, 0.111 mmol) in DCM (1.5 mL) at RT were added NEt_3 (24.62 mg, 0.034 mL, 0.243 mmol) and cyclopentyl isocyanat (16.47 mg, 0.017 mL, 0.144 mmol) and the reaction mixture was stirred at RT. During the cause of 1.5 h further NEt_3 (0.020 mL) and cyclopentyl isocyanat (0.018 mL) were added until completion of the reaction. The reaction mixture was diluted with DCM and water. Phases were separated and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried using $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel column chromatography (eluting with a gradient of DCM:MeOH = 100:0 to 80:20) yielding the title Example 88 (74 mg, 0.097 mmol, 88%) as a colourless solid. HPLC: $^{A}t_{Ret}$ = 4.81 min; LC-MS: m/z 760.9 $[M+H]^+$.

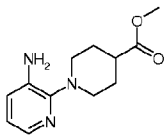
Example 89

3'-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid methyl ester.



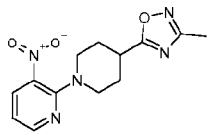
[00458] The title Example 89 (210 mg, 0.403 mmol, 30%) was obtained from Intermediate 1.3 (210 mg, 0.403 mmol) and Intermediate 89.1 (114 mg, 0.484 mmol), analogously to Example 1. HPLC: $^{A}t_{Ret}$ = 4.76 min; LC-MS: m/z 692.8 $[M+H]^+$.

[00459] Intermediate 89.1: 3'-Amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid methyl ester.



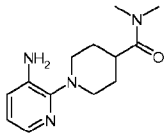
[00460] The title Intermediate 89.1 (303 mg, 1.288 mmol, 37%) was obtained as a byproduct from a standard hydrogenation reaction of Intermediate 99.2 (1.018 g, 3.52 mmol) and Pd/C (185 mg, 1.738 mmol) as a catalyst in MeOH (27 mL). HPLC: $^{A}t_{Ret}$ = 3.22 min; LC-MS: m/z 236.1 $[M+H]^+$.

[00461] Intermediate 89.2: 4-(3-Methyl-[1,2,4]oxadiazol-5-yl)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl.



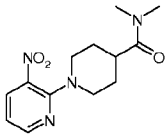
[00462] The title Intermediate 89.2 (1.018 g, 3.48 mmol, 92%) was obtained from 2-chloro-3-nitropyridine (600 mg, 3.78 mmol) and 4-(3-Methyl-[1,2,4]oxadiazol-5-yl)-piperidine (823 mg, 4.92 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.82 min; LC-MS: m/z 290.2 $[M+H]^+$.

[00463] Intermediate 90.1: 3'-Amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid dimethylamide.



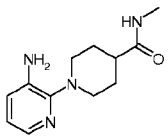
[00464] The title Intermediate 90.1 (660 mg, 2.63 mmol, 87%) was obtained as a colourless solid from Intermediate 90.2 (840 mg, 3.02 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.01 min; MS: m/z 249.2 $[M+H]^+$.

[00465] Intermediate 90.2: 3'-Nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid dimethylamide.



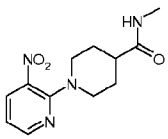
[00466] The title Intermediate 90.2 (840 mg, 2.96 mmol, 94%) was obtained from 2-chloro-3-nitropyridine (500 mg, 3.15 mmol) and N,N-dimethylpiperidine-4-carboxamide (668 mg, 3.47 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.28 min; MS: m/z 279.2 $[M+H]^+$.

[00467] Intermediate 91.1: 3'-Amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid methylamide.



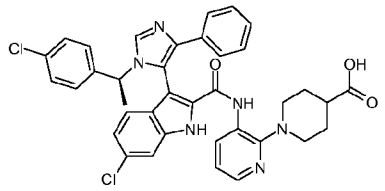
[00468] The title Intermediate 91.1 (710 mg, 2.97 mmol, quant.) was obtained as a colourless solid from Intermediate 91.2 (790 mg, 2.96 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 2.80 min; MS: m/z 235.2 $[M+H]^+$.

[00469] Intermediate 91.2: 3'-Nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid methylamide.



[00470] The title Intermediate 91.2 (790 mg, 2.96 mmol, 94%) was obtained from 2-chloro-3-nitropyridine (500 mg, 3.15 mmol) and N-methylpiperidine-4-carboxamide (493 mg, 3.47 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 3.92 min; MS: m/z 265.2 $[M+H]^+$.

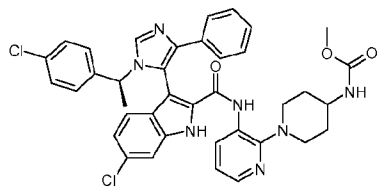
[00471] Intermediate 92.1: 3'-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid.



[00472] To a solution of Example 89 (917 mg, 1.322 mmol) in THF (8 mL) and EtOH (3 mL) was overall added 4 M aqueous solution of NaOH (6.60 mL, 26.36 mmol) at RT during the cause of 4 h. The reaction mixture was concentrated *in vacuo* and acidified to pH 5 using 2N HCl and additional water. The resulting suspension was filtered, the remaining solid was washed with water and dried at 50 °C in an vacuum oven yielding the title Intermediate 92.1 (898 mg, 1.321 mmol, quant.) as a colourless solid. HPLC: $^{A}t_{Ret}$ = 4.49 min; LC-MS: m/z 678.9 $[M+H]^+$.

Example 95

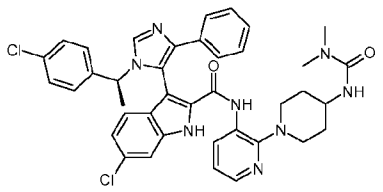
{3'-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl}-carbamic acid methyl ester.



[00473] The title Example 95 (72 mg, 0.102 mmol, 78%) was obtained from Example 2 (94 mg, 0.130 mmol) and methyl chloroformate (24.55 mg, 0.26 mmol) in pyridine (0.8 mL), analogously to Example 63. HPLC: $^{A}t_{Ret}$ = 4.63 min; LC-MS: m/z 707.9 $[M+H]^+$.

Example 97

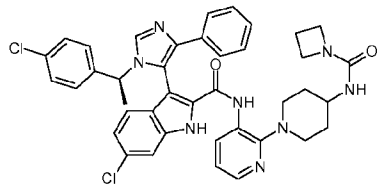
6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(3,3-dimethyl-ureido)-3,4,5,6-tetrahydro-2H-[1,2'] bipyridinyl-3'-yl]-amide.



[00474] To a suspension of Example 2 (105 mg, 0.145 mmol) in THF (2 mL) was added sodium hydride (29 mg, 0.726 mmol) at 0 °C. The suspension was allowed to warm to RT and stirred for 15 min, followed by the addition of dimethylcarbamic chloride (31.2 mg, 0.027 mL, 0.029 mmol). As no reaction conversion was observed after 1 h. DMF (3 mL) was added to solubilize the reactant and further NaH (7 equivalents) were added. The reaction mixture was quenched with water at 0°C and extracted with EtOAc. The combined organic layers were washed with brine, dried using $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel column chromatography (eluting with a gradient of DCM:MeOH = 100:0 to 80:20) yielding the title Example 97 (45 mg, 0.061 mmol, 42%) as a colourless solid. HPLC: $^{A}t_{Ret}$ = 4.60 min; LC-MS: m/z 720.9 $[M+H]^+$.

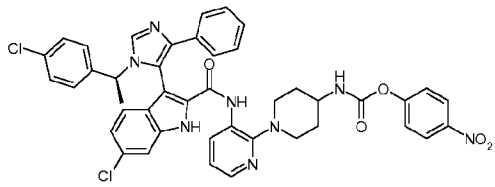
Example 99

6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {4-[(azetidine-1-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl}-amide.



[00475] To a solution of Intermediate 99.1 (130 mg, 0.159 mmol) in DCM (1 mL) was added azetidine hydrochloride (17.89 mg, 0.191 mmol) at 0 °C. The reaction mixture was allowed to warm to RT and stirring was continued for 2 h. DCM and 1M NaOH were added phases were separated and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried using $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel column chromatography (eluting with a gradient of DCM:MeOH = 100:0 to 80:20) yielding the title Example 99 (82 mg, 0.108 mmol, 68%) as a colourless solid. HPLC: $^{A}t_{Ret}$ = 4.60 min; LC-MS: m/z 732.9 $[M+H]^+$.

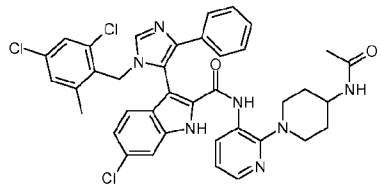
[00476] Intermediate 99.1: {3'-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl}-carbamic acid 4-nitro-phenyl ester.



[00477] The title Intermediate 99.1 (crude, 87% purity by UPLC-MS) was obtained from Example 2 (227 mg, 0.314 mmol) and 4-nitrophenyl carbonochloridate (76 mg, 0.376 mmol), analogously to Example 3. LC-MS: m/z 815.4 $[M+H]^+$.

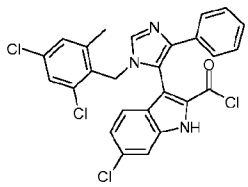
Example 103

6-Chloro-3-[3-(2,4-dichloro-6-methyl-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid (4-acetylamino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl)-amide.



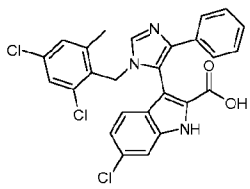
[00478] The title Example 103 (73 mg, 0.100 mmol, 14%) was obtained from Intermediate 103.1 (370 mg, 0.699 mmol) and Intermediate 80.1 (197 mg, 0.839 mmol), analogously to Example 1. HPLC: $^{C}t_{Ret}$ = 5.79 min; LC-MS: m/z 725.9 $[M+H]^+$.

[00479] Intermediate 103.1: 6-Chloro-3-[3-(2,4-dichloro-6-methyl-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carbonyl chloride.



[00480] To a suspension of Intermediate 103.2 (370 mg, 0.724 mmol) in dry DCM (2 mL) was added drop wise $(COCl)_2$ (1.10 g, 0.76 mL, 8.69 mmol) at RT. The reaction mixture was heated to 50 °C. The reaction mixture was allowed to cool to RT and was evaporated to dryness. DCM (1 mL) was added and the mixture was evaporated to dryness. The residue was dried using high vacuum to yield the title Intermediate 103.1 (380 mg, 0.718 mmol, 99%) as a solid. HPLC: $^{C}t_{Ret}$ = 6.59 min (methyl ester of 119.1).

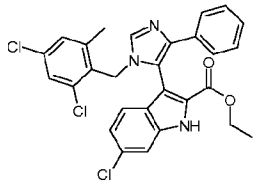
[00481] Intermediate 103.2: 6-Chloro-3-[3-(2,4-dichloro-6-methyl-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid.



[00482] To a solution of Intermediate 103.3 (2.29 g, 4.25 mmol) in EtOH (36 mL) at RT was added 2 M aqueous solution of NaOH (28.9 mL, 4.11 mmol) and the reaction mixture was heated to 60 °C for 5 h. The reaction mixture was cooled to RT and the resulting mixture was slowly acidified with 4M HCl (20 mL) upon which a precipitate formed. The resulting suspension

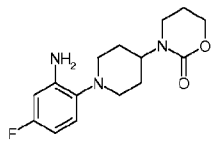
was filtered and washed with EtOH/H_2O 1/1 and the remaining crystals were dried at 70 °C in a vacuum oven yielding the title Intermediate 103.2 (2.10 g, 4.11 mmol, 97%) as a colourless solid. HPLC: $^{C}t_{Ret}$ = 6.36 min; LC-MS: m/z 509.0 $[M+H]^+$.

[00483] Intermediate 103.3: 6-Chloro-3-[3-(2,4-dichloro-6-methyl-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid ethyl ester.



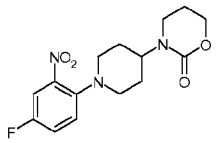
[00484] A mixture of Intermediate 1.6 (2.0 g, 7.95 mmol), 2,4-dichloro-6-methylbenzylamine (1.713 g, 8.74 mmol), Et_3N (3.32 mL, 23.84 mmol) and 1-(isocyano-phenyl-methanesulfonyl)-4-methyl-benzene (2.59 g, 9.54 mmol) in EtOH (45 mL) was heated to 65 °C for 20 h. The reaction mixture was filtered, the filtrate was concentrated to dryness, re-dissolved in EtOAc (77 mL), washed with a saturated solution of $NaHCO_3$ and brine, dried using Na_2SO_4, filtered and evaporated to dryness. The crude product was purified by silica gel column chromatography (eluting with a gradient of hexanes:TBME = 1:3 to 0:1) yielding the title Intermediate 103.3 (2.30 g, 4.27 mmol, 54%) as a colourless solid. HPLC: $^{C}t_{Ret}$ = 6.76 min; LC-MS: m/z 540.2 $[M+H]^+$.

[00485] Intermediate 105.1: 3-[1-(2-Amino-4-fluoro-phenyl)-piperidin-4-yl]-[1,3]oxazinan-2-one



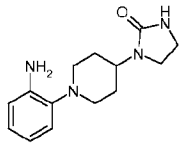
[00486] The title Intermediate 105.1 (950 mg, 3.24 mmol, 85%) was obtained as a colourless solid from Intermediate 105.2 (1.23 g, 3.80 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 4.36 min; LC-MS: m/z 294.2 $[M+H]^+$.

[00487] Intermediate 105.2: 3-[1-(4-Fluoro-2-nitro-phenyl)-piperidin-4-yl]-[1,3]oxazinan-2-one.



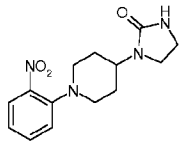
[00488] The title Intermediate 105.2 (1.23 g, 3.80 mmol, 77%) was obtained from 1,4-difluoro-2-nitrobenzene (810 mg, 4.94 mmol) and 3-piperidin-4-yl-[1,3]oxazinan-2-one (1.00 g, 5.43 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 6.05 min; LC-MS: m/z 324.2 $[M+H]^+$.

[00489] Intermediate 106.1: 1-[1-(2-Amino-phenyl)-piperidin-4-yl]-imidazolidin-2-one.



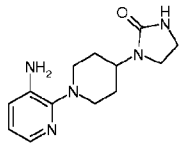
[00490] The title Intermediate 106.1 (870 mg, 3.31 mmol, 98%) was obtained as a colourless solid from Intermediate 106.2 (980 mg, 3.38 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.11 min; MS: m/z 261.2 $[M+H]^+$.

[00491] Intermediate 106.2: 1-[1-(2-Nitro-phenyl)-piperidin-4-yl]-imidazolidin-2-one.



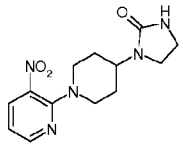
[00492] The title Intermediate 106.2 (988 mg, 3.37 mmol, 95%) was obtained from 1-fluoro-2-nitrobenzene (500 mg, 3.54 mmol) and 1-piperidin-4-yl-imidazolidin-2-one (802 mg, 3.90 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.50 min; MS: m/z 291.2 $[M+H]^+$.

[00493] Intermediate 107.1: 1-(3'-Amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-imidazolidin-2-one.



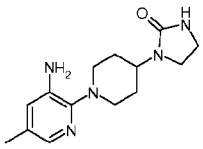
[00494] The Intermediate 107.1 (513 mg, 1.94 mmol, 93%) was obtained as a pink solid from Intermediate 107.2 (607 mg, 2.08 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 2.94 min; LC-MS: m/z 262.2 $[M+H]^+$.

[00495] Intermediate 107.2: 1-(3'-Nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-imidazolidin-2-one.



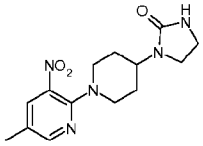
[00496] The title Intermediate 107.2 (607 mg, 2.06 mmol, 54%) was obtained from 2-chloro-3-nitropyridine (607 mg, 3.83 mmol) and 1-piperidin-4-yl-imidazolidin-2-one (945 mg, 4.59 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.16 min; LC-MS: m/z 292.2 $[M+H]^+$.

[00497] Intermediate 108.1: 1-(3'-Amino-5'-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-imidazolidin-2-one.



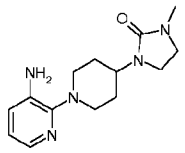
[00498] The title Intermediate 108.1 (634 mg, 2.30 mmol, 97%) was obtained as a red solid from Intermediate 108.2 (723 mg, 2.37 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.16 min; LC-MS: m/z 276.2 $[M+H]^+$.

[00499] Intermediate 108.2: 1-(5'-Methyl-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-imidazolidin-2-one.



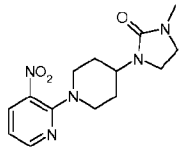
[00500] The title Intermediate 108.2 (723 mg, 2.37 mmol, 67%) was obtained from 2-chloro-5-methyl-3-nitropyridine (610 mg, 3.53 mmol) and 1-piperidin-4-yl-imidazolidin-2-one (800 mg, 3.89 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.48 min; LC-MS: m/z 306.1 $[M+H]^+$.

[00501] Intermediate 109.1: 1-(3'-Amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-3-methyl-imidazolidin-2-one.



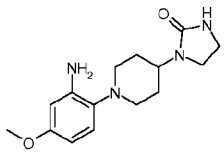
[00502] The title Intermediate 109.1 (1.13 g, 4.10 mmol, 77%) was obtained as a pink solid from Intermediate 109.2 (1.63 g, 5.34 mmol), analogously to Intermediate 1.1. HPLC: $^{B}t_{Ret}$ = 3.86 min; LC-MS: m/z 276.3 $[M+H]^+$.

[00503] Intermediate 109.2: 1-Methyl-3-(3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-imidazolidin-2-one.



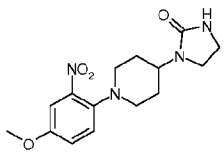
[00504] The title Intermediate 109.2 (1.65 g, 5.-40 mmol, 95%) was obtained from 2-chloro-3-nitropyridine (920 mg, 5.69 mmol) and 1-methyl-3-piperidin-4-yl-imidazolidin-2-one (1.14 g, 6.26 mmol), analogously to Intermediate 1.2. HPLC: $^{B}t_{Ret}$ = 5.57 min; LC-MS: m/z 306.2 $[M+H]^+$.

[00505] Intermediate 110.1: 1-[1-(2-Amino-4-methoxy-phenyl)-piperidin-4-yl]-imidazolidin-2-one.



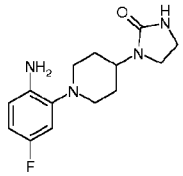
[00506] The title Intermediate 110.1 (334 mg, 1.08 mmol, 95%) was obtained as a colourless solid from Intermediate 110.2 (419 mg, 1.138 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.24 min; LC-MS: m/z 291.2 $[M+H]^+$.

[00507] Intermediate 110.2: 1-[1-(4-Methoxy-2-nitro-phenyl)-piperidin-4-yl]-imidazolidin-2-one.



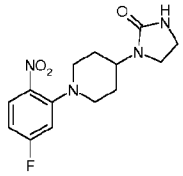
[00508] The title Intermediate 110.2 (419 mg, 1.14 mmol, 36%) was obtained from 1-chloro-4-methoxy-2-nitrobenzene (600 mg, 3.20 mmol) and 1-piperidin-4-yl-imidazolidin-2-one (724 mg, 3.52 mmol), analogously to Intermediate 1.2. HPLC: $^{B}t_{Ret}$ = 4.45 min; LC-MS: m/z 321.1 $[M+H]^+$.

[00509] Intermediate 111.1: 1-[1-(2-Amino-5-fluoro-phenyl)-piperidin-4-yl]-imidazolidin-2-one.



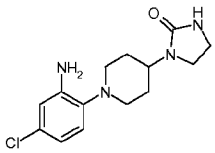
[00510] The title Intermediate 111.1 (340 mg, 1.22 mmol, 100%) was obtained as a colourless solid from Intermediate 111.2 (375 mg, 1.216 mmol), analogously to Intermediate 1.1. HPLC: $^{C}t_{Ret}$ = 4.00 min; LC-MS: m/z 279.0 $[M+H]^+$.

[00511] Intermediate 111.2: 1-[1-(5-Fluoro-2-nitro-phenyl)-piperidin-4-yl]-imidazolidin-2-one.



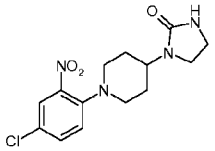
[00512] The title Intermediate 111.2 (380 mg, 1.23 mmol, 51%) was obtained from 1,4-difluoro-1-nitrobenzene (391 mg, 2.43 mmol) and 1-piperidin-4-yl-imidazolidin-2-one (500 mg, 2.43 mmol), analogously to Intermediate 1.2. HPLC: $^{C}t_{Ret}$ = 5.77 min; LC-MS: m/z 308.1 $[M+H]^+$.

[00513] Intermediate 112.1: 1-[1-(2-Amino-4-chloro-phenyl)-piperidin-4-yl]-imidazolidin-2-one.



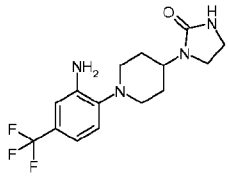
[00514] The title Intermediate 112.1 (937 mg, 2.70 mmol, 83%) was obtained as a colourless solid from Intermediate 112.2 (1.06 g, 3.26 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.79 min; LC-MS: m/z 295.1 $[M+H]^+$.

[00515] Intermediate 112.2: 1-[1-(4-Chloro-2-nitro-phenyl)-piperidin-4-yl]-imidazolidin-2-one.



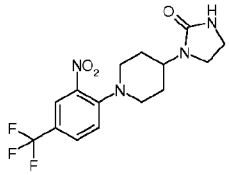
[00516] The title Intermediate 112.2 (1.06 g, 3.26 mmol, 96%) was obtained from 4-chloro-1-fluoro-2-nitrobenzene (594 mg, 3.38 mmol) and 1-piperidin-4-yl-imidazolidin-2-one (766 mg, 3.72 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 5.04 min; LC-MS: m/z 325.1 $[M+H]^+$.

[00517] Intermediate 113.1: 1-[1-(2-Amino-4-trifluoromethyl-phenyl)-piperidin-4-yl]-imidazolidin -2-one.



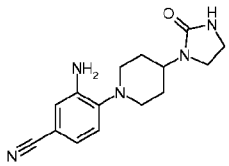
[00518] The title Intermediate 113.1 (1.08 g, 3.29 mmol, 91%) was obtained as a yellowish solid from Intermediate 113.2 (1.30 g, 3.63 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 4.44 min; LC-MS: m/z 329.2 $[M+H]^+$.

[00519] Intermediate 113.2: 1-[1-(2-Nitro-4-trifluoromethyl-phenyl)-piperidin-4-yl]-imidazolidin-2-one.



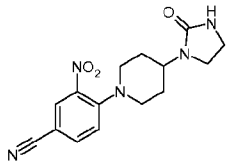
[00520] The title Intermediate 113.2 (1.30 g, 3.63 mmol, 94%) was obtained from 1-fluoro-2-nitro-4-(trifluoromethyl)benzene (805 mg, 3.85 mmol) and 1-piperidin-4-yl-imidazolidin-2-one (871 mg, 4.23 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 5.07 min; LC-MS: m/z 359.1 $[M+H]^+$.

[00521] Intermediate 114.1: 3-Amino-4-[4-(2-oxo-imidazolidin-1-yl)-piperidin-1-yl]-benzonitrile.



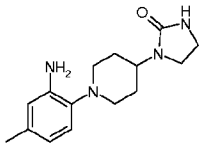
[00522] The title Intermediate 114.1 (923 mg, 3.23 mmol, 94%) was obtained as an orange solid from Intermediate 114.2 (1.09 g, 3.46 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 4.00 min; LC-MS: m/z 286.2 $[M+H]^+$.

[00523] Intermediate 114.2: 3-Nitro-4-[4-(2-oxo-imidazolidin-1-yl)-piperidin-1-yl]-benzonitrile.



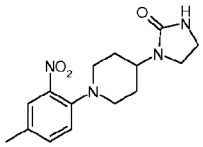
[00524] The title Intermediate 114.2 (1.09 g, 3.46 mmol, 93%) was obtained from 4-fluoro-3-nitro-4-benzonitrile (618 mg, 3.72 mmol) and 1-piperidin-4-yl-imidazolidin-2-one (842 mg, 4.09 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.40 min; LC-MS: m/z 316.1 $[M+H]^+$.

[00525] Intermediate 115.1: 1-[1-(2-Amino-4-methyl-phenyl)-piperidin-4-yl]-imidazolidin-2-one.



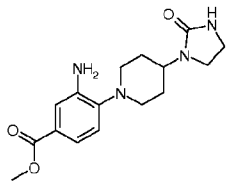
[00526] The title Intermediate 115.1 (1.2 g, 4.37 mmol, 98%) was obtained as a red solid from Intermediate 115.2 (1.36 g, 4.47 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.36 min; LC-MS: m/z 275.3 $[M+H]^+$.

[00527] Intermediate 115.2: 1-[1-(4-Methyl-2-nitro-phenyl)-piperidin-4-yl]-imidazolidin-2-one.



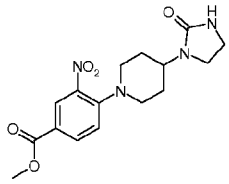
[00528] The title Intermediate 115.2 (1.36 g, 4.47 mmol, 85%) was obtained from 1-fluoro-4-methyl-2-nitrobenzene (811 mg, 5.23 mmol) and 1-piperidin-4-yl-imidazolidin-2-one (1183 mg, 5.75 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.75 min; LC-MS: m/z 305.2 $[M+H]^+$.

[00529] Intermediate 116.1: 3-Amino-4-[4-(2-oxo-imidazolidin-1-yl)-piperidin-1-yl]-benzoic acid methyl ester.



[00530] The title Intermediate 116.1 (818 mg, 2.57 mmol, 93%) was obtained as a colourless solid from Intermediate 116.2 (963 mg, 2.76 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.63 min; LC-MS: m/z 319.2 $[M+H]^+$.

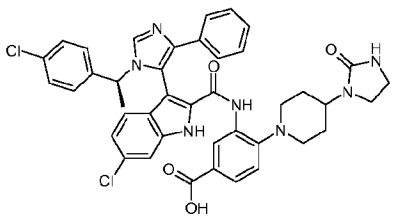
[00531] Intermediate 116.2: 3-Nitro-4-[4-(2-oxo-imidazolidin-1-yl)-piperidin-1-yl]-benzoic acid methyl ester.



[00532] The title Intermediate 116.2 (963 g, 2.76 mmol, 92%) was obtained from methyl 4-fluoro-3-nitrobenzoate (600 mg, 3.01 mmol) and 1-piperidin-4-yl-imidazolidin-2-one (682 mg, 3.31 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.63 min; LC-MS: m/z 349.2 $[M+H]^+$.

Example 117

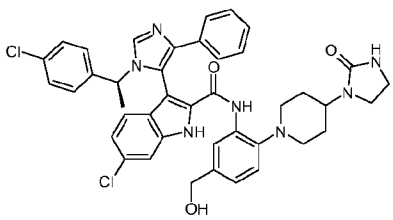
3-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-[4-(2-oxo-imidazolidin-1-yl)-piperidin-1-yl]-benzoic acid.



[00533] To a suspension of Example 116 (45 mg, 0.058 mmol) in THF/MeOH (0.29/0.29 mL) was added a 1 M aqueous solution of NaOH (0.29 mL, 0.29 mmol) at RT. After 30 min a 2 M aqueous solution of NaOH (0.1 mL, 0.2 mmol) was added and the reaction was stirred at RT for 2.5 h and 10 min at 40° C. The reaction mixture was concentrated *in vacuo*, diluted with water and acidified to pH 2-3 using 1N HCl. The resulting reaction micture was extracted with DCM (3x) and EtOAc (3x), the combined organic phases were dried using $MgSO_4$, filtered and concentrated to yield the title Example 137 (17 mg, 0.022 mmol, 39%) as a slightly yellow solid. HPLC: $^{A}t_{Ret}$ = 4.83; LC-MS: m/z 762.3 $[M+H]^+$.

Example 118

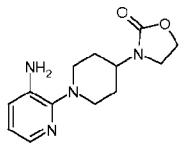
6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {5-hydroxymethyl-2-[4-(2-oxo-imidazolidin-1-yl)-piperidin-1-yl]-phenyl}-amide.



[00534] To a suspension of Example 116 (44 mg, 0.057 mmol) in EtOH (1 mL) was added $NaBH_4$ (43 mg, 1.14 mmol) and the reaction mixture was stirred at RT for 18 h. Additional $NaBH_4$ (50 mg) was added and the reaction mixture was stirred at 50° C for 3 h. Crushed ice was added and the slurry was extracted with EtOAc (3x), the combined organic phases were dried using MgSO4, filtered and concentrated. The crude product was purified by silica gel column

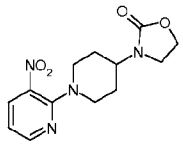
chromatography (eluting with a gradient of DCM:MeOH = 100:0 to 80:20) yielding the title Example 118 (5 mg, 6.68 μmol, 12%) as a colourless solid. HPLC: $^{A}t_{Ret}$ = 4.72; LC-MS: m/z 748.2 $[M+H]^+$.

[00535] Intermediate 119.1: 3-(3'-Amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-oxazolidin-2-one.



[00536] The title Intermediate 119.1 (290 mg, 1.095 mmol, 35%) was obtained as a colourless solid from Intermediate 119.2 (910 mg, 3.11 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 2.97 min; MS: m/z 263.2 $[M+H]^+$.

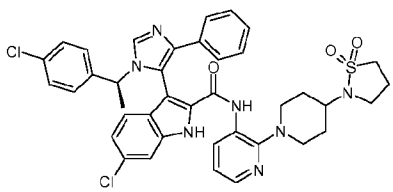
[00537] Intermediate 119.2: 3-(3'-Nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-oxazolidin-2-one.



[00538] The title Intermediate 119.2 (910 mg, 3.08 mmol, 98%) was obtained from 2-chloro-3-nitropyridine methyl (500 mg, 3.15 mmol) and 3-(piperidin-4-yl)oxazolidin-2-one (590 mg, 3.47 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.24 min; LC-MS: m/z 293.1 $[M+H]^+$.

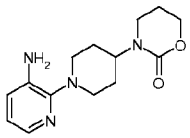
Example 120

6-chloro-3-(1-((S)-1-(4-chlorophenyl)ethyl)-4-phenyl-1H-imidazol-5-yl)-N-(2-(4-(1,1-dioxidoisothiazolidin-2-yl)piperidin-1-yl)pyridin-3-yl)-1H-indole-2-carboxamide



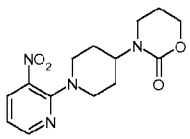
[00539] To a solution of Example 2 (108 mg, 0.149 mmol) in DMF (1 mL) was added NaH (59.7 mg, 1.493 mmol), followed by 3-chloropropane-1-sulfonyl chloride (31.7 mg, 0.022 mL, 0.179 mmol) and the reaction mixture was stirred at RT for 1 h. The reaction mixture was poured on crushed ice and the slurry was extracted with EtOAc, the combined organic phases were washed with water, dried using $MgSO_4$, filtered and concentrated. The crude product was purified by reversed phase prep-HPLC (gradient elution, MeCN/water + 0.1% TFA). Fractions containing pure material were combined, concentrated and the resulting aqueous mixture was neutralized with a saturated solution of $NaHCO_3$, followed by extraction with DCM. The organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness to yield the title Example 120 (25 mg, 0.033 mmol, 22%) as a colourless solid. HPLC: $^{A}t_{Ret}$ = 4.67; LC-MS: m/z 753.9 $[M+H]^+$.

[00540] Intermediate 125.1: 3-(3'-Amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-[1,3] oxazinan-2-one.



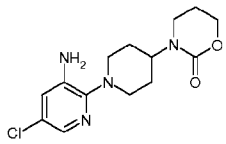
[00541] The title Intermediate 125.1 (756 mg, 2.74 mmol, 88%) was obtained as a colourless solid from Intermediate 125.2 (950 mg, 2.74 mmol), analogously to Intermediate 1.1. HPLC: $^{B}t_{Ret}$ = 3.63 min; LC-MS: m/z 277.1 $[M+H]^+$.

[00542] Intermediate 125.2: 3-(3'-Nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-[1,3]oxazinan -2-one.



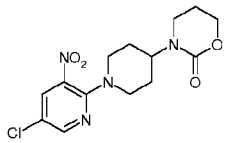
[00543] The title Intermediate 125.2 (950 g, 3.10 mmol, quantitative) was obtained from 2-chloro-3-nitropyridine (500 mg, 3.09 mmol) and 3-(piperidin-4-yl)-1,3-oxazinan-2-one (626 mg, 3.40 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 5.43 min; LC-MS: m/z 307.1 $[M+H]^+$.

[00544] Intermediate 126.1: 3-(3'-Amino-5'-chloro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-[1,3]oxazinan-2-one.



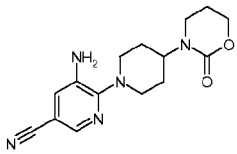
[00545] The title Intermediate 126.1 (1.80 g, 5.50 mmol, 88%) was obtained as a dark solid from Intermediate 126.2 (2.12 g, 6.22 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.54 min; LC-MS: m/z 311.3 $[M+H]^+$.

[00546] Intermediate 126.2: 3-(5'-Chloro-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-[1,3]oxazinan-2-one.



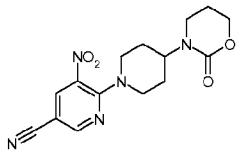
[00547] The title Intermediate 126.2 (2.12 g, 5.91 mmol, 95%) was obtained from 2,5-dichloro-3-nitropyridine (1.20 g, 6.22 mmol) and 3-(piperidin-4-yl)-1,3-oxazinan-2-one (1.26 g, 6.84 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.87 min; LC-MS: m/z 341.2 $[M+H]^+$.

[00548] Intermediate 127.1: 3'-Amino-4-(2-oxo-[1,3]oxazinan-3-yl)-3,4,5,6-tetrahydro-2H-[1,2'] bipyridinyl-5'-carbonitrile



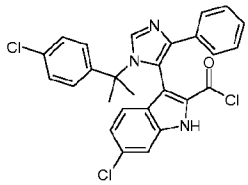
[00549] The title Intermediate 127.1 (1.07 g, 2.85 mmol, 46%, 80% purity) was obtained as a dark solid from Intermediate 127.2 (2.12 g, 6.22 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 4.30 min; LC-MS: m/z 301.3 $[M+H]^+$.

[00550] Intermediate 127.2: 3'-Nitro-4-(2-oxo-[1,3]oxazinan-3-yl)-3,4,5,6-tetrahydro-2H-[1,2'] bipyridinyl-5'-carbonitrile.



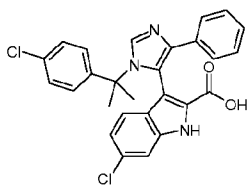
[00551] The title Intermediate 127.2 (2.04 g, 5.87 mmol, 97%) was obtained from 4-fluoro-3-nitrobenzonitrile (1.0 g, 6.02 mmol) and 3-(piperidin-4-yl)-1,3-oxazinan-2-one (1.22 g, 6.62 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.50 min; LC-MS: m/z 331.2 $[M+H]^+$.

[00552] Intermediate 128.1: 6-Chloro-3-{3-[1-(4-chloro-phenyl)-1-methyl-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl chloride.



[00553] To a suspension of Intermediate 128.2 (340 mg, 0.693 mmol) in dry DCM (3 mL) was added drop wise a total of $(COCl)_2$ (1.31 mL, 14.97 mmol) at RT. The suspension was heated up to 80 °C for 2 h. The reaction mixture was allowed to cool to RT, was evaporated to dryness followed by sonication in DCM and evaporation of solvent. The residue was dried under high vacuum at 50 °C yielding the title Intermediate 128.1 (376 mg, 0.702 mmol, quant) as a yellow solid. LC-MS: $^{A}t_{Ret}$ = 1.11 min (methyl ester of 128.1); LC-MS: m/z 501.9 [methyl ester of 128.1 + H]$^+$.

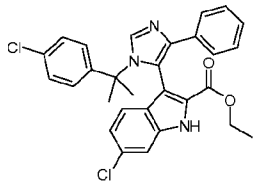
[00554] Intermediate 128.2: 6-Chloro-3-{3-[1-(4-chloro-phenyl)-1-methyl-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid.



[00555] To a mixture of Intermediate 128.3 (1.43 g, 2.76 mmol) in EtOH (14 mL) was added 2 M aqueous solution of NaOH (13.79 mL, 27.6 mmol) at RT and the reaction mixture was heated to 90 °C for 40 min. The reaction mixture was cooled, concentrated, slowly acidified to PH 6-7 using 4M HCl to form a suspension. The suspension was filtered and the solid residue was

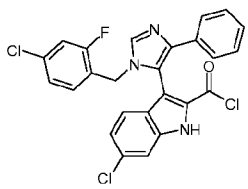
washed with water and dried. The remaining solid was taken up in MeCN, stirred for 1h, filtered and re-suspended in DCM, sonicated for 2 min, evaporated and dried to yield the title Intermediate 128.2 (1.186 g, 2.419 mmol, 88%) as a colourless solid. HPLC: $^{A}t_{Ret}$ = 4.83 min; LC-MS: m/z 488.0 $[M+H]^+$.

[00556] Intermediate 128.3: 6-Chloro-3-{3-[1-(4-chloro-phenyl)-1-methyl-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid ethyl ester.



[00557] A mixture of Intermediate 1.6 (1.25 g, 4.97 mmol), 1-(4-chloro-phenyl)-1-methyl-ethylamine (927 mg, 5.46 mmol), Et_3N (2.08 mL, 14.90 mmol) and 1-(isocyano-phenyl-methanesulfonyl)-4-methyl-benzene (1.25 g, 4.60 mmol) in EtOH (27 mL) were heated at 65 °C. After stirring over night further NEt_3 (0.6 mL) and 1-(isocyano-phenyl-methanesulfonyl)-4-methyl-benzene (370 mg, 1.36 mmol) were added and thr reaction mixture was heated at 60 °C for another night. The reaction mixture was concentrated *in vacuo*, extracted with EtOAc and aqueous $NaHCO_3$. The combined organic phases were washed with brine, dried using $MgSO_4$ and evaporated *in vacuo*. The crude product was purified by silica gel column chromatography (eluting with a gradient of EtOAc:DCM = 90:10 to 100:0) yielding the title Intermediate 128.3 (1.43 g, 2.76 µmol, 56%) as a colorless solid. HPLC: $^{A}t_{Ret}$ = 5.18 min; LC-MS: m/z 518.1 $[M+H]^+$.

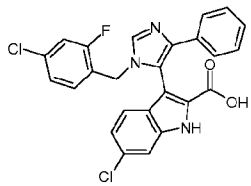
[00558] Intermediate 129.1: 6-Chloro-3-[3-(4-chloro-2-fluoro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carbonyl chloride.



[00559] To a suspension of Intermediate 129.2 (300 mg, 0.625 mmol) in dry DCM (5 mL) was added drop wise $(COCl)_2$ (0.82 mL, 9.37 mmol) at RT. The suspension was heated to 50 °C for 2 h. The reaction mixture was allowed to cool to RT, was evaporated to dryness followed

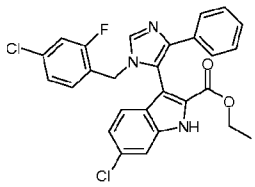
by sonication in DCM and evaporation of solvent (2x). The residue was dried under high vacuum at 50 °C yielding the title Intermediate 129.1 (376 mg, 0.702 mmol, quant) as a beige foam. HPLC: $^{B}t_{Ret}$ = 6.41 min (methyl ester of 129.1); LC-MS: m/z 494.0 [methyl ester of 129.1 + H]$^{+}$.

[00560] Intermediate 129.2: 6-Chloro-3-[3-(4-chloro-2-fluoro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid.



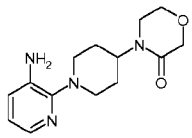
[00561] To a mixture of Intermediate 129.3 (1.80 g, 3.47 mmol) in EtOH (20 mL) was added 4 M aqueous solution of NaOH (2.0 mL, 8.0 mmol) at RT and the reaction mixture was heated to reflux for 3 h. The reaction mixture was cooled, concentrated, slowly acidified using 8M HCl. The reaction mixture was extracted with EtOAc and concentrated. The remaining solid was filtered and washed with Et_2O and dried to yield the title Intermediate 129.2 (1.3 g, 2.68 mmol, 77%) as a colourless solid. HPLC: $^{A}t_{Ret}$ = 4.76 min; MS: m/z 479.9 [M+H]$^{+}$.

[00562] Intermediate 129.3: 6-Chloro-3-[3-(4-chloro-2-fluoro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid ethyl ester.



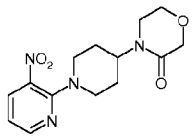
[00563] A mixture of Intermediate 1.6 (1.0 g, 3.97 mmol), (4-chloro-2-fluorophenyl)methanamine (779 mg, 3.97 mmol), Et_3N (2.77 mL, 19.87 mmol) and 1-(isocyano-phenyl-methanesulfonyl)-4-methyl-benzene (1.294 g, 4.77 mmol) in EtOH (20 mL) were heated to reflux over night. The reaction mixture was concentrated *in vacuo*, extracted with EtOAc and aqueous $NaHCO_3$. The combined organic phases were washed with water and brine and evaporated to dryness. The crude product was purified by silica gel column chromatography (eluting with DCM:EtOAc = 95:05) yielding the title Intermediate 129.3 (1.8 g, 3.44 mmol, 87%) as a colourless solid. HPLC: $^{A}t_{Ret}$ = 5.07 min; MS: m/z 507.9 [M+H]$^{+}$.

[00564] Intermediate 130.1: 4-(3'-Amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-morpholin-3-one.



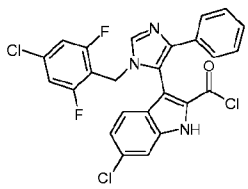
[00565] The title Intermediate 130.1 (820 mg, 2.82 mmol, 92%) was obtained as a colourless solid from Intermediate 130.2 (940 mg, 3.07 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 2.95 min; MS: m/z 277.2 $[M+H]^+$.

[00566] Intermediate 130.2: 4-(3'-Nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-morpholin-3-one.



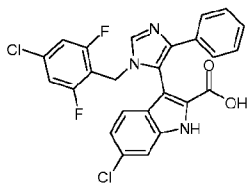
[00567] The title Intermediate 130.2 (940 mg, 3.04 mmol, 96%) was obtained from 2-chloro-3-nitropyridine methyl (500 mg, 3.15 mmol) and 4-(piperidin-4-yl)morpholin-3-one (639 mg, 3.47 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.17 min; LC-MS: m/z 307.1 $[M+H]^+$.

[00568] Intermediate 132.1: 6-Chloro-3-[3-(4-chloro-2,6-difluoro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carbonyl chloride.



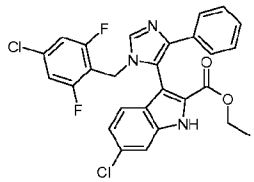
[00569] To a suspension of Intermediate 132.2 (350 mg, 0.702 mmol) in dry DCM (2 mL) was added drop wise $(COCl)_2$ (0.74 mL, 8.43 mmol) at RT. The suspension was heated to 50 °C for 1.5 h. The reaction mixture was allowed to cool to RT, was evaporated and dried under high vacuum yielding the title Intermediate 132.1 (350 mg, 0.610 mmol, 87%) as a beige solid. HPLC: $^{C}t_{Ret}$ = 6.29 min (methyl ester of 132.1); LC-MS: m/z 511.9 [methyl ester of 132.1 + H]$^+$.

[00570] Intermediate 132.2: 6-Chloro-3-[3-(4-chloro-2,6-difluoro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid.



[00571] To a mixture of Intermediate 132.3 (1.54 g, 2.90 mmol) in EtOH (10 mL) was added 4 M aqueous solution of NaOH (2.0 mL, 8.0 mmol) at RT and the reaction mixture was heated to reflux for 2 h. The reaction mixture was cooled, concentrated, slowly acidified using 8M HCl, extracted with EtOAc and concentrated. The remaining solid was filtered and washed with EtOAc and dried to yield the title Intermediate 132.2 (1.29 g, 2.47 mmol, 86%) as a colourless solid. HPLC: $^{A}t_{Ret}$ = 4.72 min; MS: m/z 497.9 $[M+H]^+$.

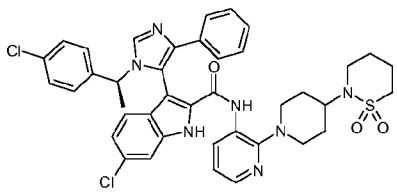
[00572] Intermediate 132.3: 6-Chloro-3-[3-(4-chloro-2,6-difluoro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid ethyl ester.



[00573] A mixture of Intermediate 1.6 (1.0 g, 3.97 mmol), 4-chloro-2,6-difluorophenyl)methanamine (706 mg, 3.97 mmol), Et_3N (2.22 mL, 15.89 mmol) and 1-(isocyano-phenyl-methanesulfonyl)-4-methyl-benzene (1.294 g, 4.77 mmol) in EtOH (20 mL) were heated to reflux for 4.5 h. The reaction mixture was concentrated *in vacuo*, extracted with EtOAc and aqueous $NaHCO_3$. The combined organic phases were washed with water and brine and evaporated to dryness. The crude product was purified by silica gel column chromatography (eluting with a gradient of DCM:EtOAc = 100:00 to 80:20) yielding the title Intermediate 132.3 (1.54 g, 2.90 mmol, 73%) as a colourless solid. HPLC: $^{A}t_{Ret}$ = 5.04 min; MS: m/z 525.9 $[M+H]^+$.

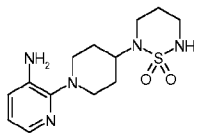
Example 133

6-chloro-3-(1-((S)-1-(4-chlorophenyl)ethyl)-4-phenyl-1H-imidazol-5-yl)-N-(2-(4-(1,1-dioxido-1,2-thiazinan-2-yl)piperidin-1-yl)pyridin-3-yl)-1H-indole-2-carboxamide.



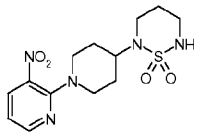
[00574] The title Example 133 (25 mg, 0.033 mmol, 23%) was obtained from Example 2 (103.5 mg, 0.143 mmol) and excess of 4-chlorobutane-1-sulfonyl chloride, analogously to Example 120. HPLC: $^{A}t_{Ret}$ = 4.797; LC-MS: m/z 767.9 $[M+H]^+$.

[00575] Intermediate 134.1: 2-(1-(3-aminopyridin-2-yl)piperidin-4-yl)-1,2,6-thiadiazinane 1,1-dioxide.



[00576] The title intermediate (330 mg, 1.06 mmol, 43%) was obtained as a colourless solid from Intermediate 134.2 (850 mg, 2.49 mmol), analogously to Intermediate 1.1. HPLC: $^{B}t_{Ret}$ = 3.85 min; LC-MS: m/z 312.1 $[M+H]^+$.

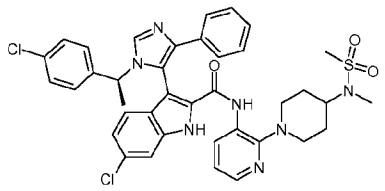
[00577] Intermediate 134.2: 2-(1-(3-nitropyridin-2-yl)piperidin-4-yl)-1,2,6-thiadiazinane 1,1-dioxide.



[00578] The title Intermediate 134.2 (855 mg, 2.50 mmol, quantitative) was obtained from 2-chloro-3-nitropyridine (500 mg, 3.09 mmol) and 2-piperidin-4-yl-[1,2,6]thiadiazinane 1,1-dioxide (586 mg, 2.67 mmol), analogously to Intermediate 1.2. HPLC: $^{B}t_{Ret}$ = 5.91 min; LC-MS: m/z 342.1 $[M+H]^+$.

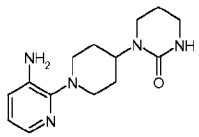
Example 136

6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(methane-sulfonyl-methyl-amino)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide.



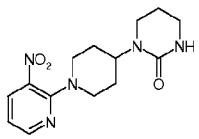
[00579] The title Example 136 (85 mg, 0.114 mmol, 70%) was obtained from Example 54 (120 mg, 0.163 mmol) and methanesulfonyl chloride (28.0 mg, 0.019 mL, 0.244 mmol), analogously to Example 3. HPLC: ^{A}tRet = 4.71; LC-MS: m/z 741.8 [M+H]+.

[00580] Intermediate 137.1: 1-(3'-Amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-tetrahydro-pyrimidin-2-one.



[00581] The title Intermediate 137.1 (378 mg, 1.373 mmol, 68%) was obtained as a colourless solid from Intermediate 137.2 (615 mg, 2.014 mmol), analogously to Intermediate 1.1. HPLC: $^{B}t_{Ret}$ = 3.71 min; LC-MS: m/z 276.3 $[M+H]^{+}$.

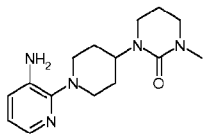
[00582] Intermediate 137.2: 1-(3'-Nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-tetrahydro-pyrimidin-2-one.



[00583] The title Intermediate 137.2 (620 mg, 2.031 mmol, quant) was obtained from 2-chloro-3-nitropyridine (320 mg, 2.018 mmol) and 1-(piperidin-4-yl)tetrahydropyrimidin-2(1H)-

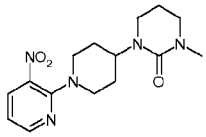
one (407 mg, 2.22 mmol), analogously to Intermediate 1.2. HPLC: $^{B}t_{Ret}$ = 5.36 min; LC-MS: m/z 306.2 $[M+H]^+$.

[00584] Intermediate 138.1: 1-(3'-Amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-3-methyl-tetrahydro-pyrimidin-2-one.



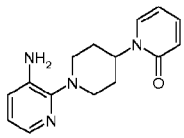
[00585] The title Intermediate 138.1 (640 mg, 2.212 mmol, 58%) was obtained as a pinkish solid from Intermediate 138.2 (1.22 g, 3.82 mmol), analogously to Intermediate 1.1. HPLC: $^{B}t_{Ret}$ = 4.04 min; LC-MS: m/z 290.2 $[M+H]^+$.

[00586] Intermediate 138.2: 1-Methyl-3-(3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-tetrahydro-pyrimidin-2-one.



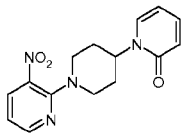
[00587] The title Intermediate 138.2 (1.23 g, 3.85 mmol, 88%) was obtained from 2-chloro-3-nitropyridine (705 mg, 4.36 mmol) and 1-methyl-3-piperidin-4-yl-tetrahydro-pyrimidin-2-one (946 mg, 4.79 mmol), analogously to Intermediate 1.2. HPLC: $^{B}t_{Ret}$ = 5.74 min; LC-MS: m/z 320.2 $[M+H]^+$.

[00588] Intermediate 139.1: 3"-Amino-3',4',5',6'-tetrahydro-2'H-[1,4';1',2"]terpyridin-2-one.



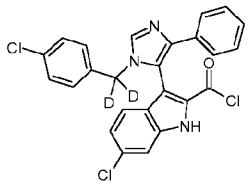
[00589] The title Intermediate 139.1 (185 mg, 0.684 mmol, 61%) was obtained as a colourless solid from Intermediate 139.2 (337 mg, 1.122 mmol), analogously to Intermediate 1.1. HPLC: $^{B}t_{Ret}$ = 3.80 min; LC-MS: m/z 271.2 $[M+H]^+$.

[00590] Intermediate 139.2: 3"-Nitro-3',4',5',6'-tetrahydro-2'H-[1,4';1',2"]terpyridin-2-one.



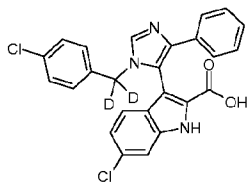
[00591] The title Intermediate 139.2 (337 mg, 1.122 mmol, 91%) was obtained from 2-chloro-3-nitropyridine (197 mg, 1.228 mmol) and 1-(piperidin-4-yl)pyridin-2(1H)-one (946 mg, 4.79 mmol), analogously to Intermediate 1.2. HPLC: $^{B}t_{Ret}$ = 5.57 min; LC-MS: m/z 301.1 $[M+H]^+$.

[00592] Intermediate 140.1: 6-Chloro-3-[3-(4-chloro-phenyl-d_2-methyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carbonyl chloride.



[00593] To a suspension of Intermediate 140.2 (400 mg, 0.861 mmol) in dry DCM (8 mL) was added drop wise $(COCl)_2$ (1.13 mL, 12.92 mmol) at RT. The suspension was heated to 50 °C for 1 h. The reaction mixture was allowed to cool to RT, was evaporated to dryness followed by sonication in DCM and evaporation of solvent. The residue was dried under high vacuum yielding the title Intermediate 140.1 (451 mg, 0.934 mmol, quant.) as a beige solid. HPLC: $^{A}t_{Ret}$ = 4.98 min (methyl ester of 140.1); LC-MS: m/z 478.0 [methyl ester of 140.1 + H]$^+$.

[00594] Intermediate 140.2: 6-Chloro-3-[3-(4-chloro- phenyl-d_2-methyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid.

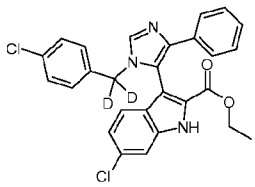


[00595] To a mixture of Intermediate 140.3 (1.40 g, 2.84 mmol) in EtOH (14 mL) was added 2 M aqueous solution of NaOH (14.2 mL, 28.44 mmol) at RT and the reaction mixture was heated to 70 °C for 1 h. The reaction mixture was cooled and slowly acidified using 4M HCl.

[00596] The slurry was extracted with EtOAc, the combined organic phases were washed with water and brine, dried using $MgSO_4$, filtered and concentrated. The remaining solid was taken up in MeOH and evaporated, followed by suspensiding it in DCM and evaporation to

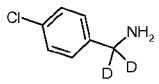
dryness to yield the title Intermediate 140.2 (1.22 g, 2.63 mmol, 92%) as a slighly yellow solid. HPLC: $^{A}t_{Ret}$ = 4.77 min; LC-MS: m/z 464.0 $[M+H]^+$.

[00597] Intermediate 140.3: 6-Chloro-3-[3-(4-chloro- phenyl-d_2-methyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid ethyl ester.



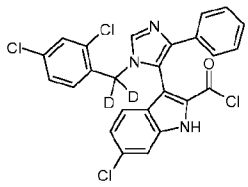
[00598] A mixture of Intermediate 1.6 (865 mg, 3.44 mmol), Intermediate 140.4 (543 mg, 3.78 mmol), Et_3N (1.43 mL, 10.31 mmol) and 1-(isocyano-phenyl-methanesulfonyl)-4-methyl-benzene (863 mg, 3.18 mmol) in EtOH (19 mL) were heated at 65 °C for 5 h. The reaction mixture was cooled to RT, concentrated *in vacuo*, extracted with EtOAc and aqueous $NaHCO_3$. The combined organic phases were washed with brine, dried using $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by silica gel column chromatography (eluting with a gradient of DCM:EtOAc = 90:10 to 0:100) yielding the title Intermediate 140.3 (1.40 g, 2.84 mmol, 83%) as a slightly yellow foam. HPLC: $^{A}t_{Ret}$ = 5.08 min; LC-MS: m/z 492.0 $[M+H]^+$.

[00599] Intermediate 140.4: 4-Chloro-(phenyl-d_2-methyl)amine.



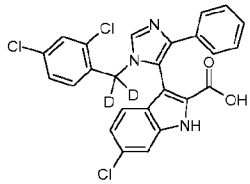
[00600] To a suspension of sodium borodeuteride (0.438 g, 10.47 mmol) in THF (3 mL) was added TFA (0.806 mL, 10.47 mmol) at RT over a period of 10 min, followed by the addition of a solution of 4-chlorobenzonitrile (1.20 g, 8.72 mmol) in THF (3 mL) at RT. The reaction mixture was stirred at RT for 23 h. D_2O (2 mL) was added dropwise followed by water (12 mL) and the reaction mixture was concentrated. The slurry was extracted with DCM, the combined organic phases were dried using $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by silica gel column chromatography (eluting with DCM:MeOH + 0.2 % NH_3 = 90:10) yielding the title Intermediate 140.4 (543 mg, 3.78 mmol, 43%) an colorless oil. HPLC: $^{A}t_{Ret}$ = 3.14 min; LC-MS: m/z 144.1 $[M+H]^+$.

[00601] Intermediate 144.1: 6-Chloro-3-[3-(2,4-dichloro-phenyl-d_2-methyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carbonyl chloride.



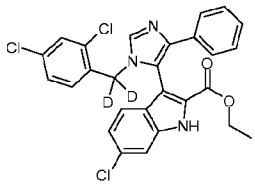
[00602] To a suspension of Intermediate 144.2 (220 mg, 0.441 mmol) in dry DCM (5 mL) was added drop wise $(COCl)_2$ (0.772 mL, 8.82 mmol) at RT. The suspension was heated to 50 °C for 1.5 h. The reaction mixture was allowed to cool to RT, was evaporated to dryness followed by sonication in DCM and evaporation of solvent (twice). The residue was dried under high vacuum yielding the title Intermediate 144.1 (232 mg, 0.449 mmol, quant.) as a brown solid. HPLC: $^{A}t_{Ret}$ = 5.08 min (methyl ester of 144.1); LC-MS: m/z 513.9 [methyl ester of 144.1 + H]$^+$.

[00603] Intermediate 144.2: 6-Chloro-3-[3-(2,4-dichloro-phenyl-d_2-methyl)-5-phenyl-3H-imidazol -4-yl]-1H-indole-2-carboxylic acid.



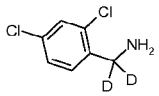
[00604] To a mixture of Intermediate 144.3 (1.14 g, 2.164 mmol) in EtOH (11 mL) was added 2 M aqueous solution of NaOH (10.82 mL, 21.64 mmol) at RT and the reaction mixture was heated to 80 °C for 1 h. The reaction mixture was cooled, concentrated and slowly acidified using 4M HCl. The slurry was extracted with EtOAc, the combined organic phases were dried using MgSO4, filtered and the residue was washed several times with DCM, EtOAc and THF. The solvent was concentrated and the remaining product was washed with MeCN, filtered and dried to yield the title Intermediate 144.2 (972 mg, 1.93 mmol, 89%) as a beige solid. HPLC: $^{A}t_{Ret}$ = 4.86 min; LC-MS: m/z 500.0 [M+H]$^+$.

[00605] Intermediate 144.3: 6-Chloro-3-[3-(2,4-dichloro-phenyl-d_2-methyl)-5-phenyl-3H-imidazol -4-yl]-1H-indole-2-carboxylic acid ethyl ester.



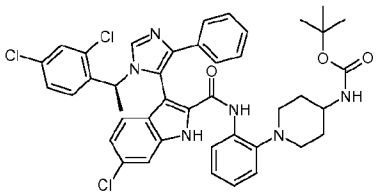
[00606] A mixture of Intermediate 1.6 (808 mg, 3.21 mmol), Intermediate 144.4 (600 mg, 3.37 mmol), Et_3N (1.34 mL, 9.63 mmol) and 1-(isocyano-phenyl-methanesulfonyl)-4-methyl-benzene (1.045 g, 3.85 mmol) in EtOH (32 mL) were heated at 65 °C for 4.5 h. The reaction mixture was cooled to RT, concentrated *in vacuo*, extracted with EtOAc and aqueous $NaHCO_3$. The combined organic phases were washed with brine, dried using $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by silica gel column chromatography (eluting with a gradient of DCM:EtOAc = 90:10 to 0:100) yielding the title Intermediate 144.3 (1.14 g, 2.16 mmol, 67%) as a beige solid. HPLC: $^{A}t_{Ret}$ = 5.18 min; LC-MS: m/z 527.9 $[M+H]^+$.

[00607] Intermediate 144.4: 2,4-Dichloro-(phenyl-d_2-methyl)amine.



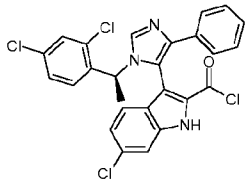
[00608] To a suspension of sodium borodeuteride (0.584 g, 13.95 mmol) in THF (8 mL) was added TFA (1.075 mL, 13.95 mmol) in THF (4 mL) at RT over a period of 10 min, followed by the addition of a solution of 2,4-dichlorobenzonitrile (2.00 g, 11.63 mmol) in THF (4 mL) at 0 °C. The reaction mixture was allowed to come to RT and stirred at RT for 3 h. D_2O (3 mL) was added dropwise followed by water (15 mL) and the reaction mixture was concentrated. The slurry was extracted with DCM, the combined organic phases were dried using $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by silica gel column chromatography (eluting with a ggradient of DCM:MeOH + 0.2 % NH_3 = 95:05 to 90:10) yielding the title Intermediate 144.4 (1.104 g, 6.20 mmol, 53%) a a colourless oil. HPLC: $^{A}t_{Ret}$ = 3.37 min; LC-MS: m/z 179.3 $[M+H]^+$.

[00609] Intermediate 148.1: (1-{2-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-phenyl}-piperidin-4-yl)-carbamic acid tert-butyl ester.



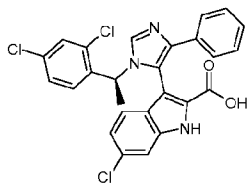
[00610] The title Intermediate 148.1 (831 mg, 1.037 mmol, 67%) was obtained from Intermediate 148.2 (900 mg, 1.54 mmol) and Intermediate 148.5 (496 mg, 1.70 mmol), analogously to Example 1. HPLC: $^{A}t_{Ret}$ = 5.62; LC-MS: m/z 785.3 $[M+H]^{+}$.

[00611] Intermediate 148.2: 6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl chloride.



[00612] To a suspension of Intermediate 148.3 (1.39 g, 2.72 mmol) in dry DCM (32 mL) was added drop wise $(COCl)_2$ (3.57 mL, 40.8 mmol) at RT. The suspension was heated to 55 °C. After a period of 3.5 h an the mixture was allowed to cool to RT, was evaporated to dryness followed by sonication in DCM and evaporation of solvent (2 times). The residue was dried under high vacuum yielding the title Intermediate 148.2 (1.47 g, 2.53 mmol, 93%) as a yellow solid. HPLC: $^{A}t_{Ret}$ = 4.98 min (methyl ester of 148.2); LC-MS: m/z 525.9 [methyl ester of 148.2 + H] $^{+}$.\

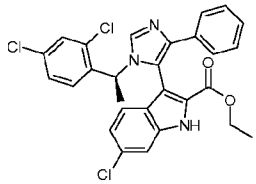
[00613] Intermediate 148.3: 6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid.



[00614] To a mixture of Intermediate 148.4 (1.80 g, 3.34 mmol) in EtOH (20 mL) was added 2 M aqueous solution of NaOH (20 mL, 40 mmol) at RT and the reaction mixture was heated to 100 °C for 1 h. The reaction mixture was concentrated to approx 10 mL, cooled to 0°C and slowly acidified using HCl_{conc} (4.5 mL). The reaction mixture was extracted with EtOAc, the combined organic phases were washed with water, dried using Na_2SO_4, filtered and concentrated

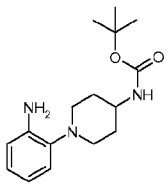
until crystallization occured. The resulting crystalls were filtered and dried in an vacuum oven at 60°C over night to yield the title Intermediate 148.3 (900 mg, 1.762 mmol, 53%) as a colourless solid. HPLC: $^{B}t_{Ret}$ = 6.36 min; LC-MS: m/z 511.8 $[M+H]^+$.

[00615] Intermediate 148.4: 6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid ethyl ester.



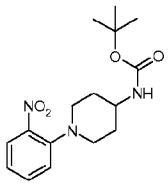
[00616] A mixture of Intermediate 1.6 (1.2 g, 4.77 mmol), (S)-1-(2,4-dichloro-phenyl)-ethylamine (906 mg, 4.77 mmol), Et_3N (2.00 mL, 17.30 mmol) and 1-(isocyano-phenyl-methanesulfonyl)-4-methyl-benzene (1.55 g, 5.72 mmol) in EtOH (30 mL) were heated at 60 °C. After stirring for 22 h, the reaction mixture was concentrated *in vacuo*, poured into aqueous $NaHCO_3$ and was extracted with EtOAc. The organic phase was washed with water, dried using Na_2SO_4 and evaporated *in vacuo*. The crude product was purified by silica gel column chromatography (eluting with EtOAc:hexanes = 1:1) yielding the title Intermediate 148.4 (1.83 g, 3.40 mmol, 71%) as a beige foam. HPLC: $^{B}t_{Ret}$ = 6.81 min; LC-MS: m/z 537.9 $[M+H]^+$.

[00617] Intermediate 148.5: [1-(2-Amino-phenyl)-piperidin-4-yl]-carbamic acid tert-butyl ester.



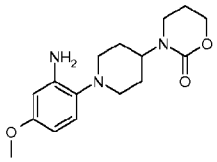
[00618] The title Intermediate 148.5 (6.21 g, 21.31 mmol, 92%) was obtained as a colourless solid from Intermediate 148.6 (7.44 g, 23.15 mmol), analogously to Intermediate 1.1. HPLC: $^{B}t_{Ret}$ = 5.11 min; LC-MS: m/z 292.2 $[M+H]^+$.

[00619] Intermediate 148.6: 1-(2-Nitro-phenyl)-piperidin-4-yl]-carbamic acid tert-butyl ester.



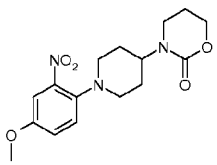
[00620] The title Intermediate 148.6 (7.45 g, 23.18 mmol, 99%) was obtained from 1-fluoro-2-nitrobenzene (3.30 g, 23.39 mmol) and piperidin-4-yl-carbamic acid tert-butyl ester (5.37 g, 25.70 mmol), analogously to Intermediate 1.2. HPLC: $^{B}t_{Ret}$ = 7.12 min; LC-MS: m/z 322.2 $[M+H]^+$.

[00621] Intermediate 154.1: 3-[1-(2-Amino-4-methoxy-phenyl)-piperidin-4-yl]-[1,3]oxazinan-2-one.



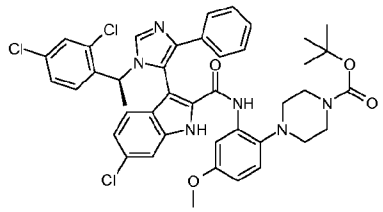
[00622] The title Intermediate 154.1 (1.49 g, 4.88 mmol, 97%) was obtained as a grey solid from Intermediate 154.2 (1.68 g, 4.88 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.35 min; LC-MS: m/z 306.4 $[M+H]^+$.

[00623] Intermediate 154.2: 3-[1-(4-Methoxy-2-nitro-phenyl)-piperidin-4-yl]-[1,3]oxazinan-2-one.



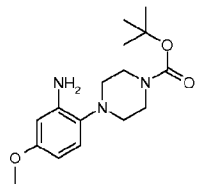
[00624] The title Intermediate 154.2 (1.68 g, 5.01 mmol, 86%) was obtained from 1-fluoro-4-methoxy-2-nitrobenzene (1.00 g, 5.84 mmol) and 3-piperidin-4-yl-[1,3]oxazinan-2-one (1.40 g, 7.60 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.61 min; LC-MS: m/z 336.3 $[M+H]^+$.

[00625] Intermedaite 155.1: 4-{2-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-methoxy-phenyl}-piperazine-1-carboxylic acid tert-butyl ester.



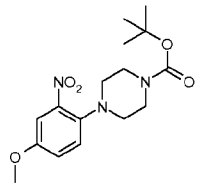
[00626] The title Intermedaite 155.1 (434 mg, 0.526 mmol, 61%) was obtained from Intermediate 148.2 (500 mg, 0.869 mmol) and Intermediate 155.2 (294 mg, 0.956 mmol), analogously to Example 1. HPLC: $^{A}t_{Ret}$ = 5.77; LC-MS: m/z 801.0 $[M+H]^+$.

[00627] Intermediate 155.2: 4-(2-Amino-4-methoxy-phenyl)-piperazine-1-carboxylic acid tert-butyl ester.



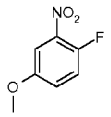
[00628] The title Intermediate 155.2 (1.78 g, 5.62 mmol, 99%) was obtained as a colourless solid from Intermediate 155.3 (1.92 g, 5.69 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 4.24 min; LC-MS: m/z 308.3 $[M+H]^+$.

[00629] Intermediate 155.3: 4-(4-Methoxy-2-nitro-phenyl)-piperazine-1-carboxylic acid tert-butyl ester.



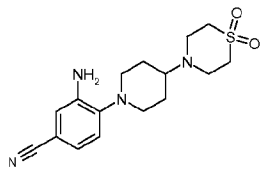
[00630] The title Intermediate 155.3 (1.92 g, 5.50 mmol, 87%) was obtained from Intermediate 155.4 (1.09 g, 6.35 mmol) and 3-piperidin-4-yl-[1,3]oxazinan-2-one (1.30 g, 6.98 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 5.52 min; LC-MS: m/z 338.1 $[M+H]^+$.

[00631] Intermediate 155.4: 1-Fluoro-4-methoxy-2-nitro-benzene.



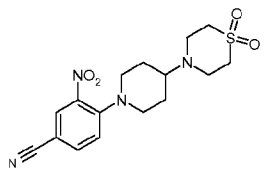
[00632] To a solution of 4-fluoro-3-nitro-phenol (4.62 g, 29.4 mmol) in acetone (160 mL) was added K_2CO_3 (12.19 g, 88 mmol) and methyl iodide (6.26 g, 2.76 mL, 44.1 mmol) at 0°C. The reaction mixture was allowed to warm to RT and continued to stirr over night upon which precipitation occured. The Solid was filtered and purified by silica gel column chromatography (eluting with a gradient of EtOAc:heptane = 05:95 to 100:0) yielding the title Intermediate 180.3 (4.33 g, 24.80 mmol, 84%) as a yellow solid. HPLC: $^{A}t_{Ret}$ = 4.71 min; LC-MS: m/z 141.0 $[M\text{-}OMe]^+$.

[00633] Intermediate 156.1: 3-amino-4-(4-(1,1-dioxidothiomorpholino)piperidin-1-yl)benzonitrile.



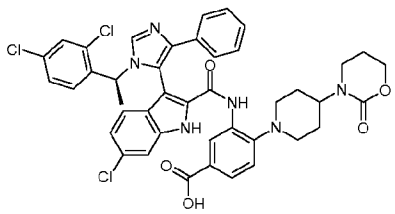
[00634] The title Intermediate 156.1 (1.04 g, 3.02 mmol, 96%) was obtained as a yellow solid from Intermediate 156.2 (1.15 g, 3.16 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.41 min; LC-MS: m/z 335.1 $[M+H]^+$.

[00635] Intermediate 156.2: 4-(4-(1,1-dioxidothiomorpholino)piperidin-1-yl)-3-nitrobenzonitrile.



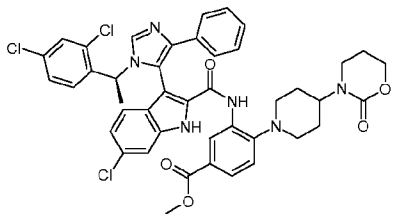
[00636] The title Intermediate 156.2 (1.12 g, 2.98 mmol, 99%) was obtained from 4-fluoro-3-nitrobenzonitrile (500 mg, 3.01 mmol) and 4-piperidin-4-yl-thiomorpholine 1,1-dioxide (920 mg, 3.61 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 3.69 min; LC-MS: m/z 365.0 $[M+H]^+$.

[00637] Intermediate 157.1: 3-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-benzoic acid.



[00638] The title Intermediate 157.1 (60 mg, 0.072 mmol, 43%) was obtained from Intermediate 157.2 (138 mg, 0.167 mmol), analogously to Example 67. HPLC: $^{A}t_{Ret}$ = 4.96; LC-MS: m/z 813.0 $[M+H]^+$.

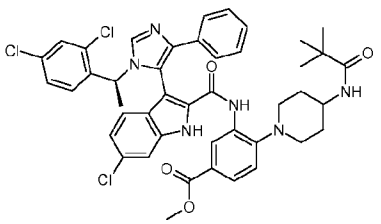
[00639] Intermediate 157.2: 3-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-benzoic acid methyl ester.



[00640] The title Intermediate 157.2 (155 mg, 0.176 mmol, 31%) was obtained from Intermediate 148.2 (300 mg, 0.567 mmol) and Intermediate 66.1 (138 mg, 0.567 mmol), analogously to Example 1. HPLC: $^{A}t_{Ret}$ = 5.27; LC-MS: m/z 827.0 $[M+H]^+$.

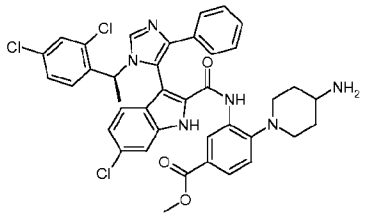
Example 160

3-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol -4-yl}-1H-indole-2-carbonyl)-amino]-4-[4-(2,2-dimethyl-propionylamino)-piperidin-1-yl]-benzoic acid methyl ester.



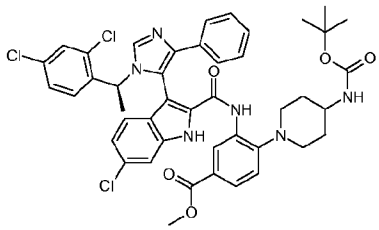
[00641] The title Example 160 (90 mg, 0.107 mmol, 33%) was obtained from Intermediate 160.1 (250 mg, 0.321 mmol) and pivaloyl chloride (58.10 mg, 0.059 mL, 0.482 mmol), analogously to Example 3. HPLC: $^{A}t_{Ret}$ = 5.45; LC-MS: m/z 827.0 $[M+H]^+$.

[00642] Intermediate 160.1: 4-(4-Amino-piperidin-1-yl)-3-[(6-chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-benzoic acid methyl ester.



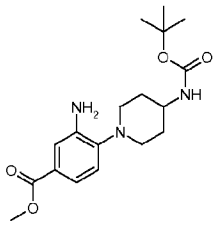
[00643] The title Intermediate 160.1 (902 mg, 1.124 mmol, quant.) was obtained from Intermediate 160.2 (945 mg, 1.122 mmol), analogously to Example 2. HPLC: $^{A}t_{Ret}$ = 4.61; LC-MS: m/z 743.1 $[M+H]^+$.

[00644] Intermediate 160.2: 4-(4-tert-Butoxycarbonylamino-piperidin-1-yl)-3-[(6-chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-benzoic acid methyl ester.



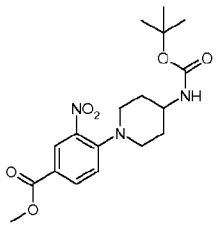
[00645] The title Intermediate 160.2 (955 mg, 1.11 mmol, 64%) was obtained from Intermediate 148.2 (970 mg, 1.741 mmol) and Intermediate 160.3 (669 mg, 1.915 mmol), analogously to Example 1. HPLC: $^{A}t_{Ret}$ = 5.67; LC-MS: m/z 843.3$[M+H]^+$.

[00646] Intermediate 160.3: 3-Amino-4-(4-tert-butoxycarbonylamino-piperidin-1-yl)-benzoic acid methyl ester.



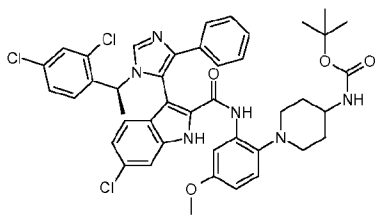
[00647] The title Intermediate 160.3 (6.60 g, 24.61 mmol, quant.) was obtained as a colourless solid from Intermediate 160.4 (9.34 g, 24.62 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 5.90 min; LC-MS: m/z 350.3 $[M+H]^+$.

[00648] Intermediate 160.4: 4-(4-tert-Butoxycarbonylamino-piperidin-1-yl)-3-nitro-benzoic acid methyl ester.



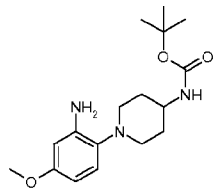
[00649] The title Intermediate 160.4 (9.34 g, 24.62 mmol, quant.) was obtained as yellow crystalls from methyl 4-chloro-3-nitrobenzoate (5.40 g, 24.55 mmol) and tert-butyl piperidin-4-ylcarbamate (5.46 g, 27.0 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 7.14 min; LC-MS: m/z 380.2 $[M+H]^+$.

[00650] Intermediate 162.1: (1-{2-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-methoxy-phenyl}-piperidin-4-yl)-carbamic acid tert-butyl ester.



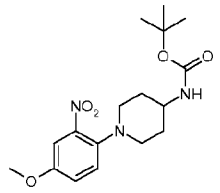
[00651] The title Intermediate 162.1 (475 mg, 0.583 mmol, 60%) was obtained from Intermediate 148.2 (555 mg, 0.970 mmol) and Intermediate 162.2 (355 mg, 1.139 mmol), analogously to Example 1. HPLC: $^{A}t_{Ret}$ = 5.54; LC-MS: m/z 815.2 $[M+H]^+$.

[00652] Intermediate 162.2: [1-(2-Amino-4-methoxy-phenyl)-piperidin-4-yl]-carbamic acid tert-butyl ester.



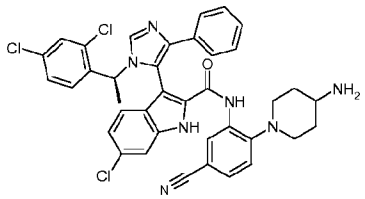
[00653] The title Intermediate 162.2 (3.22 g, 10.02 mmol, quant.) was obtained as a brown foam from Intermediate 162.3 (3.48 g, 9.90 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 4.05 min; LC-MS: m/z 322.2 $[M+H]^+$.

[00654] Intermediate 162.3: [1-(4-Methoxy-2-nitro-phenyl)-piperidin-4-yl]-carbamic acid tert-butyl ester.



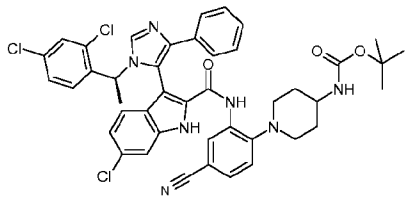
[00655] The title Intermediate 162.3 (3.48 g, 9.90 mmol, 83%) was obtained as an orange solid from 1-fluoro-4-methoxy-2-nitrobenzene (2.03 g, 11.86 mmol) and tert-butyl piperidin-4-yl-carbamate (3.09 g, 15.42 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 5.23 min; LC-MS: m/z 352.2 $[M+H]^+$.

[00656] Intermediate 165.1: 6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-amino-piperidin-1-yl)-5-cyano-phenyl]-amide HCl salt.



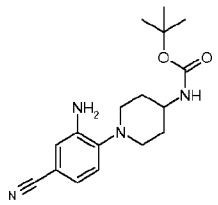
[00657] The title intermediate 165.1 (1.19 g, 1.47 mmol, quantitative) was obtained from intermediate 165.2 (1.19 g, 1.47 mmol), analogously to Example 2. HPLC: $^{A}t_{Ret}$ = 4.48; LC-MS: m/z 710.0 $[M+H]^+$.

[00658] Intermediate 165.2: (1-{2-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-cyano-phenyl}-piperidin-4-yl)-carbamic acid tert-butyl ester.



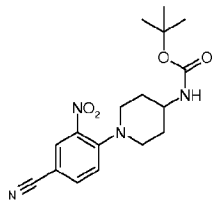
[00659] The title Intermediate 165.2 (1.19 g, 1.47 mmol, 50%) was obtained from Intermediate 148.2 (1.70 g, 2.96 mmol) and Intermediate 165.3 (1.118 g, 3.25 mmol), analogously to Example 1. HPLC: $^{A}t_{Ret}$ = 5.62; LC-MS: m/z 810.0 $[M+H]^+$.

[00660] Intermediate 165.3: [1-(2-Amino-4-cyano-phenyl)-piperidin-4-yl]-carbamic acid tert-butyl ester.



[00661] The title Intermediate 165.3 (2.76 g, 8.03 mmol, 94%) was obtained as a colourless solid from Intermediate 165.4 (2.97 g, 8.57 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 4.90 min; LC-MS: m/z 317.2 $[M+H]^+$.

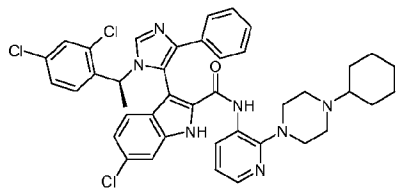
[00662] Intermediate 165.4: [1-(4-Cyano-2-nitro-phenyl)-piperidin-4-yl]-carbamic acid tert-butyl ester.



[00663] The title Intermediate 165.4 (2.97 g, 8.57 mmol, 95%) was obtained from 4-fluoro-3-nitrobenzonitrile (1.50 g, 9.03 mmol) and tert-butyl piperidin-4-ylcarbamate (1.98 g, 9.93 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 5.15 min; LC-MS: m/z 347.0 $[M+H]^+$.

Example 171

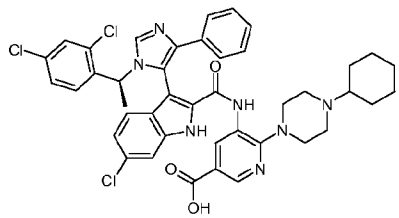
6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-cyclohexyl-piperazin-1-yl)-pyridin-3-yl]-amide.



[00664] A solution of Intermediate 148.2 (150 mg, 0.294 mmol) and Intermediate 11.1 (76 mg, 0.294 mmol) was cooled to -20 °C and $POCl_3$ (49.5 mg, 0.030 mL, 0.323 mmol) was added. The suspension was stirred at -20 °C for 20 min, warmed to 0 °C and stirred for additional 30 min. The reaction mixture was diluted with water, $NaHCO_3$ and EtOAc. Phases were separated and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine and dried using Na_2SO_4, filtered and evaporated. The crude product was purified by silica gel column chromatography (eluting with a gradient of EtOAc:EtOH + 2.5% NH_3 = 99:1 to 90:10) yielding the title Example 171 (72.8 mg, 0.097 mmol, 33%) as a colourless solid. HPLC: ${}^{C}t_{Ret}$ = 6.47; LC-MS: m/z 754.2 $[M+H]^+$.

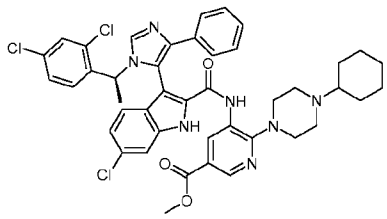
Example 172

5-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol -4-yl}-1H-indole-2-carbonyl)-amino]-6-(4-cyclohexyl-piperazin-1-yl)-nicotinic acid.



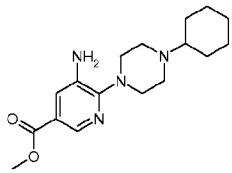
[00665] The title Example 172 (721 mg, 0.877 mmol, 96%) was obtained from Intermediate 172.1 (744 mg, 0.917 mmol), analogously to Example 117. HPLC: $^{A}t_{Ret}$ = 4.67; LC-MS: m/z 798.0 $[M+H]^+$.

[00666] Intermediate 172.1: 5-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-6-(4-cyclohexyl-piperazin-1-yl)-nicotinic acid methyl ester .



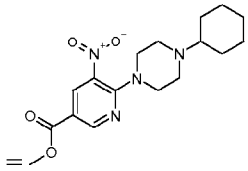
[00667] The title Intermediate 172.1 (744 mg, 0.890 mmol, 39%) was obtained from Intermediate 148.2 (1.35 g, 2.296 mmol) and Intermediate 172.3 (0.846 g, 2.35 mmol), analogously to Example 1. HPLC: $^{A}t_{Ret}$ = 4.87; LC-MS: m/z 812.0 $[M+H]^+$.

[00668] Intermediate 172.3: 5-Amino-6-(4-cyclohexyl-piperazin-1-yl)-nicotinic acid methyl ester.



[00669] The title Intermediate 172.3 (958 mg, 2.92 mmol, 95%) was obtained as a colourless solid from Intermediate 172.4 (1.069 g, 3.07 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.62 min; LC-MS: m/z 319.2 $[M+H]^+$.

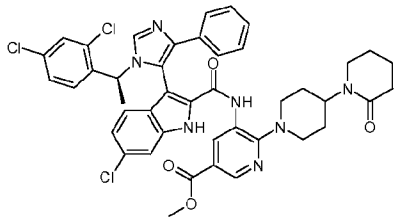
[00670] Intermediate 172.4: 6-(4-Cyclohexyl-piperazin-1-yl)-5-nitro-nicotinic acid methyl ester.



[00671] The title Intermediate 172.4 (1.069 g, 2.98 mmol, 86%) was obtained from methyl 6-chloro-5-nitronicotinate (753 mg, 3.48 mmol) and 1-cyclohexylpiperazine (878 mg, 5.22 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.09 min; LC-MS: m/z 349.2 $[M+H]^+$.

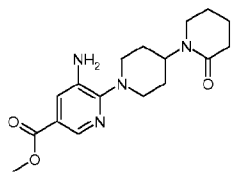
Example 176

3"-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-2-oxo-3,4,5,6,3',4',5',6'-octahydro-2H,2'H-[1,4';1',2"]terpyridine-5"-carboxylic acid methyl ester.



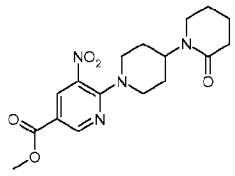
[00672] The title Example 176 (1.13 g, 1.369 mmol, 58%) was obtained from Intermediate 148.2 (1.385 g, 2.355 mmol) and Intermediate 176.1 (1.07 g, 2.77 mmol), analogously to Example 1. HPLC: $^{A}t_{Ret}$ = 5.18; LC-MS: m/z 826.3 $[M+H]^+$.

[00673] Intermediate 176.1: 3"-Amino-2-oxo-3,4,5,6,3',4',5',6'-octahydro-2H,2'H-[1,4';1',2"] terpyridine-5"-carboxylic acid methyl ester.



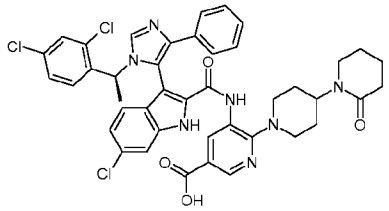
[00674] The title Intermediate 176.1 (1.14 g, 2.95 mmol, 76%) was obtained as a colourless solid from Intermediate 176.2 (1.40 g, 3.86 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.48 min; LC-MS: m/z 333.4 $[M+H]^+$.

[00675] Intermediate 176.2: 3"-Nitro-2-oxo-3,4,5,6,3',4',5',6'-octahydro-2H,2'H-[1,4';1',2"] terpyridine-5"-carboxylic acid methyl ester.



[00676] The title Intermediate 176.2 (1.40 g, 3.86 mmol, 91%) was obtained from methyl 6-chloro-5-nitronicotinate (915 mg, 4.22 mmol) and 1,4'-bipiperidin-2-one (847 mg, 4.65 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.95 min; LC-MS: m/z 363.3 $[M+H]^+$.

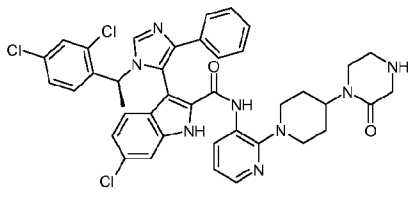
[00677] Intermediate 177.1: 3"-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-2-oxo-3,4,5,6,3',4',5',6'-octahydro-2H,2'H-[1,4';1',2"]terpyridine-5"-carboxylic acid.



[00678] The title Intermediate 177.1 (392 mg, 0.483 mmol, 35%) was obtained from Example 176 (1.13 g, 1.369 mmol), analogously to Example 117. HPLC: $^{A}t_{Ret}$ = 4.84; LC-MS: m/z 812.0 $[M+H]^+$.

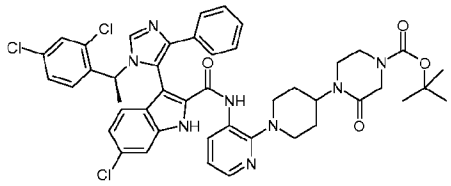
Example 178

6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(2-oxo-piperazin-1-yl)-3,4,5,6-tetrahydro-2H-[1,2'] bipyridinyl-3'-yl]-amide.



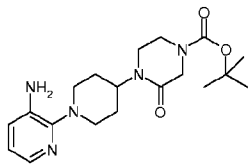
[00679] The title Example 178 (346 mg, 0.417 mmol, 96%) was obtained from Intermediate 178.1 (379 mg, 0.437 mmol), analogously to Example 2. HPLC: $^{A}t_{Ret}$ = 4.17; LC-MS: m/z 769.0 $[M+H]^+$.

[00680] Intermediate 178.1: 4-{3'-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl}-3-oxo-piperazine-1-carboxylic acid tert-butyl ester.



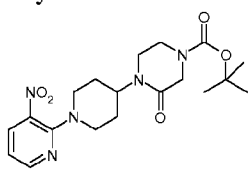
[00681] The title Intermediate 178.1 (379 g, 0.423 mmol, 67%) was obtained from Intermediate 148.2 (393 mg, 0.631 mmol) and Intermediate 178.2 (284 mg, 0.757 mmol), analogously to Example 1. HPLC: $^{A}t_{Ret}$ = 4.93; LC-MS: m/z 869.4 $[M+H]^+$.

[00682] Intermediate 178.2: 4-(3'-Amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-3-oxo-piperazine-1-carboxylic acid tert-butyl ester.



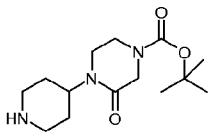
[00683] The title Intermediate 178.2 (1.03 g, 2.61 mmol, 94%) was obtained as a colourless solid from Intermediate 178.3 (1.12 g, 2.76 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.76 min; LC-MS: m/z 376.3 $[M+H]^+$.

[00684] Intermediate 178.3: 4-(3'-Nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-3-oxo-piperazine-1-carboxylic acid tert-butyl ester.



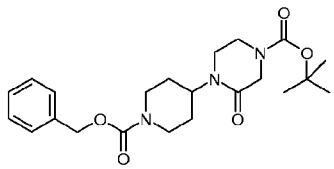
[00685] The title Intermediate 178.3 (1.12 g, 2.486 mmol, 80%) was obtained from 2-chloro-3-nitropyridine (540 mg, 3.41 mmol) and Intermediate 178.4 (878 mg, 3.10 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.96 min; LC-MS: m/z 406.0 $[M+H]^+$.

[00686] Intermediate 178.4: 3-Oxo-4-piperidin-4-yl-piperazine-1-carboxylic acid tert-butyl ester.



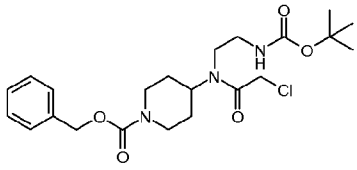
[00687] The title Intermediate 178.4 (5.66 g, 17.18 mmol, 86%) was obtained as a ellow resin by hydrogenation reaction of Intermediate 178.5 (8.33 g, 19.95 mmol) with H_2 gas and Pd/C 10% (1.0 g, 19.95 mmol) in MeOH (150 mL) at RT for 8 h. HPLC: $^{E}t_{Ret}$ = 0.49 min; LC-MS: m/z 284.3 $[M+H]^+$.

[00688] Intermediate 178.5: 4-(1-Benzyloxycarbonyl-piperidin-4-yl)-3-oxo-piperazine-1-carboxylic acid tert-butyl ester.



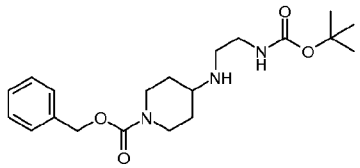
[00689] To a solution of Intermediate 178.6 (11.80 g, 26.00 mmol) in DMF (250 mL) was added potassium tert-butoxide (6.42 g, 57.20 mmol) and the reaction mixture was heated to 80°C over night. Toluene was added, the reaction was quenched with water and extreacted with toluene. The combined organic phases were dried using Na_2SO_4, filtered and concentrated to yield the title Intermediate 178.4 (8.14 g, 19.50mmol) as a yellow oil. HPLC: $^{E}t_{Ret}$ = 1.05 min; LC-MS: m/z 435.4 $[M+NH_4]^+$.

[00690] Intermediate 178.6: 4-[(2-tert-Butoxycarbonylamino-ethyl)-(2-chloro-acetyl)-amino]-piperidine-1-carboxylic acid benzyl ester.



[00691] To a solution of Intermediate 178.7 (27.30 g, 64.40 mmol) and DIPEA (24.96 g, 33.7 mL, 193.00 mmol) in DCM (300 mL) at 0°C was added chloroacetyl chloride (8.72 g, 6.15 mL, 77.00 mmol) dropwise and the reaction mixture was allowed to war to RT and stirred over night. The reaction mixture was diluted with DCM and extracted. The combined organic phases were washed with a saturated solution of $NaHCO_3$ and water, dried using Na_2SO_4, filtered and concentrated. The crude product was purified by silica gel column chromatography (eluting with a gradient of heptane:EtOAc = 100:00 to 00:100) yielding the title Example 178.6 (12.1 g, 26.70 mmol, 41%) as an orange foam. HPLC: $^{E}t_{Ret}$ = 1.08 min; LC-MS: m/z 471.3 $[M+NH_4]^+$.

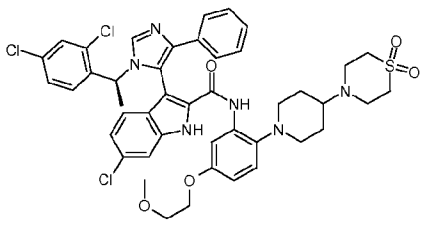
[00692] Intermediate 178.7: 4-(2-tert-Butoxycarbonylamino-ethylamino)-piperidine-1-carboxylic acid benzyl ester.



[00693] To a solution of 1-Z-4-piperidinone (15.0 g, 64.30 mmol) and N-Boc-ethylendiamine (10.51 g, 64.3 mmol) in DCM (200 mL) was added acetic acid (7.88 g, 5.51 mL, 131 mmol) and sodium triacetoxyborohydride (17.65 g, 79 mmol) portionwise at RT. The reaction mixture was stirred for 1.5 h, diluted with DCM, quenched with $NaHCO_3$ and extracted with DCM. The combined organic phases were washed with water, dried using Na_2SO_4, filtered and evaporated yielding the title Intermediate 178.7 (27.3 g, 64.4 mmol, 89%) as a yellow resin. HPLC: $^{E}t_{Ret}$ = 0.73 min; LC-MS: m/z 378.3 $[M+H]^+$.

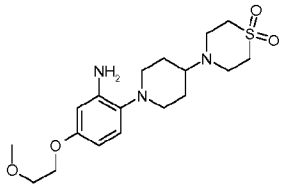
Example 180

6-chloro-3-(1-((S)-1-(2,4-dichlorophenyl)ethyl)-4-phenyl-1H-imidazol-5-yl)-N-(2-(4-(1,1-dioxidothiomorpholino)piperidin-1-yl)-5-(2-methoxyethoxy)phenyl)-1H-indole-2-carboxamide.



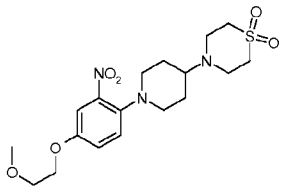
[00694] The title Example 180 (340 mg, 0.388 mmol, 70%) was obtained from Intermediate 148.2 (320 mg, 0.556 mmol) and Intermediate 180.1 (224 mg, 0.58 mmol), analogously to Example 1. HPLC: $^{B}t_{Ret}$ = 6.19; LC-MS: m/z 877.4 $[M+H]^+$.

[00695] Intermediate 180.1: 4-(1-(2-amino-4-(2-methoxyethoxy)phenyl)piperidin-4-yl)thiomorpholine 1,1-dioxide.



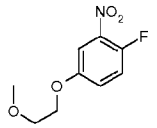
[00696] The title Intermediate 180.1 (395 mg, 1.03 mmol, 50%) was obtained as a beige solid from Intermediate 180.2 (850 mg, 2.05 mmol), analogously to Intermediate 1.1. HPLC: $^{B}t_{Ret}$ = 3.77 min; LC-MS: m/z 348.3 $[M+H]^+$.

[00697] Intermediate 180.2: 4-{1-[4-(2-Methoxy-ethoxy)-2-nitro-phenyl]-piperidin-4-yl}-thiomorpholine 1,1-dioxide.



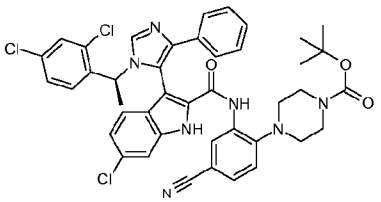
[00698] The title Intermediate 180.2 (857 mg, 2.07 mmol, 89%) was obtained from Intermediate 180.3 (500 mg, 2.32 mmol) and 4-piperidin-4-yl-thiomorpholine 1,1-dioxide (439 mg, 1.72 mmol), analogously to Intermediate 1.2. HPLC: $^{B}t_{Ret}$ = 4.76 min; LC-MS: m/z 414.3 $[M+H]^+$.

[00699] Intermediate 180.3: 1-Fluoro-4-(2-methoxy-ethoxy)-2-nitro-benzene.



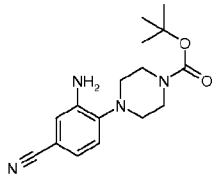
[00700] To a solution of 4-fluoro-3-nitrophenol (5.00 g, 31.20 mmol,) at 0 °C was added K2CO3 (12.93 g, 94.00 mmol) and 2-bromoethyl methyl ether (6.50 g, 4.40 mL, 46.80 mmol). After 30 min of stirring the suspension was allowed to war to RT and stirring was continued for 1 h. The reaction mixture was heated to 50 °C and stirred for 20 h. The suspension was filtered and the solvent was concentrated. The crude product was purified by silica gel column chromatography (eluting with DCM) yielding the title Intermediate 180.3 (2.12 g, 9.85 mmol, 32%) as a yellow oil. HPLC: $^{B}t_{Ret}$ = 6.05 min; LC-MS: m/z 215.0 $[M+H]^+$.

[00701] Intermediate 181.1: 4-{2-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-cyano-phenyl}-piperazine-1-carboxylic acid tert-butyl ester.



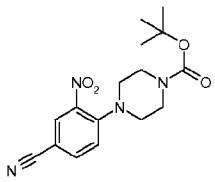
[00702] The title Intermediate 181.1 (134 mg, 0.16 mmol, 19%) was obtained from Intermediate 148.2 (500 mg, 0.87 mmol) and Intermediate 181.2 (289 mg, 0.95 mmol), analogously to Example 1. HPLC: $^{A}t_{Ret}$ = 5.63; LC-MS: m/z 796.0 $[M+H]^+$.

[00703] Intermediate 181.2: 4-(2-Amino-4-cyano-phenyl)-piperazine-1-carboxylic acid tert-butyl ester.



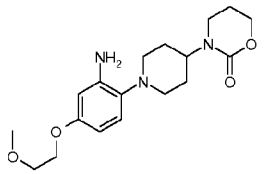
[00704] The title Intermediate 181.2 (2.02 g, 6.35 mmol, 100%) was obtained as a beige solid from Intermediate 181.3 (2.11 g, 6.35 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 5.02 min; LC-MS: m/z 303.0 $[M+H]^+$.

[00705] Intermediate 181.3: 4-(4-Cyano-2-nitro-phenyl)-piperazine-1-carboxylic acid tert-butyl ester.



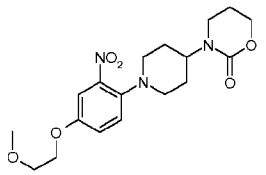
[00706] The title Intermediate 181.3 (2.11 g, 6.16 mmol, 90%) was obtained from 4-chloro-3-nitrobenzonitrile (1.40 g, 7.53 mmol) and nitrobenzonitrile (1.25 g, 6.85 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 5.24 min; LC-MS: m/z 333.2 $[M+H]^+$.

[00707] Intermediate 183.1: 3-{1-[2-Amino-4-(2-methoxy-ethoxy)-phenyl]-piperidin-4-yl}-[1,3] oxazinan-2-one.



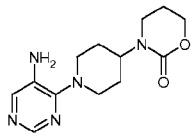
[00708] The title Intermediate 183.1 (1.02 g, 2.63 mmol, 90%) was obtained as a beige solid from Intermediate 183.2 (1.55 g, 2.85 mmol), analogously to Intermediate 1.1. HPLC: $^{D}t_{Ret}$ = 0.84 min; LC-MS: m/z 350.3 $[M+H]^+$.

[00709] Intermediate 183.2: 3-{1-[4-(2-Methoxy-ethoxy)-2-nitro-phenyl]-piperidin-4-yl}-[1,3] oxazinan-2-one.



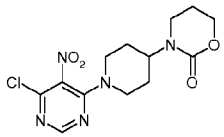
[00710] The title Intermediate 183.2 (1.55 g, 2.85 mmol, 62%) was obtained from Intermediate 180.3 (988 mg, 4.59 mmol) and 3-(piperidin-4-yl)-1,3-oxazinan-2-one (888 mg, 4.82 mmol), analogously to Intermediate 1.2. HPLC: $^{D}t_{Ret}$ = 1.05 min; LC-MS: m/z 380.3 $[M+H]^+$.

[00711] Intermediate 184.1: 3-[1-(5-Amino-pyrimidin-4-yl)-piperidin-4-yl]-[1,3]oxazinan-2-one.



[00712] The title Intermediate 184.1 (0.68 g, 2.20 mmol, 31%) was obtained as a brown solid from Intermediate 184.2 (2.42 g, 7.08 mmol), analogously to Intermediate 1.1. HPLC (SQ22): $^{X}t_{Ret}$ = 0.23 min; LC-MS: m/z 278.1 $[M+H]^+$.

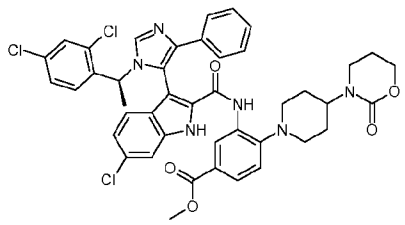
[00713] Intermediate 184.2: 3-[1-(6-Chloro-5-nitro-pyrimidin-4-yl)-piperidin-4-yl]-[1,3]oxazinan-2-one.



[00714] The title Intermediate 184.2 (2.42 g, 7.08 mmol, 69%) was obtained from 4,6-dichloro-5-nitropyrimidine (2.00 g, 10.31 mmol) and 3-(piperidin-4-yl)-1,3-oxazinan-2-one (1.90 g, 10.3 mmol), analogously to Intermediate 1.2. HPLC (SQ22): $^{X}t_{Ret}$ = 0.81 min; LC-MS: m/z 342.0 $[M+H]^+$.

Example 185

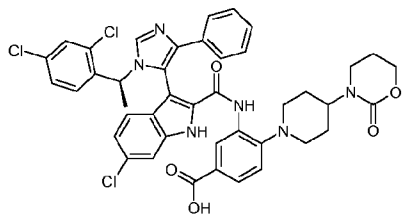
3-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol -4-yl}-1H-indole-2-carbonyl)-amino]-4-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-benzoic acid methyl ester.



[00715] The title Example 185 (1.33 g, 1.56 mmol, 74%) was obtained from Intermediate 148.2 (1.25 g, 2.12 mmol) and Intermediate 66.1 (0.78 g, 2.34 mmol), analogously to Example 1. HPLC: $^{A}t_{Ret}$ = 5.27; LC-MS: m/z 827.0 $[M+H]^+$.

Example 186

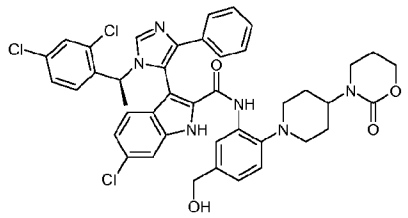
3-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol -4-yl}-1H-indole-2-carbonyl)-amino]-4-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-benzoic acid.



[00716] The title Example 186 (1.41 g, 1.68 mmol, 99%) was obtained from Example 185 (1.41 g, 1.70 mmol), analogously to Example 117. HPLC: $^{A}t_{Ret}$ = 4.96; LC-MS: m/z 813.0 $[M+H]^+$.

Example 187

6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {5-hydroxymethyl-2-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-phenyl}-amide.

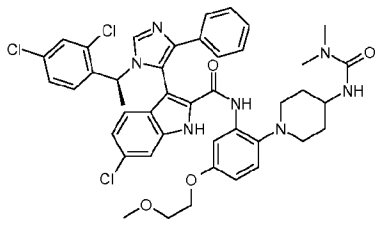


[00717] To a solution of Example 186 (130 mg, 0.160 mmol) in THF (2 mL) at 0 °C was added NEt_3 (24.30 mg, 0.033 mL, 0.240 mmol) and ethyl chloroformate (26.1 mg, 0.023 mL, 0.240 mmol). The reaction mixture was allowed to warm to RT and stirred for 2 h. The crude intermediate was filtered over a pad of celite and the residue was washed with THF. The filtrate was concentrated, diluted with EtOH (2 mL) and sodium borhydride (91 mg, 2.401 mmol) was

added at 0 °C. The reaction mixture was allowed to warm to RT, stirred for 2 h, quenched with water at 0 °C and extracted with DCM. The combined organic phases were dried using $MgSO_4$, filtered and evaporated. The crude product was purified by silica gel column chromatography (eluting with a gradient of DCM:MeOH = 100:0 to 80:20) yielding the title Example 187 (56 mg, 0.069 mmol, 43%) as a yellow solid. HPLC: $^{A}t_{Ret}$ = 4.81; LC-MS: m/z 799.0 $[M+H]^+$.

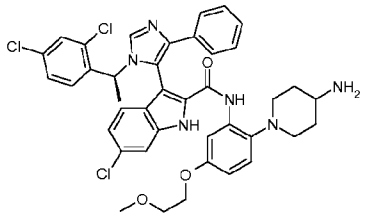
Example 189

6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-[4-(3,3-dimethyl-ureido)-piperidin-1-yl]-5-(2-methoxy-ethoxy)-phenyl]-amide.



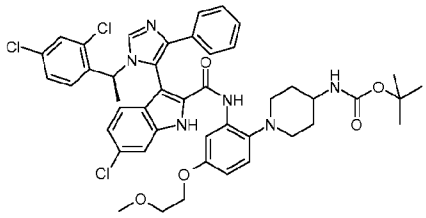
[00718] The title Example 189 (180 mg, 0.22 mmol, 64%) was obtained from Intermediate 189.1 (300 mg, 0.34 mmol) and dimethylcarbamic chloride (72.7 mg, 0.062 mL, 0.67 mmol), analogously to Example 97. HPLC: $^{B}t_{Ret}$ = 6.43; LC-MS: m/z 830.4 $[M+H]^+$.

[00719] Intermediate 189.1: 6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-amino-piperidin-1-yl)-5-(2-methoxy-ethoxy)-phenyl]-amide HCl salt.



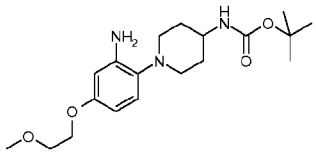
[00720] The title Intermediate 189.1 (1.27 g, 1.53 mmol, 97%) was obtained from Intermediate 189.2 (1.35 g, 1.57 mmol), analogously to Example 2. HPLC: $^{B}t_{Ret}$ = 5.83; LC-MS: m/z 759.4 $[M+H]^+$.

[00721] Intermediate 189.2: {1-[2-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-(2-methoxy-ethoxy)-phenyl]-piperidin-4-yl}-carbamic acid tert-butyl ester.



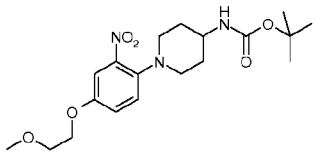
[00722] The title Intermediate 189.2 (1.36 g, 1.58 mmol, 56%) was obtained from Intermediate 148.2 (1.55 g, 2.69 mmol) and Intermediate 189.3 (1.03 g, 2.83 mmol), analogously to Example 1. HPLC: $^{B}t_{Ret}$ = 7.19; LC-MS: m/z 859.4 $[M+H]^+$.

[00723] Intermediate 189.3: {1-[2-Amino-4-(2-methoxy-ethoxy)-phenyl]-piperidin-4-yl}-carbamic acid tert-butyl ester.



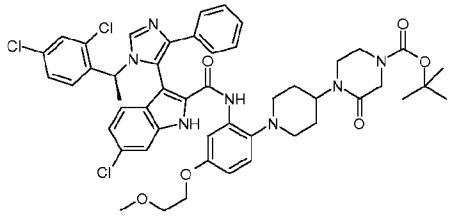
[00724] The title Intermediate 189.3 (1.04 g, 2.85 mmol, 99%) was obtained as a colorless solid from Intermediate 189.4 (1.13 g, 2.87 mmol), analogously to Intermediate 1.1. HPLC: $^{B}t_{Ret}$ = 5.11 min; LC-MS: m/z 366.3 $[M+H]^+$.

[00725] Intermediate 189.4: {1-[4-(2-Methoxy-ethoxy)-2-nitro-phenyl]-piperidin-4-yl}-carbamic acid tert-butyl ester.



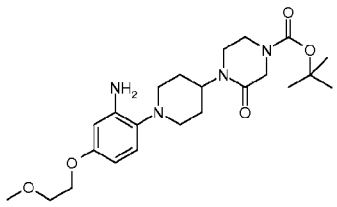
[00726] The title Intermediate 189.4 (1.14 g, 2.88 mmol, 75%) was obtained from Intermediate 180.3 (830 mg, 3.86 mmol) and tert-butyl piperidin-4-ylcarbamate (796 mg, 3.97 mmol), analogously to Intermediate 1.2. HPLC: $^{B}t_{Ret}$ = 6.87 min; LC-MS: m/z 396.1 $[M+H]^+$.

[00727] Intermediate 190.1: 4-{1-[2-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-(2-methoxy-ethoxy)-phenyl]-piperidin-4-yl}-3-oxo-piperazine-1-carboxylic acid tert-butyl ester.



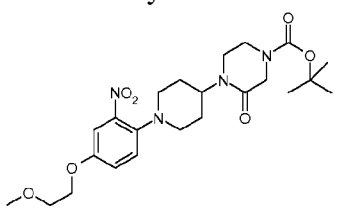
[00728] The title Intermediate 190.1 (404 mg, 0.43 mmol, 72%) was obtained from Intermediate 148.2 (370 mg, 0.59 mmol) and from Intermediate 190.2 (359 mg, 0.731 mmol), analogously to Example 1. HPLC: $^{A}t_{Ret}$ = 5.45; LC-MS: m/z 942.6 $[M+H]^+$.

[00729] Intermediate 190.2: 4-{1-[2-Amino-4-(2-methoxy-ethoxy)-phenyl]-piperidin-4-yl}-3-oxo-piperazine-1-carboxylic acid tert-butyl ester.



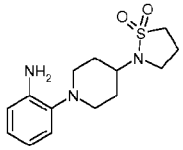
[00730] The title Intermediate 190.2 (748 mg, 1.48 mmol, 89%) was obtained as a colorless solid from Intermediate 190.3 (800 mg, 1.67 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.90 min; LC-MS: m/z 449.3 $[M+H]^+$.

[00731] Intermediate 190.3: 4-{1-[4-(2-Methoxy-ethoxy)-2-nitro-phenyl]-piperidin-4-yl}-3-oxo-piperazine-1-carboxylic acid tert-butyl ester.



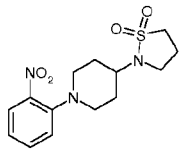
[00732] The title Intermediate 190.3 (800 mg, 1.438 mmol, 68%) was obtained from Intermediate 180.3 (458 mg, 2.13 mmol) and tert-butyl 3-oxo-4-(piperidin-4-yl)piperazine-1-carboxylate (842 mg, 2.56 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 5.18 min; LC-MS: m/z 479.4 $[M+H]^+$.

[00733] Intermediate 191.1: 2-(1-(2-aminophenyl)piperidin-4-yl)isothiazolidine 1,1-dioxide.



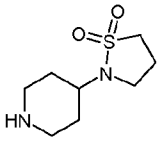
[00734] The title Intermediate 191.1 (417 mg, 1.41 mmol, 95%) was obtained as a pink solid from Intermediate 234.2 (486 mg, 1.49 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.38 min; LC-MS: m/z 296.0 $[M+H]^+$.

[00735] Intermediate 191.2: 2-(1-(2-nitrophenyl)piperidin-4-yl)isothiazolidine 1,1-dioxide.



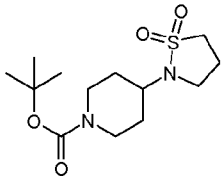
[00736] The title Intermediate 191.2 (486 mg, 1.49 mmol, 75%) was obtained from 1-fluoro-2-nitrobenzene (281 mg, 1.99 mmol) and Intermediate 191.3 (503 mg, 2.09 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.681 min; LC-MS: m/z 326.0 $[M+H]^+$.

[00737] Intermediate 191.3: 2-(piperidin-4-yl)isothiazolidine 1,1-dioxide HCl salt.



[00738] The title compound (1.09 g, 4.53 mmol, quantitative) was obtained as a colourless solid from Intermediate 191.4 (1.35 g, 4.43 mmol) analogously to Example 2. LC-MS: m/z 205 $[M+H]^+$.

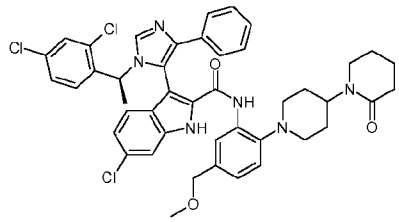
[00739] Intermediate 191.4: tert-butyl 4-(1,1-dioxidoisothiazolidin-2-yl)piperidine-1-carboxylate.



[00740] To a suspension of 4-Amino-1-Boc-piperidine 998 mg, 4.98 mmol) in DMF (10 mL) was added sodium hydride (698 mg, 17.44 mmol) at 0°C, followed by the addition of 3-chloropropanesulfonyl chloride (970 mg, 0.67 mL, 5.48 mmol) dropwise. The reaction mixture was allowed to warm to RT and stirred for 1 h. It was quenched with ice water and extracted with EtOAc. The combined organic layers were washed with water, brine, dried using $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by silica gel column chromatography (eluting with a gradient of DCM:EtOAc = 75:25 to 50:50) yielding the title Example 191.4 (1.40 g, 4.60 mmol, 92%) as colourless crystals. HPLC: $^{A}t_{Ret}$ = not detected; LC-MS: m/z 303.2 $[M-H]^-$.

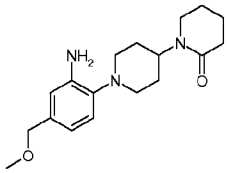
Example 192

6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [5-methoxymethyl-2-(2-oxo-[1,4']bipiperidinyl-1'-yl)-phenyl]-amide.



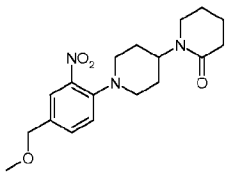
[00741] The title Example 192 (151 mg, 0.19 mmol, 64%) was obtained from Intermediate 148.2 (150 mg, 0.29 mmol) and from Intermediate 192.1 (98 mg, 0.31 mmol), analogously to Example 1. HPLC: $^{C}t_{Ret}$ = 6.77; LC-MS: m/z 811.4 $[M+H]^+$.

[00742] Intermediate 192.1: 1'-(2-Amino-4-methoxymethyl-phenyl)-[1,4']bipiperidinyl-2-one.



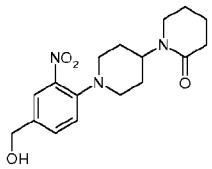
[00743] The title Intermediate 192.1 (580 mg, 1.77 mmol, 94%) was obtained as a colorless solid from Intermediate 192.2 (655 mg, 1.88 mmol), analogously to Intermediate 1.1. HPLC: $^{C}t_{Ret}$ = 4.26 min; LC-MS: m/z 318.3 $[M+H]^+$.

[00744] Intermediate 192.2: 1'-(4-Methoxymethyl-2-nitro-phenyl)-[1,4']bipiperidinyl-2-one.



[00745] To a solution of Intermediate 192.3 (1.25 g, 3.67 mmol) in DMF (7.3 mL) at 0 °C was added NaH (0.184 g, 4.59 mmol, 60% dispersion in oil) and the suspension was stirred for 30 min. Methyl iodide (0.782 g, 0.345 mL, 5.51 mmol) in DMF (1 mL) was added and the reaction mixture was allowed to war to RT and stirred over night. The reaction mixture was concentrated, quenched with water and extracted with EtOAc. The combined organic phases were dried using Na_2SO_4, filtered and evaporated. The crude product was purified by silica gel column chromatography (eluting with a gradient of EtOAc:EtOH + 0.25% NH_3 = 100:0 to 80:20) yielding the title Intermediate 192.2 (656 mg, 1.851 mmol, 50%) as an orange solid. HPLC: $^{C}t_{Ret}$ = 6.14 min; LC-MS: m/z 348.3 $[M+H]^+$.

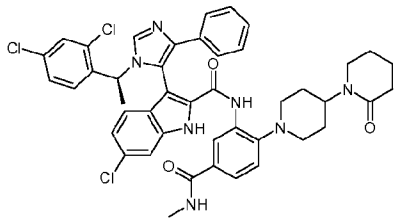
[00746] Intermediate 192.3: 1'-(4-Hydroxymethyl-2-nitro-phenyl)-[1,4']bipiperidinyl-2-one.



[00747] The title Intermediate 192.3 (2.89 g, 8.47 mmol, quantitative) was obtained as an orange solid from (4-fluoro-3-nitrophenyl)methanol (1.45 g, 8.47 mmol) and 1,4'-bipiperidin-2-one (1.62 g, 8.90 mmol), analogously to Intermediate 1.1. HPLC: $^{C}t_{Ret}$ = 5.24 min; LC-MS: m/z 334.3 $[M+H]^+$.

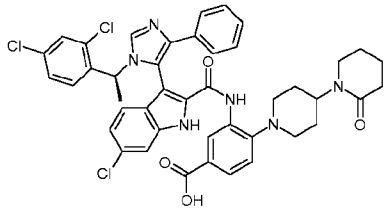
Example 193

6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [5-methyl-carbamoyl-2-(2-oxo-[1,4']bipiperidinyl-1'-yl)-phenyl]-amide.



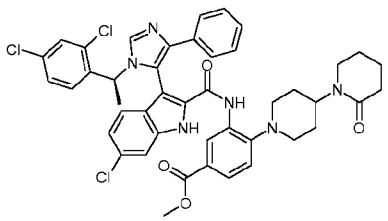
[00748] The title Example 193 (125 mg, 0.147 mmol, 94%) was obtained from Intermediate 193.1 (127 mg, 0.157 mmol) and methyl amine hydrochloride (21.17 mg, 0.314 mmol), analogously to Example 68. HPLC: $^{A}t_{Ret}$ = 5.03; LC-MS: m/z 824.0 $[M+H]^+$.

[00749] Intermediate 193.1: 3-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-(2-oxo-[1,4']bipiperidinyl-1'-yl)-benzoic acid.



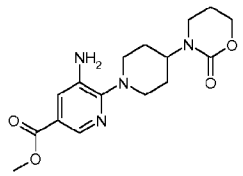
[00750] The title Intermediate 193.1 (1.16 g, 1.39 mmol, 93%) was obtained from Intermediate 193.2 (1.23 g, 1.49 mmol), analogously to Example 117. HPLC: $^{A}t_{Ret}$ = 5.06; LC-MS: m/z 811.0 $[M+H]^+$.

[00751] Intermediate 193.2: 3-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-(2-oxo-[1,4']bipiperidinyl-1'-yl)-benzoic acid methyl ester.



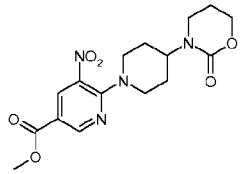
[00752] The title Intermediate 193.2 (1.13 g, 1.33 mmol, 63%) was obtained from Intermediate 148.2 (1.25 g, 2.13 mmol) and Intermediate 69.1 (0.77 g, 2.34 mmol), analogously to Example 1. HPLC: $^{A}t_{Ret}$ = 5.38; LC-MS: m/z 825.0 $[M+H]^+$.

[00753] Intermediate 194.1: 3'-Amino-4-(2-oxo-[1,3]oxazinan-3-yl)-3,4,5,6-tetrahydro-2H-[1,2'] bipyridinyl-5'-carboxylic acid methyl ester.



[00754] The title Intermediate 194.1 (1.09 g, 3.26 mmol, 85%) was obtained as a yellow solid from Intermediate 194.2 (1.39 g, 3.81 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.26 min; LC-MS: m/z 335.4 $[M+H]^+$.

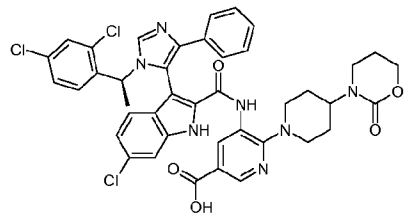
[00755] Intermediate 194.2: 3'-Nitro-4-(2-oxo-[1,3]oxazinan-3-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid methyl ester.



[00756] The title Intermediate 194.2 (1.39 g, 3.81 mmol, 90%) was obtained from methyl 6-chloro-5-nitronicotinate (915 mg, 4.22 mmol) and 3-(piperidin-4-yl)-1,3-oxazinan-2-one (856 mg, 4.65 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.55 min; LC-MS: m/z 365.3 $[M+H]^+$.

Example 195

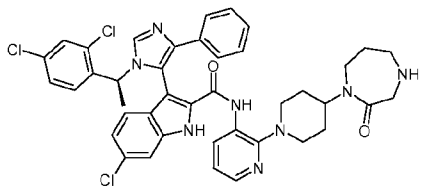
3'-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-(2-oxo-[1,3]oxazinan-3-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid.



[00757] The title Example 195 (1.26 g, 1.33 mmol, 91%) was obtained from Example 194 (1.40 g, 1.69 mmol), analogously to Example 117. HPLC: $^{A}t_{Ret}$ = 4.70; LC-MS: m/z 814.0 $[M+H]^+$.

Example 198

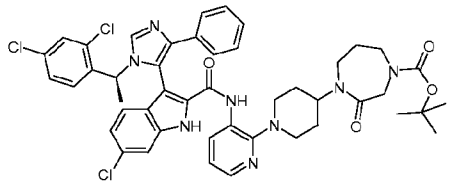
6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(2-oxo-[1,4]diazepan-1-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide.



[00758] The title Example 198 (105 mg, 0.134 mmol, 36%) was obtained from Intermediate 198.1 (300 mg, 0.340 mmol), analogously to Example 2. HPLC: $^{E}t_{Ret}$ = 1.03; LC-MS: m/z 783.4 $[M+H]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) ppm 1.09 (t, *J*=6.96 Hz, 2 H) 1.21 - 1.36 (m, 3 H) 1.55 (d, *J*=6.86 Hz, 3 H) 1.61 (dd, *J*=12.21, 3.33 Hz, 3 H) 2.81 - 2.92 (m, 4 H) 3.26 (d, *J*=8.68 Hz, 2 H) 3.36 - 3.41 (m, 2 H) 4.11 - 4.23 (m, 1 H) 5.47 - 5.53 (m, 1 H) 6.35 (d, *J*=8.68

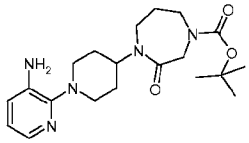
Hz, 1 H) 6.67 (d, *J*=8.48 Hz, 1 H) 6.82 (d, *J*=8.48 Hz, 1 H) 7.01 (s, 1 H) 7.08 (d, *J*=7.47 Hz, 1 H) 7.11 - 7.19 (m, 4 H) 7.42 (s, 1 H) 7.45 (d, *J*=7.87 Hz, 2 H) 8.08 - 8.15 (m, 1 H) 8.46 (d, *J*=7.47 Hz, 1 H) 8.49 (s, 1 H) 8.66 (s, 1 H) 12.41 (s, 1 H).

[00759] Intermediate 198.1: 4-{3'-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl}-3-oxo-[1,4]diazepane-1-carboxylic acid tert-butylester.



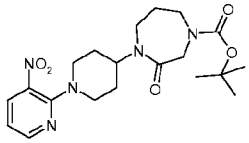
[00760] The title Intermediate 198.1 (320 mg, 0.36 mmol, 73%) was obtained from Intermediate 148.2 (290 mg, 0.50 mmol) and Intermediate 198.2 (214 mg, 0.46 mmol), analogously to Example 1. HPLC: $^{E}t_{Ret}$ = 1.40; LC-MS: m/z 883.4 $[M+H]^+$.

[00761] Intermediate 198.2: 4-(3'-Amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-3-oxo-[1,4] diazepane-1-carboxylic acid tert-butyl ester.



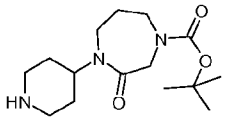
[00762] The title Intermediate 198.2 (219 mg, 0.56 mmol, 81%) was obtained as a colourless solid from Intermediate 198.3 (290 mg, 0.69 mmol), analogously to Intermediate 1.1. HPLC (SQ22): $^{X}t_{Ret}$ = 0.77 min; LC-MS: m/z 390.2 $[M+H]^+$.

[00763] Intermediate 198.3: 4-(3'-Nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-3-oxo-[1,4] diazepane-1-carboxylic acid tert-butyl ester.



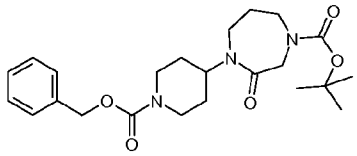
[00764] The title Intermediate 198.3 (290 mg, 0.691 mmol, 91%) was obtained from 2-chloro-3-nitropyridine (120 mg, 0.757 mmol) and Intermediate 198.4 (225 mg, 0.757 mmol), analogously to Intermediate 1.2. HPLC: $^{E}t_{Ret}$ = 1.63 min; LC-MS: m/z 420.2 $[M+H]^+$.

[00765] Intermediate 198.4: 3-Oxo-4-piperidin-4-yl-[1,4]diazepane-1-carboxylic acid tert-butyl ester.



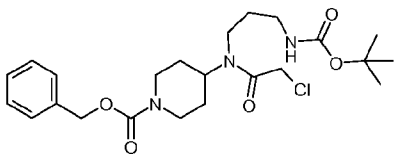
[00766] The title Intermediate 198.4 (60 mg, 2.018 mmol, 100%) was obtained as a colourless solid by hydrogenation reaction of Intermediate 198.5 (0.870 g, 2.016 mmol) with H_2 gas and Pd/C (50 mg, 2.016 mmol) in MeOH (40 mL) at RT over night. HPLC: t_{Ret} = not found; LC-MS: m/z 298.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) ppm 1.25 - 1.51 (m, 11 H), 1.59 (br. s., 2 H), 2.43 (td, J=11.91, 2.34 Hz, 2 H), 2.92 (d, J=11.71 Hz, 2 H), 3.30 (br. s., 4 H), 3.42 (br. s., 2 H), 3.97 (s, 2 H), 4.10 - 4.22 (m, 1 H).

[00767] Intermediate 198.5: 4-(1-Benzyloxycarbonyl-piperidin-4-yl)-3-oxo-[1,4]diazepane-1-carboxylic acid tert-butyl ester.



[00768] To a solution of Intermediate 198.6 (1.14 g, 2.436 mmol) in DMF (30 mL) was added potassium tert-butoxide (0.620 mg, 5.36 mmol) and the reaction mixture was heated at 80°C for 3 h. The reaction mixture was diluted with toluene, extracted and the combined organic layers were washed with a saturated solution of aqueous $NaHCO_3$, brine, dried using Na_2SO_4, filtered and concentrated to yield the title Intermediate 198.5 (0.87 g, 2.016 mmol) as a beige solid. HPLC (SQ22): $^X t_{Ret}$ = 1.70 min; LC-MS: m/z 432.2 $[M+H]^+$.

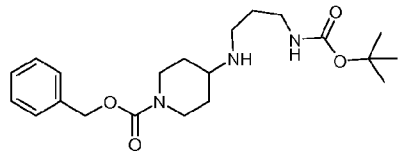
[00769] Intermediate 198.6: 4-[(3-tert-Butoxycarbonylamino-propyl)-(2-chloro-acetyl)-amino]-piperidine-1-carboxylic acid benzyl ester.



[00770] To a solution of Intermediate 198.7 (2.45 g, 6.26 mmol) and DIPEA (2.43 g, 2.28 mL, 18.77 mmol) in DCM (100 mL) at 0°C was added chloroacetyl chloride (0.848 g, 0.59

mL, 7.51 mmol) dropwise and the reaction mixture was allowed to war to RT and stirred over night. The reaction mixture was diluted with DCM and extracted. The combined organic phases were washed with a saturated solution of $NaHCO_3$ and water, dried using Na_2SO_4, filtered and concentrated. The crude product was purified by silica gel column chromatography (eluting with a gradient of heptane:EtOAc = 100:00 to 00:100) yielding the title Example 198.6 (1.35 g, 2.88 mmol, 46%) as a brownish resin. HPLC (SQ22): $^{X}t_{Rel}$ = 1.79 min; LC-MS: m/z 468.2 $[M+H]^+$.

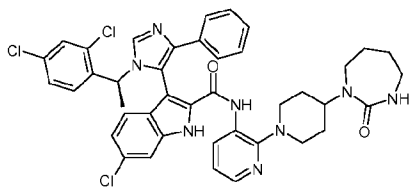
[00771] Intermediate 198.7: 4-(3-tert-Butoxycarbonylamino-propylamino)-piperidine-1-carboxylic acid benzyl ester.



[00772] To a solution of 1-Z-4-Piperidinone (1.5 g, 6.43 mmol) and N-Boc-propylendiamine (1.155 g, 6.43 mmol) in DCM (10 mL) was added acetic acid (0.751 mL, 13.12 mmol) and sodium triacetoxyborohydride (1.676 g, 7.91 mmol) portionwise at RT. The reaction mixture was stirred for 3 h, diluted with EtOAc, quenched with $NaHCO_3$ and extracted. The combined organic phases were dried using Na_2SO_4, filtered and evaporated yielding the title Intermediate 198.7 (2.45 g, 6.26 mmol, 97%) as a colourless residue. HPLC (SQ22): $^{X}t_{Rel}$ = 0.94 min; LC-MS: m/z 392.3 $[M+H]^+$.

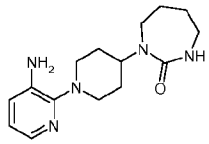
Example 199

6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(2-oxo-[1,3]diazepan-1-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide.



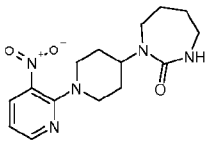
[00773] The title Example 199 (110 mg, 0.14 mmol, 27%) was obtained from Intermediate 148.2 (300 mg, 0.52 mmol) and Intermediate 199.1 (157 mg, 0.54 mmol), analogously to Example 1. HPLC: $^{B}t_{Ret}$ = 6.04; LC-MS: m/z 783.4 $[M+H]^+$.

[00774] Intermediate 199.1: 1-(3'-Amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-[1,3] diazepan-2-one.



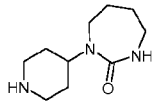
[00775] The title Intermediate 199.1 (210 mg, 0.726 mmol, 80%) was obtained as a colourless solid from Intermediate 199.2 (290 mg, 0.908 mmol), analogously to Intermediate 1.1. HPLC: $^{B}t_{Ret}$ = 4.09; LC-MS: m/z 290.3 $[M+H]^+$.

[00776] Intermediate 199.2: 1-(3'-Nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-[1,3] diazepan-2-one.



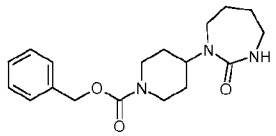
[00777] The title Intermediate 199.2 (294 mg, 0.921 mmol, 100%) was obtained from 2-chloro-3-nitropyridine (146 mg, 0.921 mmol) and Intermediate 199.3 (200 mg, 1.013 mmol), analogously to Intermediate 1.2. HPLC: $^{B}t_{Ret}$ = 5.87 min; LC-MS: m/z 320.3 $[M+H]^+$.

[00778] Intermediate 199.3: 1-Piperidin-4-yl-[1,3]diazepan-2-one.



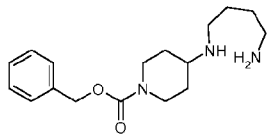
[00779] The title Intermediate 199.3 (1.04 g, 5.27 mmol, 99%) was obtained as a colourless solid by hydrogenation reaction of Intermediate 199.4 (1.77 g, 5.34 mmol) with H_2 gas and Pd/C (0.4 g, 0.376 mmol) in MeOH/THF 1/1 (60 mL) at RT for 2.5 h. HPLC: $^{B}t_{Ret}$ = 3.24 min; LC-MS: m/z 198.1 $[M+H]^+$.

[00780] Intermediate 199.4: 4-(2-Oxo-[1,3]diazepan-1-yl)-piperidine-1-carboxylic acid benzyl ester.



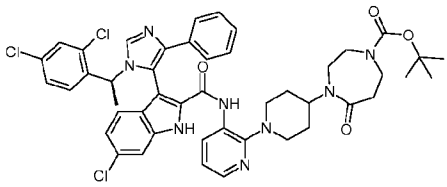
[00781] A solution of Intermediate 119.5 (5.02 g, 12.66 mmol) and CDI (4.10 g, 25.30 mmol) in chloroform (100 mL) was refluxed for 6 h. The reaction mixture was allowed to warm to RT and was stirred for 17 h. DCM (500 mL) was added and the solution was extracted with 1N HCl (300 mL). The organic phase was washed with $NaHCO_3$ and brine, was dried using Na_2SO_4 filtered and concentrated to dryness. The crude product was purified by silica gel column chromatography (eluting first with a gradient of DCM:EtOAc = 70:30 followed by DCM:MeOH = 95:05) yielding the title Intermediate 199.4 (1.77 g, 5.34 mmol, 42%) as a colourless solid. HPLC: $^{B}t_{Ret}$ = 6.08 min; LC-MS: m/z 332.1 $[M+H]^+$.

[00782] Intermediate 199.5: 4-(4-Amino-butylamino)-piperidine-1-carboxylic acid benzyl ester.



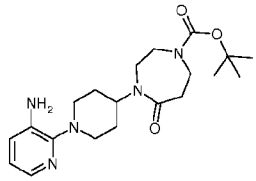
[00783] To a solution of 1,4-Diaminobutane (3.78 g, 4.29 mL, 42.9 mmol) and acetic acid (2.57 g, 2.45 mL, 42.9 mmol) in MeOH (55 mL) was added a solution of 1-Z-4-piperidinone (5.0 g, 21.44 mmol) in MeOH (15 mL), after stirring for 5 min a solution of sodium cyanoborohydride (2.69 g, 42.9 mmol) in MeOH (10 mL) and the solution was continued to stirr at RT for 18 h. The reaction mixture was cooled with an ice bath and carefully quenched first with 1N HCl followed by HClconc. The aqueous phase was extracted with DCM and the organic phase was discarded, the pH of the water phase was adjusted to pH10 using an aqueous solution of NaOH (30%) and extracted with DCM. The combined organic phases were dried using Na_2SO_4, filtered and evaporated yielding the title Intermediate 199.5 (5.66 g, 14.27 mmol, 77%) as a yellow oil. HPLC: $^{B}t_{Ret}$ = 4.33 min; LC-MS: m/z 306.2 $[M+H]^+$.

[00784] Intermediate 200.1: 4-{3'-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl}-5-oxo-[1,4]diazepane-1-carboxylic acid tert-butyl ester.



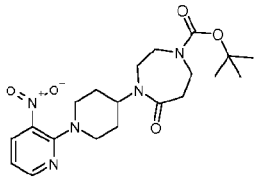
[00785] The title Intermediate 200.1 (200 mg, 0.227 mmol, 59%) was obtained from Intermediate 148.2 (224 mg, 0.385 mmol) and from Intermediate 200.2 (165 mg, 0.424 mmol), analogously to Example 1. HPLC: $^{E}t_{Ret}$ = 1.76; LC-MS: m/z 883.3 $[M+H]^+$.

[00786] Intermediate 200.2: 4-(3'-Amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-5-oxo-[1,4]diazepane-1-carboxylic acid tert-butyl ester.



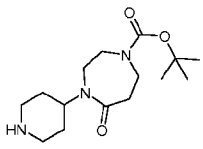
[00787] The title Intermediate 200.2 (165 mg, 0.424 mmol, 81%) was obtained as a yellow oil from Intermediate 200.3 (220 mg, 0.524 mmol), analogously to Intermediate 1.1. HPLC (SQ22): $^{X}t_{Ret}$ = 0.98; LC-MS: m/z 390.8 $[M+H]^+$.

[00788] Intermediate 200.3: 4-(3'-Nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-5-oxo-[1,4]diazepane-1-carboxylic acid tert-butyl ester.



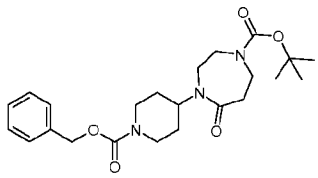
[00789] The title Intermediate 200.3 (220 mg, 0.524 mmol, 74%) was obtained from 2-chloro-3-nitropyridine (112 mg, 0.706 mmol) and Intermediate 200.4 (112 mg, 0.706 mmol), analogously to Intermediate 1.2. HPLC (SQ22): $^{X}t_{Ret}$ = 2.26 min; LC-MS: m/z 420.3 $[M+H]^+$.

[00790] Intermediate 200.4: 5-Oxo-4-piperidin-4-yl-[1,4]diazepane-1-carboxylic acid tert-butyl ester.



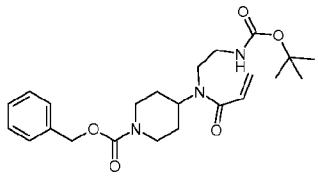
[00791] The title Intermediate 200.4 (363 mg, 1.221 mmol, 99%) was obtained as a colourless solid by hydrogenation reaction of Intermediate 200.5 (0.53 g, 1.228 mmol) with H_2 gas and Pd/C (0.09 g) in MeOH/THF/NH_3 7M in MeOH 2/2/1 (25 mL) at RT for 45.5 h. LC-MS: t_{Ret} = not found; LC-MS: m/z 298.3 $[M+H]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) ppm 1.28 - 1.67 (m, 11 H), 2.39 - 2.50 (m, 2 H), 2.66 (br. s., 2 H), 2.90- 2.99 (m, 2 H), 3.20 - 3.79 (m, 8 H), 4.03 - 4.30 (m, 1 H).

[00792] Intermediate 200.5: 4-(1-Benzyloxycarbonyl-piperidin-4-yl)-5-oxo-[1,4]diazepane-1-carboxylic acid tert-butyl ester.



[00793] To a solution of Intermedaite 200.6 (1.70 g, 3.94 mmol) in DMF (15 mL) was added potassium tert-butoxide (0.0088 g, 0.788 mmol) and the reaction was stirred at RT over night. The reaction mixture was quenched with water (200 mL), the precipitate was filtered, washed with water and dried in vacuo to yield the title Intermediate 200.5 (0.50 g, 1.159 mmol) as a colourless solid.

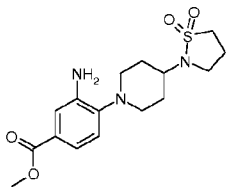
[00794] Intermediate 200.6: 4-[Acryloyl-(2-tert-butoxycarbonylamino-ethyl)-amino]-piperidine-1-carboxylic acid benzyl ester.



[00795] To a solution of 1-Z-4-piperidinone (1.5 g, 6.43 mmol) and N-Boc-ethylendiamine (1.03 g, 6.43 mmol) in DCM (20 mL) was added acetic acid (0.79 g, 0.75 mL, 13.12 mmol) and sodium triacetoxyborohydride (1.765 g, 7.91 mmol) and the reaction mixture was continued to stirr at RT for 1 h. The reaction mixture was basified with $NaHCO_3$, then acryloyl chloride (0.585 mL, 7.20 mmol) was added and the reaction mixture was continued to stirr for for 1 h. DCM was added and phases were separated, the organic phase was washed with water, dried using Na_2SO_4, filtered and concentrated. The crude product was purified by silica gel

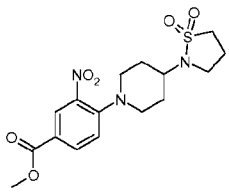
column chromatography (eluting with a gradient of heptane:EtOAc = 100:0 to 0:100) yielding the title Intermediate 200.6 (1.92 g, 4.45 mmol, 69%) as a colourless foam. HPLC (SQ22): $^{X}t_{Ret}$ = 1.07 min; LC-MS: m/z 432.2 $[M+H]^+$.

[00796] Intermediate 201.1: methyl 3-amino-4-(4-(1,1-dioxidoisothiazolidin-2-yl)piperidin-1-yl)benzoate.



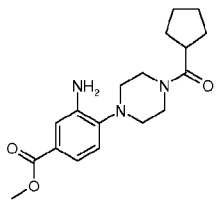
[00797] The title Intermediate 201.1 (692 mg, 1.80 mmol, 95%) was obtained as a red solid from Intermediate 201.2 (727 mg, 1.89 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.89 min; LC-MS: m/z 354.0 $[M+H]^+$.

[00798] Intermediate 201.2: methyl 4-(4-(1,1-dioxidoisothiazolidin-2-yl)piperidin-1-yl)-3-nitrobenzoate.



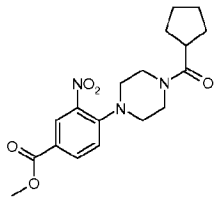
[00799] The title Intermediate 201.2 (727 mg, 1.89 mmol, 80%) was obtained from methyl 4-chloro-3-nitrobenzoate (510 mg, 2.36 mmol) and Intermediate 191.3 (598 mg, 2.48 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.773 min; LC-MS: m/z 384.0 $[M+H]^+$.

[00800] Intermediate 202.1: 3-Amino-4-(4-cyclopentanecarbonyl-piperazin-1-yl)-benzoic acid methyl ester.



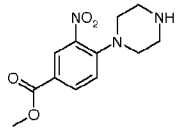
[00801] The title Intermediate 202.1 (953 mg, 2.88 mmol, 97%) was obtained as a beige solid from Intermediate 202.2 (1.07 g, 2.97 mmol), analogously to Intermediate 1.1. HPLC (ZQ01): $^{X}t_{Ret}$ = 1.03 min; LC-MS: m/z 332.5 $[M+H]^+$.

[00802] Intermediate 202.2: 4-(4-Cyclopentanecarbonyl-piperazin-1-yl)-3-nitro-benzoic acid methyl ester.



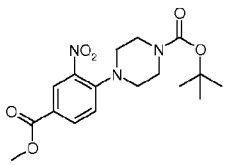
[00803] The title Intermediate 202.2 (1.85 g, 5.13 mmol, 82%) was obtained from Intermediate 202.3 (2.00 g, 6.23 mmol) and cyclopentane-carbonyl chloride (937 mg, 0.86 mL, 13.08 mmol), analogously to Example 3. HPLC (ZQ01): $^{X}t_{Ret}$ = 1.10 min; LC-MS: m/z 326.3 $[M+H]^+$.

[00804] Intermediate 202.3: 3-Nitro-4-piperazin-1-yl-benzoic acid methyl ester HCl salt.



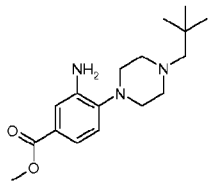
[00805] The title Intermediate 202.3 (17.59 g, 54.8 mmol, 81%) was obtained from Intermediate 202.2 (24.61 g, 67.4 mmol), analogously to Example 2. HPLC (ZQ01): $^{X}t_{Ret}$ = 0.66; LC-MS: m/z 266.4 $[M+H]^+$.

[00806] Intermediate 202.4: 4-(4-Methoxycarbonyl-2-nitro-phenyl)-piperazine-1-carboxylic acid tert-butyl ester.



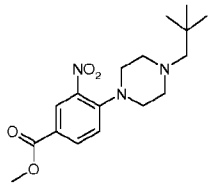
[00807] The title Intermediate 202.4 (27.1 g, 66.8 mmol, 98%) was obtained from methyl 4-chloro-3-nitrobenzoate (14.9 g, 68.4 mmol) and 1-boc-piperazine (13.65 g, 71.8 mmol), analogously to Intermediate 1.2. HPLC (SQ22): $^{X}t_{Rel}$ = 1.36 min; LC-MS: m/z 366.1 $[M+H]^+$.

[00808] Intermediate 203.1: 3-Amino-4-[4-(2,2-dimethyl-propyl)-piperazin-1-yl]-benzoic acid methyl ester.



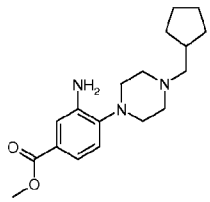
[00809] The title Intermediate 203.1 (258 mg, 0.80 mmol, 90%) was obtained as a colorless solid from Intermediate 203.2 (300 mg, 0.89 mmol), analogously to Intermediate 1.1. HPLC (ZQ01): $^{X}t_{Ret}$ = 0.73 min; LC-MS: m/z 306.3 $[M+H]^+$.

[00810] Intermediate 203.2: 4-[4-(2,2-Dimethyl-propyl)-piperazin-1-yl]-3-nitro-benzoic acid methyl ester.



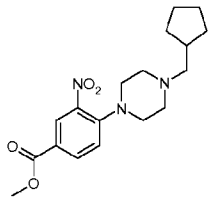
[00811] To a solution of Intermediate 202.3 (500 mg, 6.23 mmol) and trimethylacetaldehyde (428 mg, 0.55 mL, 4.97 mmol) in DCM (7 mL) was added sodium triacetoxyborohydride (1.76 g, 8.29 mmol) portionwise at RT. The reaction mixture was stirred for 72 h, diluted with EtOAc and $NaHCO_3$ and extracted with EtOAc. The combined organic phases were dried using Na_2SO_4, filtered and evaporated. The crude product was purified by silica gel column chromatography (eluting with a gradient of DCM:MeOH = 100:0 to 95:05) yielding the title Intermediate 247.2 (323 mg, 0.915 mmol, 55%)as a yellow solid. LC-MS: m/z 336.4 $[M+H]^+$.

[00812] Intermediate 204.1: 3-Amino-4-(4-cyclopentylmethyl-piperazin-1-yl)-benzoic acid methyl ester.



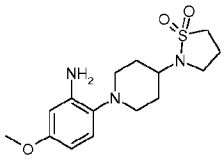
[00813] The title Intermediate 204.1 (299 mg, 0.84 mmol, 92%) was obtained as a colorless solid from Intermediate 204.2 (368 mg, 0.91 mmol), analogously to Intermediate 1.1. LC-MS: m/z 318.5 $[M+H]^+$.

[00814] Intermediate 204.2: 4-(4-Cyclopentylmethyl-piperazin-1-yl)-3-nitro-benzoic acid methyl ester.



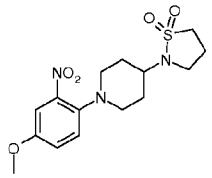
[00815] The title Intermediate 204.2 (841 mg, 2.42 mmol, 42%) was obtained as a yellow solid from Intermediate 202.3 (1.65 g, 5.47 mmol), analogously to Intermediate 203.2. LC-MS: m/z 348.4 $[M+H]^+$.

[00816] Intermediate 206.1: 2-(1-(2-amino-4-methoxyphenyl)piperidin-4-yl)isothiazolidine 1,1-dioxide.



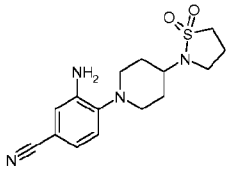
[00817] The title Intermediate 206.1 (583 mg, 1.68 mmol, 92%) was obtained as a red solid from Intermediate 206.2 (648 mg, 1.82 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.49 min; LC-MS: m/z 326.2 $[M+H]^+$.

[00818] Intermediate 206.2: 2-(1-(4-methoxy-2-nitrophenyl)piperidin-4-yl)isothiazolidine 1,1-dioxide.



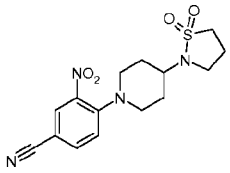
[00819] The title Intermediate 206.2 (648 mg, 1.82 mmol, 69%) was obtained from 1-fluoro-4-methoxy-2-nitrobenzene (450 mg, 2.63 mmol) and Intermediate 191.3 (665 mg, 2.73 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.70 min; LC-MS: m/z 356.0 $[M+H]^+$.

[00820] Intermediate 207.1: 3-amino-4-(4-(1,1-dioxidoisothiazolidin-2-yl)piperidin-1-yl)benzonitrile.



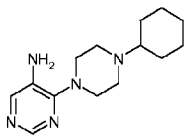
[00821] The title Intermediate 207.1 (353 mg, 1.10 mmol, 54%) was obtained as a colorless solid from Intermediate 207.2 (710 mg, 2.026 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 4.12 min; LC-MS: m/z 321.3 $[M+H]^+$.

[00822] Intermediate 207.2: 4-(4-(1,1-dioxidoisothiazolidin-2-yl)piperidin-1-yl)-3-nitrobenzonitrile.



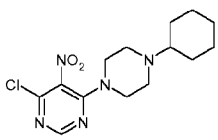
[00823] The title Intermediate 207.2 (721 mg, 2.06 mmol, 75%) was obtained from 4-chloro-3-nitrobenzonitrile (500 mg, 2.74 mmol) and Intermediate 191.3 (692 mg, 2.88 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.573 min; LC-MS: m/z 351.1 $[M+H]^+$.

[00824] Intermediate 211.1: 4-(4-Cyclohexyl-piperazin-1-yl)-pyrimidin-5-ylamine.



[00825] The title Intermediate 211.1 (1.74 g, 6.32 mmol, 95%) was obtained as a beige solid from Intermediate 211.2 (2.58 g, 7.92 mmol), analogously to Intermediate 1.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.09 (d, *J*=14.06 Hz, 1 H), 1.26 (d, *J*=12.89 Hz, 2 H), 1.36 - 1.50 (m, 2 H), 1.60 (d, *J*=12.50 Hz, 1 H), 1.82 (d, *J*=13.28 Hz, 2 H), 2.08 (d, *J*=10.93 Hz, 2 H), 3.09 - 3.25 (m, 4 H), 3.45 (br. s., 2 H), 3.82 – 3.95 (m, 2 H), 5.00 - 5.22 (m, 1 H), 7.92 (s, 1 H), 8.14 (s, 1 H), 10.37 - 10.55 (m, 2 H).

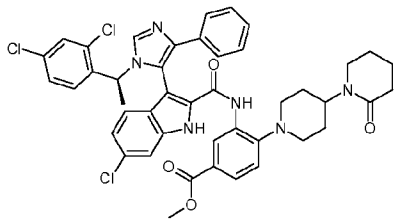
[00826] Intermediate 211.2: 4-Chloro-6-(4-cyclohexyl-piperazin-1-yl)-5-nitro-pyrimidine.



[00827] The title Intermediate 211.2 (2.58 g, 7.92 mmol, 77%) was obtained from 4,6-dichloro-5-nitropyrimidine (2.00 g, 10.31 mmol) and 1-cycloexyl-piperazine (1.73 g, 10.31 mmol), analogously to Intermediate 1.2. HPLC: $^{E}t_{Ret}$ = 0.53 min; LC-MS: m/z 326.1 $[M+H]^+$.

Example 212

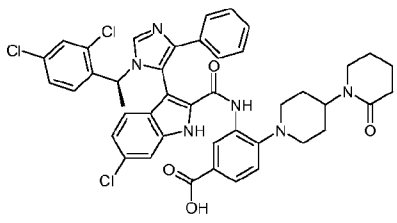
3-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol -4-yl}-1H-indole-2-carbonyl)-amino]-4-(2-oxo-[1,4']bipiperidinyl-1'-yl)-benzoic acid methyl ester.



[00828] The title Example 212 (283 mg, 0.33 mmol, 59%) was obtained from Intermediate 148.2 (300 mg, 0.567 mmol) and Intermediate 69.1 (207 mg, 0.62 mmol), analogously to Example 1. HPLC: $^{A}t_{Ret}$ = 5.47; LC-MS: m/z 825.2 $[M+H]^+$.

Example 213

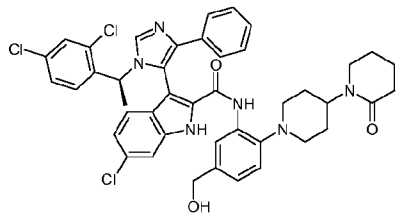
3-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-(2-oxo-[1,4']bipiperidinyl-1'-yl)-benzoic acid.



[00829] The title Example 213 (90 mg, 0.108 mmol, 94%) was obtained from Example 212 (94 mg, 0.114 mmol), analogously to Example 117. HPLC: $^{A}t_{Ret}$ = 5.13; LC-MS: m/z 811.3 $[M+H]^+$.

Example 215

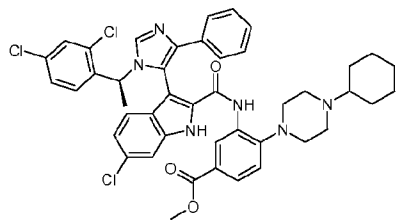
6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [5-hydroxymethyl-2-(2-oxo-[1,4']bipiperidinyl-1'-yl)-phenyl]-amide.



[00830] The title Example 215 (76 mg, 0.093 mmol, 58%) was obtained from Example 213 (130 mg, 0.160 mmol), analogously to Example 187. HPLC: $^{A}t_{Ret}$ = 4.95; LC-MS: m/z 797.0 $[M+H]^+$.

Example 216

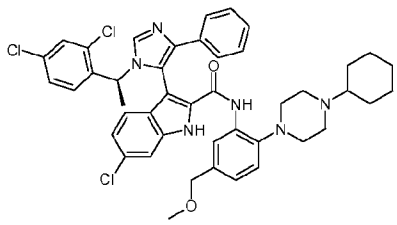
3-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol -4-yl}-1H-indole-2-carbonyl)-amino]-4-(4-cyclohexyl-piperazin-1-yl)-benzoic acid methyl ester.



[00831] The title Example 216 (128 mg, 0.158 mmol, 31%) was obtained from Intermediate 148.2 (300 mg, 0.510 mmol) and Intermediate 70.1 (170 mg, 0.536 mmol), analogously to Example 1. HPLC: $^{A}t_{Ret}$ = 5.05; LC-MS: m/z 811.2 $[M+H]^+$.

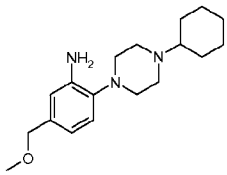
Example 222

6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-cyclohexyl-piperazin-1-yl)-5-methoxymethyl-phenyl]-amide.



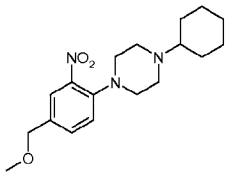
[00832] The title Example 222 (347 mg, 0.436 mmol, 73%) was obtained from Intermediate 148.2 (306 mg, 0.60 mmol) and Intermediate 222.1 (191 mg, 0.63 mmol), analogously to Example 1. HPLC: $^{C}t_{Ret}$ = 6.77; LC-MS: m/z 797.4 $[M+H]^+$.

[00833] Intermediate 222.1: 2-(4-Cyclohexyl-piperazin-1-yl)-5-methoxymethyl-phenylamine.



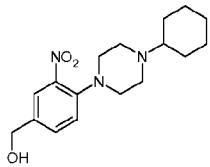
[00834] The title Intermediate 222.1 (680 mg, 2.24 mmol, 97%) was obtained as a colorless solid from Intermediate 222.2 (0.77 g, 2.31 mmol), analogously to Intermediate 1.1. HPLC: $^{C}t_{Ret}$ = 3.92 min; LC-MS: m/z 304.3 $[M+H]^+$.

[00835] Intermediate 222.2: 1-Cyclohexyl-4-(4-methoxymethyl-2-nitro-phenyl)-piperazine.



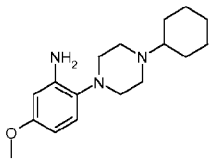
[00836] A solution of Intermediate 222.3 (0.798 g, 2.500 mmol) in DMF (5 mL) at 0 °C was added NaH (0.125 mg, 3.13 mmol, 60%) and the suspension was stirred for 30 min. A solution of methyl iodide (0.532 mg, 0.234 mL, 3.75 mmol) in DMF (1 mL) was added dropwise at 0 °C, the reaction mixture was allowed to warm to RT and stirring was continued for 30 min. The reaction mixture was concentrated, diluted with EtOAc and water and extracted with EtOAc. The combined organic phases were washed with water and brine, dried using Na_2SO_4, filtered and evaporated. The desired product crystallized upon concentration of the solvents yielding the title Intermediate 270.2 (0.77 g, 2.31 mmol, 92%) as an orange solid. HPLC: $^{C}t_{Ret}$ = 5.24 min; LC-MS: m/z 334.3 $[M+H]^+$.

[00837] Intermediate 222.3: [4-(4-Cyclohexyl-piperazin-1-yl)-3-nitro-phenyl]-methanol.



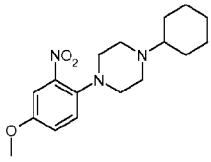
[00838] The title Intermediate 222.3 (2.74 g, 8.58 mmol, 86%) was obtained from (4-fluoro-3-nitrophenyl)methanol (1.711 g, 10.00 mmol) and 1-cyclohexylpiperazine (1.85 g, 11.0 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.66 min; LC-MS: m/z 320.1 $[M+H]^+$.

[00839] Intermediate 223.1: 2-(4-Cyclohexyl-piperazin-1-yl)-5-methoxy-phenylamine.



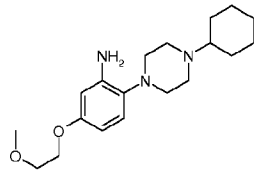
[00840] The title Intermediate 223.1 (1.497 g, 5.17 mmol, 101%) was obtained as a colorless solid from Intermediate 223.2 (1.63 g, 5.10 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.26 min; LC-MS: m/z 290.4 $[M+H]^+$.

[00841] Intermediate 223.2: 1-Cyclohexyl-4-(4-methoxy-2-nitro-phenyl)-piperazine.



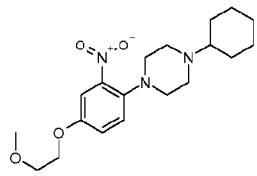
[00842] The title Intermediate 223.2 (1.63 g, 5.10 mmol, 87%) was obtained from 1-fluoro-4-methoxy-2-nitrobenzene (1.00 g, 5.84 mmol) and cyclohexylpiperazine (1.18 g, 7.01 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.34 min; LC-MS: m/z 320.2 $[M+H]^+$.

[00843] Intermediate 224.1: 2-(4-Cyclohexyl-piperazin-1-yl)-5-(2-methoxy-ethoxy)-phenylamine.



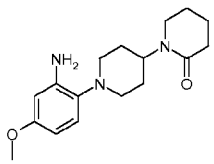
[00844] The title Intermediate 224.1 (385 mg, 1.155 mmol, 92%) was obtained as a colorless solid from Intermediate 224.2 (455 mg, 1.252 mmol), analogously to Intermediate 1.1. HPLC: $^{B}t_{Ret}$ = 4.08 min; LC-MS: m/z 334.4 $[M+H]^+$.

[00845] Intermediate 224.2: 1-Cyclohexyl-4-[4-(2-methoxy-ethoxy)-2-nitro-phenyl]-piperazine.



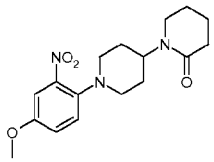
[00846] The title Intermediate 224.2 (460 mg, 1.266 mmol, 91%) was obtained from 1-fluoro-4-(2-methoxyethoxy)-2-nitrobenzene (300 mg, 1.394 mmol) and cyclohexylpiperazine (242 mg, 1.436 mmol), analogously to Intermediate 1.2. HPLC: $^{B}t_{Ret}$ = 5.34 min; LC-MS: m/z 364.2 $[M+H]^+$.

[00847] Intermediate 225.1: 1'-(2-Amino-4-methoxy-phenyl)-[1,4']bipiperidinyl-2-one.



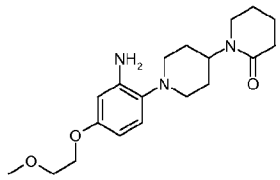
[00848] The title Intermediate 225.1 (1.04 g, 3.43 mmol, 95%) was obtained as a colourless solid from Intermediate 225.2 (1.20 g, 3.43 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.52 min; LC-MS: m/z 304.4 $[M+H]^+$.

[00849] Intermediate 225.2: 1'-(4-Methoxy-2-nitro-phenyl)-[1,4']bipiperidinyl-2-one.



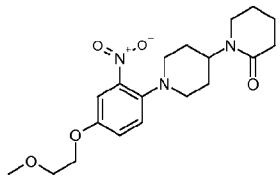
[00850] The title Intermediate 225.2 (1.20 g, 3.60 mmol, 73%) was obtained from 1-fluoro-4-methoxy-2-nitrobenzene (850 mg, 4.97 mmol) and 1,4'-bipiperidin-2-one (925 mg, 5.08 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 5.02 min; LC-MS: m/z 334.3 $[M+H]^+$.

[00851] Intermediate 226.1: 1'-[2-Amino-4-(2-methoxy-ethoxy)-phenyl]-[1,4']bipiperidinyl-2-one.



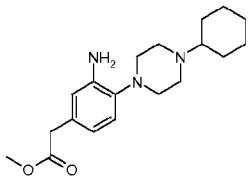
[00852] The title Intermediate 226.1 (1.121 g, 3.23 mmol, 96%) was obtained as a brownish foam from Intermediate 226.2 (1.266 g, 3.35 mmol), analogously to Intermediate 1.1. HPLC: $^{D}t_{Ret}$ = 0.93 min; LC-MS: m/z 348.3 $[M+H]^+$.

[00853] Intermediate 226.2: 1'-[4-(2-Methoxy-ethoxy)-2-nitro-phenyl]-[1,4']bipiperidinyl-2-one.



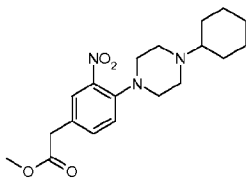
[00854] The title Intermediate 226.2 (1.266 g, 3.35 mmol, 80%) was obtained from 1-fluoro-4-(2-methoxyethoxy)-2-nitrobenzene (900 mg, 4.18 mmol) and 1,4'-bipiperidin-2-one (800 mg, 4.39 mmol), analogously to Intermediate 1.2. HPLC: $^{D}t_{Ret}$ = 1.13 min; LC-MS: m/z 378.2 $[M+H]^+$.

[00855] Intermediate 227.1: [3-Amino-4-(4-cyclohexyl-piperazin-1-yl)-phenyl]-acetic acid methyl ester.



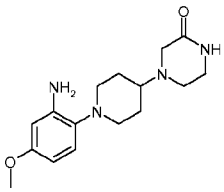
[00856] The title Intermediate 227.1 (1.81 g, 5.46 mmol, 95%) was obtained as a colorless solid from Intermediate 227.2 (1.99 g, 5.51 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.30 min; LC-MS: m/z 332.5 $[M+H]^+$.

[00857] Intermediate 227.2: [4-(4-Cyclohexyl-piperazin-1-yl)-3-nitro-phenyl]-acetic acid methyl ester.



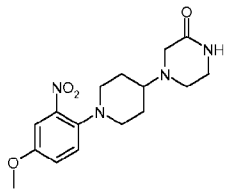
[00858] The title Intermediate 227.2 (1.99 g, 5.51 mmol, 77%) was obtained from methyl 2-(4-fluoro-3-nitrophenyl)acetate (1.52 g, 7.13 mmol) and 1-cyclohexylpiperazine (1.32 g, 7.84 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 4.225 min; LC-MS: m/z 362.3 $[M+H]^+$.

[00859] Intermediate 231.1: 4-[1-(2-Amino-4-methoxy-phenyl)-piperidin-4-yl]-piperazin-2-one.



[00860] The title Intermediate 231.1 (460 mg, 1.48 mmol, 99%) was obtained as a beige solid from Intermediate 231.2 (500 mg, 1.49 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 2.86 min; LC-MS: m/z 305.4 $[M+H]^+$.

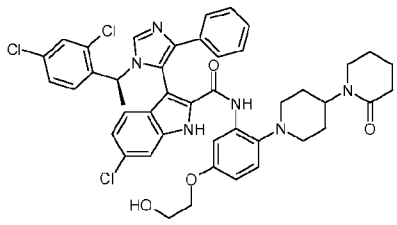
[00861] Intermediate 231.2: 4-[1-(4-Methoxy-2-nitro-phenyl)-piperidin-4-yl]-piperazin-2-one.



[00862] The title Intermediate 231.2 (500 mg, 1.42 mmol, 41%) was obtained from 1-fluoro-4-methoxy-2-nitrobenzene (600 mg, 3.51 mmol) and 4-(piperidin-4-yl)piperazin-2-one (707 mg, 3.86 mmol), analogously to Intermediate 1.2. HPLC: $^{A}t_{Ret}$ = 3.70 min; LC-MS: m/z 335.2 $[M+H]^+$.

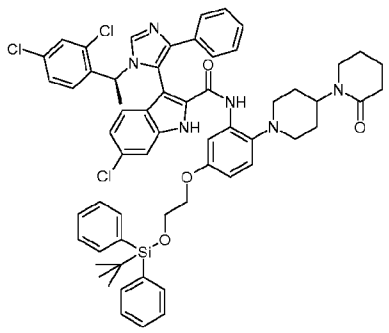
Example 232

6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [5-(2-hydroxy-ethoxy)-2-(2-oxo-[1,4']bipiperidinyl-1'-yl)-phenyl]-amide.



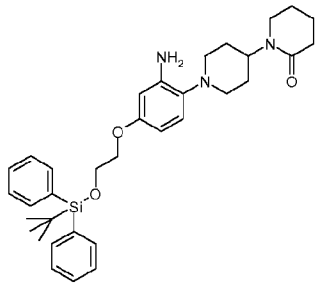
[00863] To a solution of Intermediate 232.1 (584 mg, 0.548 mmol) in THF (5 mL) was added a 1 M solution of TBAF in THF (0.548 mL, 0.548 mmol) at RT and the reaction mixture was stirred for 1 h. The solvent was evaporated and the residue was taken up in DCM and purified by silica gel column chromatography (eluting with a gradient of DCM:(DCM/EtOH 9:1) = 1:0 to 0:1) yielding the title Example 232 (430 mg, 0.521 mmol, 95%) as a yellow solid. HPLC: $^{D}t_{Ret}$ = 1.403; LC-MS: m/z 827.4 $[M+H]^+$.

[00864] Intermedaite 232.1: 6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [5-[2-(tert-butyl-diphenyl-silanyloxy)-ethoxy]-2-(2-oxo-[1,4']bipiperidinyl-1'-yl)-phenyl]-amide.



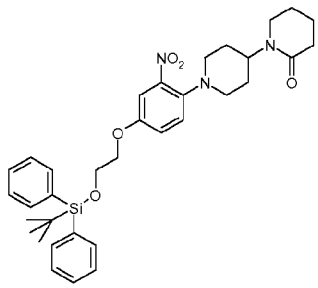
[00865] The title Intermediate 232.1 (584 mg, 0.548 mmol, 79%) was obtained from Intermediate 148.2 (400 mg, 0.695 mmol) and Intermediate 232.2 (417 mg, 0.730 mmol), analogously to Example 1. HPLC: $^{D}t_{Ret}$ = 1.85; LC-MS: m/z 1065.5 $[M+H]^+$.

[00866] Intermediate 232.2: 1'-{2-Amino-4-[2-(tert-butyl-diphenyl-silanyloxy)-ethoxy]-phenyl}-[1,4']bipiperidinyl-2-one.



[00867] The title Intermediate 232.2 (716 mg, 1.25 mmol, 65%) was obtained as a beige solid from Intermediate 232.3 (1.16 g, 1.92 mmol), analogously to Intermediate 1.1. HPLC: $^{D}t_{Ret}$ = 1.64; LC-MS: m/z 527.4 $[M+H]^+$.

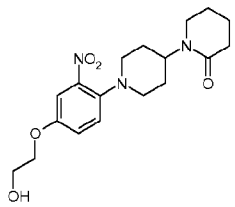
[00868] Intermediate 232.3: 1'-{4-[2-(tert-Butyl-diphenyl-silanyloxy)-ethoxy]-2-nitro-phenyl}-[1,4']bipiperidinyl-2-one.



[00869] To a solution of Intermediate 232.4 (766 mg, 2.108 mmol) in DCM (20 mL) was added NEt_3 (533 mg, 0.735 mL, 5.27 mmol) and DMAP (2.58 mg, 0.021 mmol). The red

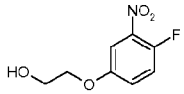
solution was cooled to 0 °C and TBDPS-chloride (695 mg, 0.650 mL, 2.53 mmol) was added dropwise. The reaction mixture was allowed to warm to RT, additional TBDPS-chloride (0.109 mL) was added during the cause of approximately 16 h. A saturated solution of $NaHCO_3$ was added and the reaction mixture was extracted with DCM. The combined organic phases were washed with water, brine, dried using Na_2SO_4, filtered and solvents were concentrated. The crude product was purified by silica gel column chromatography (eluting with a gradient of DCM:(DCM/EtOH 9:1) = 1:0 to 0:1) yielding the title Intermediate 232.3 (1.159 g, 1.926 mmol, 91%) as an orange solid. HPLC: $^{D}t_{Ret}$ = 1.70; LC-MS: m/z 602.4 $[M+H]^+$.

[00870] Intermediate 232.4: 1'-[4-(2-Hydroxy-ethoxy)-2-nitro-phenyl]-[1,4']bipiperidinyl-2-one.



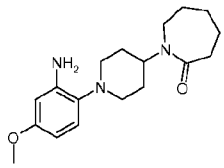
[00871] The title Intermediate 232.4 (766 mg, 2.11 mmol, 39%) was obtained from Intermediate 232.5 (1.35 g, 5.37 mmol) and 1,4'-bipiperidin-2-one (1.028 g, 5.64 mmol), analogously to Intermediate 1.2. HPLC: $^{D}t_{Ret}$ = 0.99 min; LC-MS: m/z 364.3 $[M+H]^+$.

[00872] Intermediate 232.5: 2-(4-Fluoro-3-nitro-phenoxy)-ethanol.



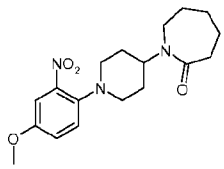
[00873] To a suspension of 4-fluoro-3-nitro-phenol (2.50 g, 15.91 mmol) and K_2CO_3 (4.40g, 31.8 mmol) in acetone (70 mL) at 0 °C was added a total of 2-bromoethanol (3.22 g, 1.82 mL, 25.79 mmol) and the reaction mixture was heated to reflux for overall 48 h. The reaction mixture was filtered and the filtrate was concentrated. The crude orange oil was purified by silica gel column chromatography (eluting with a gradient of DCM:(DCM/EtOH 9:1) = 1:0 to 0:1) yielding the title Intermediate 232.5 (1.56 g, 4.96 mmol, 31%) as an orange solid. HPLC: $^{D}t_{Ret}$ = 0.82; LC-MS: m/z not found $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) ppm 3.67 – 3.72 (m, 2 H), 4.04 – 4.08 (m, 2 H), 4.90 (t, *J*=5.47 Hz, 1 H), 7.37 (dt, *J*=9.09, 3.47 Hz, 1 H), 7.46 - 7.54 (m, 1 H), 7.61 (dd, *J*=5.87, 3.13 Hz, 1 H).

[00874] Intermediate 233.1: 1-[1-(2-Amino-4-methoxy-phenyl)-piperidin-4-yl]-azepan-2-one.



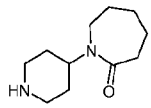
[00875] The title Intermediate 233.1 (500 mg, 1.57 mmol, 64%) was obtained as a colorless solid from Intermediate 233.2 (850 mg, 2.44 mmol), analogously to Intermediate 1.1. HPLC: $^{B}t_{Ret}$ = 4.52 min; LC-MS: m/z 318.3 $[M+H]^+$.

[00876] Intermediate 233.2: 1-[1-(4-Methoxy-2-nitro-phenyl)-piperidin-4-yl]-azepan-2-one.



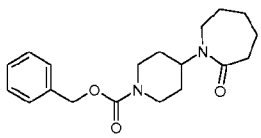
[00877] The title Intermediate 233.2 (854 mg, 2.45 mmol, 76%) was obtained from 1-fluoro-4-methoxy-2-nitrobenzene (550 mg, 3.21 mmol) and 1-(piperidin-4-yl)azepan-2-one (650 mg, 3.31 mmol), analogously to Intermediate 1.2. HPLC: $^{B}t_{Ret}$ = 6.55 min; LC-MS: m/z 348.3 $[M+H]^+$.

[00878] Intermediate 233.3: 1-Piperidin-4-yl-azepan-2-one.



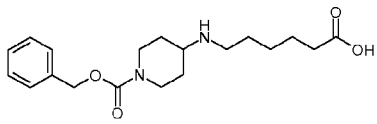
[00879] The title Intermediate 233.3 (1.32 g, 6.72 mmol, 99%) was obtained as a colorless solid from Intermediate 233.4 (2.25 g, 6.81 mmol), analogously to Intermediate 1.1. HPLC: $^{B}t_{Ret}$ = 3.53 min; LC-MS: m/z 197.2 $[M+H]^+$.

[00880] Intermediate 233.4: 4-(2-Oxo-azepan-1-yl)-piperidine-1-carboxylic acid benzyl ester.



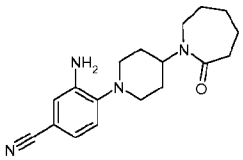
[00881] The title Intermediate 233.4 (2.255 g, 6.82 mmol, 60%) was obtained as a yellow oil from Intermediate 233.5 (3.95 g, 11.34 mmol), analogously to Intermediate 37.2. HPLC: $^{B}t_{Ret}$ = 6.28 min; LC-MS: m/z 331.2 $[M+H]^+$.

[00882] Intermediate 233.5: 4-(5-Carboxy-pentylamino)-piperidine-1-carboxylic acid benzyl ester.



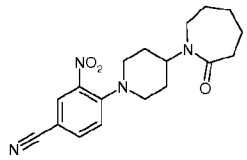
[00883] To a suspension of 6-Aminocaproic acid (3.37 g, 25.50 mmol) in 1,2-dichloroethan (60 mL) was added sodium triacetoxyboronhydride (3.37 g, 25.5 mmol), followed by the addition of 1-(benzyloxycarbonyl)-4-piperidinone (5.0 g, 21.22 mmol) in 1,2-dichloroethan (30 mL). The resulting suspension was first stirr at RT for 5 h and then heated to 60°C for 40 h. The reaction mixture was quenched with water, acidified using HCl conc, extracted with EtOAc, the combined organic phases were washed with water, dried using Na_2SO_4, filtered and evaporated during which crystallization occured. The crystalls that were obtained after multiple recrystallizations were filtered, washed with EtOAc and dried to yield the title Intermediate 233.5 (3.965 g, 11.38 mmol, 54%) as colourles crystalls. HPLC: $^{B}t_{Ret}$ = 4.89 min; LC-MS: m/z 349.2 $[M+H]^+$.

[00884] Intermediate 234.1: 3-Amino-4-[4-(2-oxo-azepan-1-yl)-piperidin-1-yl]-benzonitrile.



[00885] The title Intermediate 234.1 (765 mg, 2.45 mmol, 89%) was obtained as a beige solid from Intermediate 234.2 (945 mg, 2.76 mmol), analogously to Intermediate 1.1. HPLC: $^{B}t_{Ret}$ = 5.81 min; LC-MS: m/z 313.3 $[M+H]^+$.

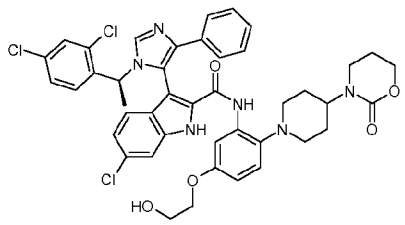
[00886] Intermediate 234.2: 3-Nitro-4-[4-(2-oxo-azepan-1-yl)-piperidin-1-yl]-benzonitrile.



[00887] The title Intermediate 234.2 (949 mg, 2.77 mmol, 85%) was obtained from 4-fluoro-3-nitrobenzonitrile (550 mg, 3.24 mmol) and Intermediate 233.2 (656 mg, 3.34 mmol), analogously to Intermediate 1.2. HPLC: $^{B}t_{Ret}$ = 6.30 min; LC-MS: m/z 343.1 $[M+H]^+$.

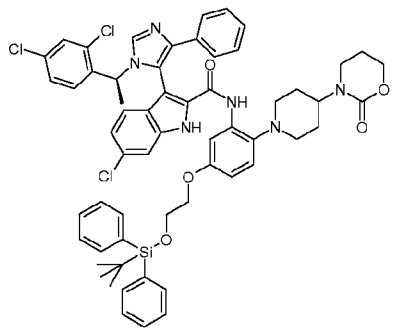
Example 235

6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {5-(2-hydroxy-ethoxy)-2-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-phenyl}-amide.



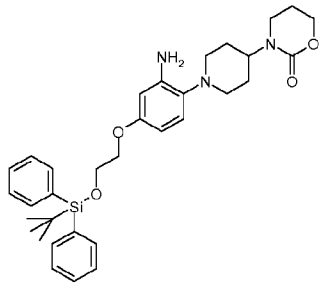
[00888] The title Example 235 (322 mg, 0.389 mmol, 80%) was obtained from Intermediate 235.1 (516 mg, 0.484 mmol), analogously to Example 232. HPLC: $^{D}t_{Ret}$ = 1.32; LC-MS: m/z 829.4 $[M+H]^+$.

[00889] Intermedaite 235.1: 6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {5-[2-(tert-butyl-diphenyl-silanyloxy)-ethoxy]-2-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-phenyl}-amide.



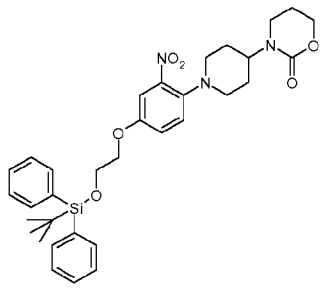
[00890] The title Intermediate 235.1 (516 mg, 0.48 mmol, 68%) was obtained from Intermediate 148.2 (412 mg, 0.71 mmol) and Intermediate 235.2 (427 mg, 0.74 mmol), analogously to Example 1. HPLC: $^{D}t_{Ret}$ = 1.822; LC-MS: m/z 1067.6 $[M+H]^+$.

[00891] Intermediate 235.2: 3-(1-{2-Amino-4-[2-(tert-butyl-diphenyl-silanyloxy)-ethoxy]-phenyl}-piperidin-4-yl)-[1,3]oxazinan-2-one.



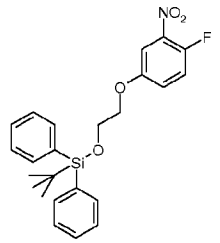
[00892] The title Intermediate 235.2 (313 mg, 0.54 mmol, 32%) was obtained as a brown foam from Intermediate 235.3 (1.04 g, 1.73 mmol), analogously to Intermediate 1.1. HPLC: $^{D}t_{Ret}$ = 1.58; LC-MS: m/z 574.2 $[M+H]^+$.

[00893] Intermediate 235.2: 3-(1-{4-[2-(tert-Butyl-diphenyl-silanyloxy)-ethoxy]-2-nitro-phenyl}-piperidin-4-yl)-[1,3]oxazinan-2-one.



[00894] The title Intermediate 235.2 (649 mg, 1.07 mmol, 21%) was obtained from Intermediate 235.3 (2.20 g, 5.01 mmol) and 3-(piperidin-4-yl)-1,3-oxazinan-2-one (969 mg, 5.26 mmol), analogously to Intermediate 1.2. HPLC: $^{B}t_{Ret}$ = 1.64 min; LC-MS: m/z 604.1 $[M+H]^+$.

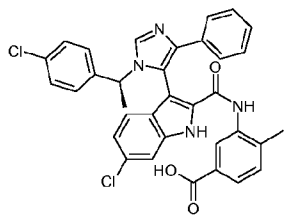
[00895] Intermediate 235.3: tert-Butyl-[2-(4-fluoro-3-nitro-phenoxy)-ethoxy]-diphenyl-silane.



[00896] The title Intermediate 235.3 (2.20 g, 4.51 mmol, 91%) was obtained from Intermediate 232.5 (1.56 g, 4.96 mmol) and TBDPS-chloride (1.36 g, 1.27 mL, 4.96 mmol), analogously to Intermediate 232.3. HPLC: $^{D}t_{Ret}$ = 1.701; m/z not found $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) ppm 0.92 - 0.99 (m, 9 H), 3.92 - 3.97 (m, 2 H), 4.19 - 4.24 (m, 2 H), 7.31 - 7.53 (m, 8 H) 7.61 (dd, *J*=7.82, 1.56 Hz, 5 H).

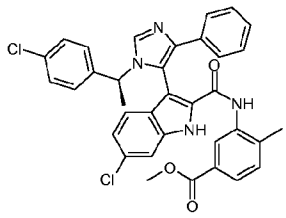
Example 236

3-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-methyl-benzoic acid.



[00897] The title compound (143 mg, 0.23 mmol, 67.8%) was obtained as a yellow solid from Intermediate 236.1 (207 mg, 0.33 mmol), analogously to Intermediate 1.4. HPLC: $^{A}t_{Ret}$ = 5.00; LC-MS: m/z 609.1$[M+H]^+$.

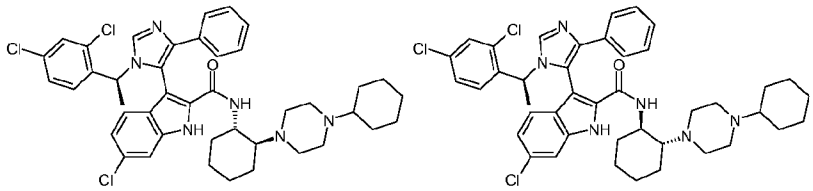
[00898] Intermediate 236.1: 3-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-methyl-benzoic acid methyl ester.



[00899] The title compound (295 mg, 0.47 mmol, 76%) was obtained as a slightly yellow solid from 3-amino-4-methyl-benzoic acid methyl ester (1.20 mL, 1.21 mmol) and Intermediate 1.3 (300 mg, 0.60 mmol), analogously to Example 1. HPLC: $^{A}t_{Ret}$ = 5.26; LC-MS: m/z 623$[M+H]^{+}$.

Examples 237 & 238

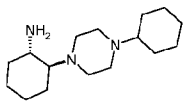
6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [(1S,2S)-2-(4-cyclohexyl-piperazin-1-yl)-cyclohexyl]-amide and 6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [(1R,2R)-2-(4-cyclohexyl-piperazin-1-yl)-cyclohexyl]-amide.



[00900] A mixture of Intermediate 148.3 (521 mg, 1.02 mmol), Intermediate 237.1 (450 mg, 1.02 mmol), HATU (776 mg, 2.04 mmol) and N-methylmorpholine (1.12 ml, 10.2 mmol) in DMF (5 mL) was stirred at RT. After 1 h, the reaction mixture was diluted with water and then extracted with DCM. The organic phases were washed with brine, dried over $MgSO_4$, filtered and solvents were concentrated. The crude product was purified by silica gel column chromatography (eluting with a gradient of DCM/MeOH = 100:0 to 80:20) yielding the mixture of diastereomers (732 mg, 0.96 mmol, 92%) as a yellow solid. The diastereomers (200 mg, 0.26 mmol) were

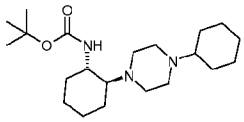
separated by reversed phase prep-HPLC (eluting with a gradient of MeCN:water + 0.1% TFA). Fractions containing pure material were combined, concentrated and the resulting aqueous mixture was neutralized with a saturated solution of $NaHCO_3$ followed by extraction with DCM. The organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness to yield the title Example 237 (20 mg, 0.026 mmol, 19.6%) HPLC: $^{A}t_{Ret} = 4.79$; LC-MS: m/z 759$[M+H]^+$. and Example 238 (27 mg, 0.035 mmol, 26.5%). HPLC: $^{A}t_{Ret} = 4.95$; LC-MS: m/z 759$[M+H]^+$.

[00901] Intermediate 237.1: (1S*,2S*)-2-(4-Cyclohexyl-piperazin-1-yl)-cyclohexylamine 3HCl salt.



[00902] The title compound (614 mg, 1.64 mmol, quantitative) was obtained as a white solid from Intermediate 237.2 (602 mg, 1.64 mmol), analogously to Example 2. LC-MS: m/z 266$[M+H]^+$.

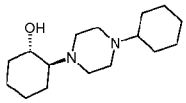
[00903] Intermediate 237.2: [(1S*,2S*)-2-(4-Cyclohexyl-piperazin-1-yl)-cyclohexyl]-carbamic acid tert-butyl ester.



[00904] To a mixture of Intermediate 237.3 (800 mg, 3.0 mmol), Et_3N (1.25 mL, 9.0 mmol) in THF (15 mL) was added MsCl (0.28 ml, 3.6 mmol) at 0 °C and the reaction mixture was stirred at RT. After 1 h, to the resulting suspension was added Et_3N (0.84 mL, 6.0 mmol) and $aqNH_3OH$ (7.0 mL, 44.9 mmol) at RT and stirred for 16 h. Argon gas was bubbled into the reaction mixture and then the resulting mixture was concentrated *in vacuo* in order to remove ammonia and the solvent. Obtained crude material was dissolved in EtOAc (15 mL) and $(Boc)_2O$ (1.97 g, 9.0 mmol) was added. After stirring for 2 h at RT, the reaction mixture was diluted with water and then extracted with EtOAc two times. The combined organic phases were washed with water, brine, dried using $MgSO_4$, filtered and solvents were concentrated. The crude product was purified by silica gel column chromatography (eluting with a gradient of DCM:(DCM/MeOH 9:1)

= 100:0 to 80:20) yielding the title Intermediate 237.2 (602 mg, 1.64 mmol, 52.1%) as a colorless oil. LC-MS: m/z 366 $[M+H]^+$.

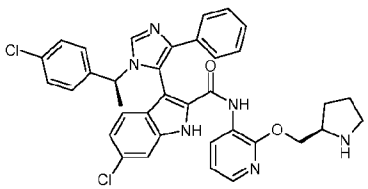
[00905] Intermediate 237.3 : (1S*,2S*)-2-(4-Cyclohexyl-piperazin-1-yl)-cyclohexanol.



[00906] A mixture of 7-oxa-bicyclo[4.1.0]heptane (1.2 mL, 11.88 mmol) and 1-cyclohexyl-piperazine (1.0 g, 5.94 mmol) in EtOH (5 mL) was heated at 80 °C. After 7 h, the reaction mixture was concentrated *in vacuo*. Dry with high vacumm gave the title Intermediate 237.3 (1.55 g, 5.81 mmol, 93%) as a white solid. LC-MS: m/z 366.5 $[M+H]^+$.

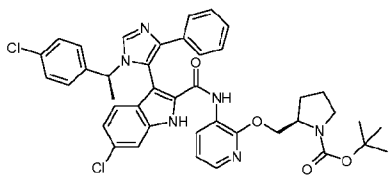
Example 239

6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-((R)-1-pyrrolidin-2-ylmethoxy)-pyridin-3-yl]-amide.



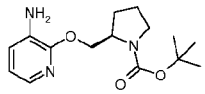
[00907] The title compound (360 mg, 0.50 mmol, 80%) was obtained as a white solid from Intermediate 239.1 (455 mg, 0.60 mmol), analogously to Example 2. HPLC: $^{A}t_{Ret} = 4.71$; LC-MS: m/z 650.9$[M+H]^+$.

[00908] Intermediate 239.1: (R)-2-{3-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-pyridin-2-yloxymethyl}-pyrrolidine-1-carboxylic acid tert-butyl ester.



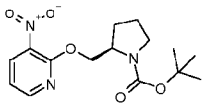
[00909] The title compound (468 mg, 0.62 mmol, 45.5%) was obtained as a yellow solid from Intermediate 1.3 (650 mg, 1.31 mmol) and Intermediate 239.2 (0.42 g, 1.44 mmol), analogously to Example 1. HPLC: $^{A}t_{Ret}$ = 6.12; LC-MS: m/z 751/749$[M+H]^+$.

[00910] Intermediate 239.2: (R)-2-(3-Amino-pyridin-2-yloxymethyl)-pyrrolidine-1-carboxylic acid tert-butyl ester.



[00911] The title compound (1.34 g, 4.56 mmol, 92%) was obtained as a white solid from Intermediate 239.3 (1.55 g, 4.79 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 4.34; LC-MS: m/z 294$[M+H]^+$.

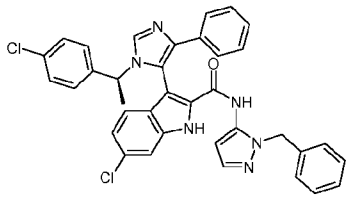
[00912] Intermediate 239.3: (R)-2-(3-Nitro-pyridin-2-yloxymethyl)-pyrrolidine-1-carboxylic acid tert-butyl ester.



[00913] A mixture of 2-chloro-3-nitro-pyridine (1.0 g, 6.31 mmol), (R)-2-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (1.39 g, 6.94 mmol), tris-[2-(2-methoxy-ethoxy)-ethyl]-amine (0.20 ml, 0.63 mmol), K_2CO_3 (1.48 g, 10.7 mmol) and KOH (0.60 g, 10.7 mmol) in toluene (17 ml) was stirred at RT. After 39 h, the reaction mixture was filtered and the insolubles were washed with EtOAc. The filtrate was concentrated *in vacuo* and then washed with water, brine, dried using $MgSO_4$, filtered and solvents were concentrated. The crude product was purified by silica gel column chromatography (eluting with a gradient of DCM:EtOAc = 100:0 to 0:100) yielding the title Intermediate 239.3 (1.55 g, 4.79 mmol, 76%) as an orange oil. HPLC: $^{A}t_{Ret}$ = 5.42; LC-MS: m/z 324$[M+H]^+$.

Example 240

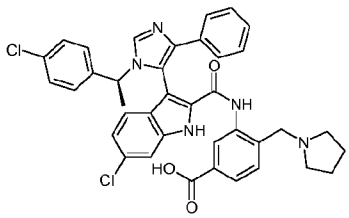
6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (2-benzyl-2H-pyrazol-3-yl)-amide.



[00914] A mixture of Intermediate 1.4 (250 mg, 0.52 mmol), 2-benzyl-2H-pyrazol-3-ylamine (144 mg, 0.78 mmol), HATU (299 mg, 0.78 mmol) and N-methylmorpholine (0.17 ml, 1.57 mmol) in DMF (4 mL) was heated at 50 °C. After 2 h, the reaction mixture was diluted with EtOAc, washed with a saturated solution of $NaHCO_3$. The combined organic phases were washed with water, brine, dried over $MgSO_4$, filtered and solvents were concentrated. The crude product was purified by reversed phase prep-HPLC (eluting with a gradient of MeCN:water + 0.1% TFA). Fractions containing pure material were combined, concentrated and the resulting aqueous mixture was neutralized with a saturated solution of $NaHCO_3$ followed by extraction with DCM. The organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness to yield the title Example 240 (48 mg, 0.076 mmol, 14.5%) as a ??. HPLC: $^{B}t_{Ret}$ = 6.57; LC-MS: m/z 630.8$[M+H]^+$.

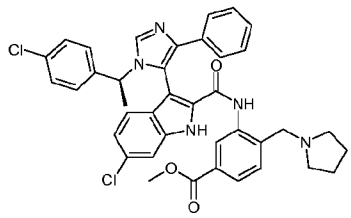
Example 241

3-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-pyrrolidin-1-ylmethyl-benzoic acid.



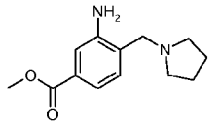
[00915] The title compound (68 mg, 0.10 mmol, 39.6%) was obtained as a white solid from Intermediate 241.1 (170 mg, 0.24 mmol), analogously to Intermediate 1.4. HPLC: $^{A}t_{Ret}$ = 4.55; LC-MS: m/z 678$[M+H]^+$.

[00916] Intermediate 241.1: 3-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-pyrrolidin-1-ylmethyl-benzoic acid methyl ester.



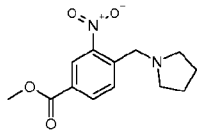
[00917] The title compound (294 mg, 0.42 mmol, 67.9%) was obtained as a slightly yellow solid from Intermediate 241.2 (156 mg, 0.66 mmol) and Intermediate 1.3 (300 mg, 0.60 mmol), analogously to Example 1. HPLC: $^{A}t_{Ret}$ = 4.73; LC-MS: m/z 692/694$[M+H]^+$.

[00918] Intermediate 241.2: 3-Amino-4-pyrrolidin-1-ylmethyl-benzoic acid methyl ester.



[00919] The title compound (275 mg, 1.17 mmol, 34.5%) was obtained as a white solid from Intermediate 241.3 (873 mg, 3.30 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.31; LC-MS: m/z 235$[M+H]^+$.

[00920] Intermediate 241.3: 3-Nitro-4-pyrrolidin-1-ylmethyl-benzoic acid methyl ester.

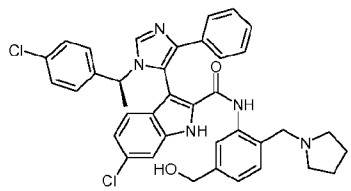


[00921] To a mixture of 4-formyl-3-nitro-benzoic acid methyl ester (1.0 g, 4.78 mmol), pyrrolidine (0.47 ml, 5.74 mmol) and sodium acetate (0.78 g, 9.56 mmol) in AcOH (0.55 ml) and THF (20 ml) added $NaBH(OAc)_3$ (3.0 g, 14.3 mmol) at RT. After 1 h, the reaction mixture was quenched with a saturated solution of $NaHCO_3$ and extracted with DCM. The combined organic phases were washed with water, brine, dried over $MgSO_4$, filtered and solvents were concentrated. The crude product was purified by silica gel column chromatography (eluting with a gradient of

DCM:MeOH = 100:0 to 80:20) yielding the title Intermediate 241.3 (876 mg, 3.31 mmol, 67.9%) as a yellow oil. HPLC: $^{A}t_{Ret}$ = 3.36; LC-MS: m/z 265[M+H]$^{+}$.

Example 242

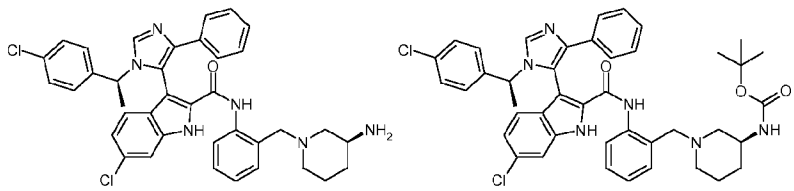
6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (5-hydroxy-methyl-2-pyrrolidin-1-ylmethyl-phenyl)-amide.



[00922] To a solution of Example 241 (90 mg, 0.13 mmol) in THF (2 ml) was added LiAlH4 (9.9 mg, 0.26 mmol) at 0 °C. After stirring for 2 h at RT, the reaction mixture was quenched with water and extracted with DCM. The combined organic phases were washed with water, brine, dried over $MgSO_4$, filtered and solvents were concentrated. The crude product was purified by silica gel column chromatography (eluting with a gradient of DCM:MeOH = 100:0 to 80:20) yielding the title Example 242 (54 mg, 0.08 mmol, 60.7%) as a yellow solid. HPLC: $^{A}t_{Ret}$ = 4.53; LC-MS: m/z 664[M+H]$^{+}$.

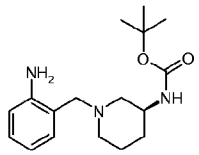
Example 243 & Intermediate 243.1

6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-((S)-3-amino-piperidin-1-ylmethyl)-phenyl]-amide and ((S)-1-{2-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-benzyl}-piperidin-3-yl)-carbamic acid tert-butyl ester.



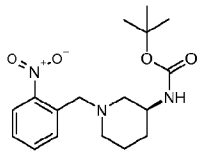
[00923] Example 243 (181 mg, 0.27 mmol, 27%) and the title Intermediate 243.1 (175 mg, 0.23 mmol, 22.6%) were obtained as a solid from Intermediate 243.2 (324 mg, 1.06 mmol) and Intermediate 1.3 (500 mg, 1.01 mmol), analogously to Example 1. Example 243: HPLC: $^{A}t_{Ret}$ = 4.31; LC-MS: m/z 663.2$[M+H]^+$. Intermediate 243.1: HPLC: $^{A}t_{Ret}$ = 4.96; LC-MS: m/z 763$[M+H]^+$.

[00924] Intermediate 243.2: [(S)-1-(2-Amino-benzyl)-piperidin-3-yl]-carbamic acid tert-butyl ester.



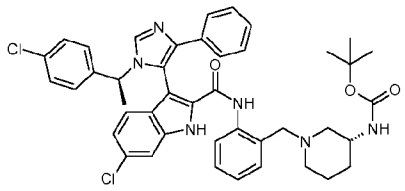
[00925] The title compound (1.03 g, 3.27 mmol, 93%) was obtained as a white solid from Intermediate 243.3 (873 mg, 3.30 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 3.85; LC-MS: m/z 306$[M+H]^+$.

[00926] Intermediate 243.3: [(S)-1-(2-Nitro-benzyl)-piperidin-3-yl]-carbamic acid tert-butyl ester.



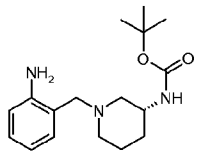
[00927] The title compound (1.21 g, 3.60 mmol, 80%) was obtained as a yellow oil from 2-nitro-benzaldehyde (688 mg, 4.55 mmol) and (S)-piperidin-3-yl-carbamic acid tert-butyl ester (957 mg, 4.78 mmol), analogously to Intermediate 241.3. HPLC: $^{A}t_{Ret}$ = 3.99; LC-MS: m/z 336$[M+H]^+$.

[00928] Intermediate 244.1: ((R)-1-{2-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-benzyl}-piperidin-3-yl)-carbamic acid tert-butyl ester.



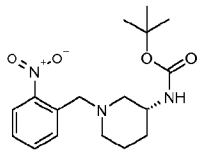
[00929] The title compound (300 mg, 0.39 mmol, 37.7%) was obtained as a yellow solid from Intermediate 244.2 (339 mg, 1.12 mmol) and Intermediate 1.3 (500 mg, 1.01 mmol), analogously to Example 1. HPLC: $^{A}t_{Ret}$ = 4.96; LC-MS: m/z 763$[M+H]^{+}$.

[00930] Intermediate 244.2: [(R)-1-(2-Amino-benzyl)-piperidin-3-yl]-carbamic acid tert-butyl ester.



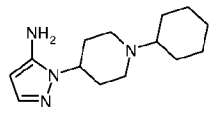
[00931] The title compound (760 Mg, 2.48 mmol, 63.5%) was obtained as a yellow oil from Intermediate 244.3 (1.31 g, 3.92 mmol), analogously to Intermediate 243.2. HPLC: $^{A}t_{Ret}$ = 3.85; LC-MS: m/z 306$[M+H]^{+}$.

[00932] Intermediate 244.3: [(R)-1-(2-Nitro-benzyl)-piperidin-3-yl]-carbamic acid tert-butyl ester.



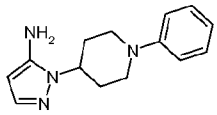
[00933] The title compound (1.31 g, 3.90 mmol, 84%) was obtained as a yellow oil from 2-nitro-benzaldehyde (704 mg, 4.66 mmol) and (R)-piperidin-3-yl-carbamic acid tert-butyl ester (980 mg, 4.89 mmol), analogously to Intermediate 243.3. HPLC: $^{A}t_{Ret}$ = 3.99; LC-MS: m/z 336$[M+H]^{+}$.

[00934] Intermediate 262.1: 2-(1-Cyclohexyl-piperidin-4-yl)-2H-pyrazol-3-ylamine.



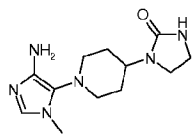
[00935] To a solution of acrylonitrile (0.36 ml, 5.52 mmol) in THF (3 ml) was added hydrazine hydrate (0.27 mL, 5.52 mmol) at 0 °C. After stirring for 2 h at RT, a solution of 1-cyclohexyl-piperidin-4-one (1.0 g, 5.52 mmol) in THF (3 mL) was added to the reaction mixture. After stirring for 18 h at RT, the reaction mixture was concentrated *in vacuo*, and then dissolved in 1-butanol (3 ml). A solution of sodium (0.12 g, 5.52 mmol) in 1-butanol (5 mL) was added to the reaction mixture, and it was heated at 120 °C. After 5 h heating, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic phases were washed with water, brine, dried over $MgSO_4$, filtered and solvents were concentrated. The crude product was purified by silica gel column chromatography yielding the title Intermediate 262.1 (351 mg, 1.41 mmol, 25.6%) as a yellow solid. HPLC: $^{B}t_{Ret}$ = 3.69; LC-MS: m/z 249.2$[M+H]^+$.

[00936] Intermediate 263.1: 2-(1-Phenyl-piperidin-4-yl)-2H-pyrazol-3-ylamine.



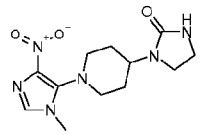
[00937] The title compound (310 mg, 1.28 mmol, 11.7%) was obtained from 1-phenyl-piperidin-4-one (2.0 g, 10.96 mmol), analogously to Intermediate 262.1. HPLC: $^{B}t_{Ret}$ = 3.77; LC-MS: m/z 243.2$[M+H]^+$.

[00938] Intermediate 264.1: 1-[1-(5-Amino-3-methyl-3H-imidazol-4-yl)-piperidin-4-yl]-imidazolidin-2-one.



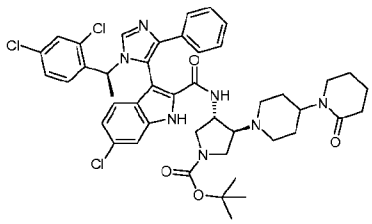
[00939] The title compound (159 mg, 0.60 mmol, 47%) was obtained as a green solid from Intermediate 264.2 (377 mg, 1.28 mmol), analogously to Intermediate 1.1. HPLC: $^{A}t_{Ret}$ = 2.95; LC-MS: m/z 265$[M+H]^+$.

[00940] Intermediate 264.2: 1-[1-(3-Methyl-5-nitro-3H-imidazol-4-yl)-piperidin-4-yl]-imidazolidin -2-one.



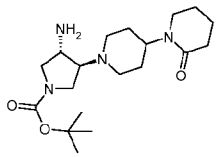
[00941] To a mixture of 5-chloro-1-methyl-4-nitro-1H-imidazole (569 mg, 3.52 mmol) and K_2CO_3 (1.95 g, 14.1 mmol) in MeCN was aded 1-piperidin-4-yl-imidazolidin-2-one HCl salt (797 mg, 3.87 mmol) at RT. After stirring for 16.5 h at RT, the reaction mixture was heated at 60-75 °C. After heating for a few day, the reaction mixture was filtered and washed with THF and MeCN. The filtrate was concentrated in vacuo and diluted with water and extracted with EtOAc. The combined organic phases were washed with water, brine, dried over $MgSO_4$, filtered and solvents were concentrated. The crude product was purified by silica gel column chromatography yielding the title Intermediate 264.2 (377 mg, 1.28 mmol, 36.4%) as a yellow solid. HPLC: $^{A}t_{Ret}$ = 3.40; LC-MS: m/z 295$[M+H]^+$.

[00942] Intermediate 265.1: (3S*,4S*)-3-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-(2-oxo-[1,4']bipiperidinyl-1'-yl)-pyrrolidine-1-carboxylic acid tert-butyl ester.



[00943] The title compound (575 mg, 0.67 mmol, 70.9%) was obtained as a slightly yellow solid from Intermediate 148.3 (696 mg, 1.83 mmol) and Intermediate 265.2 (369 mg, 1.00 mmol), analogously to Example 240. HPLC: $^{A}t_{Ret}$ = 4.79; LC-MS: m/z 860$[M+H]^+$.

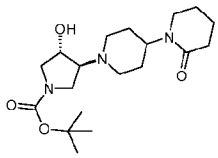
[00944] Intermediate 265.2: (3S*,4S*)-3-Amino-4-(2-oxo-[1,4']bipiperidinyl-1'-yl)-pyrrolidine-1-carboxylic acid tert-butyl ester.



[00945] To a mixture of Intermediate 265.3 (700 mg, 1.90 mmol), Et_3N (0.79 mL, 5.71 mmol) in THF (15 mL) was added MsCl (0.18 mL, 2.29 mmol) at 0 °C and the reaction mixture

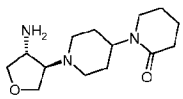
was stirred at RT. After 1 h, to the resulting suspension was added Et_3N (0.53 mL, 3.81 mmol) and aqNH_3OH (4.45 mL, 28.6 mmol) at RT and stirred for 16 h. Argon gas was bubbled into the reaction mixture and then the resulting mixture was concentrated *in vacuo* in order to remove ammonia and the solvent. The crude product was purified by silica gel column chromatography (eluting with a gradient of DCM/MeOH = 100:0 to 80:20) yielding the title compound (369 mg, 1.00 mmol, 50.2%) as a white solid. LC-MS: m/z 367.4 $[M+H]^+$.

[00946] Intermediate 265.3: (3S*,4S*)-3-Hydroxy-4-(2-oxo-[1,4']bipiperidinyl-1'-yl)-pyrrolidine-1-carboxylic acid tert-butyl ester.



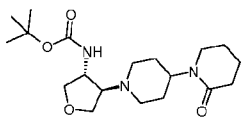
[00947] The title compound (701 mg, 1.90 mmol, 72.6%) was obtained as a yellow solid from 6-oxa-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid tert-butyl ester (513 mg, 2.77 mmol) and 1,4']bipiperidinyl-2-one (455 mg, 2.49 mmol), analogously to Intermediate 237.3. LC-MS: m/z 368$[M+H]^+$.

[00948] Intermediate 268.1: 1'-((3R*,4R*)-4-Amino-tetrahydro-furan-3-yl)-[1,4']bipiperidinyl-2-one.



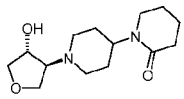
[00949] The title compound (140 mg, 0.46 mmol, quantitative) was obtained as a white solid from Intermediate 268.2 (169 mg, 0.46 mmol), analogously to Example 2. LC-MS: m/z 268$[M+H]^+$.

[00950] Intermediate 268.2: [(3R*,4R*)-4-(2-Oxo-[1,4']bipiperidinyl-1'-yl)-tetrahydro-furan-3-yl]-carbamic acid tert-butyl ester.



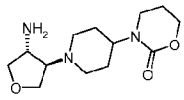
[00951] The title compound (169 mg, 0.46 mmol, 53.1%) was obtained as a white form from Intermediate 268.3 (250 mg, 0.866 mmol), analogously to Intermediate 237.2. LC-MS: m/z 368$[M+H]^+$.

[00952] Intermediate 268.3: 1'-((3S*,4R*)-4-Hydroxy-tetrahydro-furan-3-yl)-[1,4']bipiperidinyl-2-one.



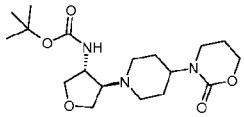
[00953] The title compound (833 mg, 3.10 mmol, 91%) was obtained as a white solid from 3,6-dioxa-bicyclo[3.1.0]hexane (548 mg, 6.36 mmol) and [1,4']bipiperidinyl-2-one (580 mg, 3.18 mmol), analogously to Intermediate 237.3. LC-MS: m/z 269$[M+H]^+$.

[00954] Intermediate 269.1: 3-[1-((3R*,4R*)-4-Amino-tetrahydro-furan-3-yl)-piperidin-4-yl]-[1,3]oxazinan-2-one.



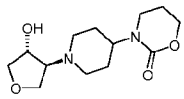
[00955] The title compound (302 mg, 0.99 mmol, quantitative) was obtained as a white solid from Intermediate 269.2 (367 mg, 0.99 mmol), analogously to Example 2. LC-MS: m/z 270$[M+H]^+$.

[00956] Intermediate 269.2: {(3R,4R)-4-[4-(2-Oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-tetrahydro-furan-3-yl}-carbamic acid tert-butyl ester.



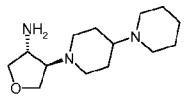
[00957] The title compound (367 mg, 0.99 mmol, 39%) was obtained as a white solid from Intermediate 269.3 (654 mg, 2.41 mmol), analogously to Intermediate 237.2. LC-MS: m/z 368$[M+H]^+$.

[00958] Intermediate 269.3: 3-[1-((3S,4R)-4-Hydroxy-tetrahydro-furan-3-yl)-piperidin-4-yl]-[1,3] oxazinan-2-one.



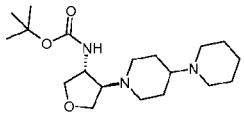
[00959] The title compound (654 mg, 2.41 mmol, 85%) was obtained as a brown oil from 3,6-dioxa-bicyclo[3.1.0]hexane (280 mg, 3.26 mmol) and 3-piperidin-4-yl-[1,3]oxazinan-2-one (500 mg, 2.71 mmol), analogously to Intermediate 237.3. LC-MS: m/z 271$[M+H]^+$.

[00960] Intermediate 270.1: (3R*,4R*)-4-[1,4']Bipiperidinyl-1'-yl-tetrahydro-furan-3-ylamine 3HCl salt.



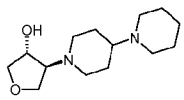
[00961] The title compound (626 mg, 1.72 mmol, 97%) was obtained as a white solid from Intermediate 270.2 (628 mg, 1.77 mmol), analogously to Example 2. LC-MS: m/z 254$[M+H]^+$.

[00962] Intermediate 270.2 : ((3R*,4R*)-4-[1,4']Bipiperidinyl-1'-yl-tetrahydro-furan-3-yl)-carbamic acid tert-butyl ester.



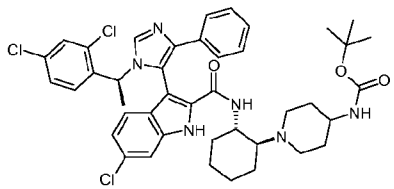
[00963] The title compound (628 mg, 1.77 mmol, 58.2%) was obtained as an orange solid from Intermediate 270.3 (777 mg, 3.05 mmol), analogously to Intermediate 237.2. LC-MS: m/z 368$[M+H]^+$.

[00964] Intermediate 270.3: (3R*,4S*)-4-[1,4']Bipiperidinyl-1'-yl-tetrahydro-furan-3-ol.



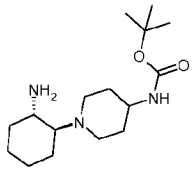
[00965] The title compound (1.49 g, 5.85 mmol, 97%) was obtained as a white solid from 3,6-dioxa-bicyclo[3.1.0]hexane (1.02 g, 11.89 mmol) and [1,4']bipiperidiny (1.0 g, 5.94 mmol), analogously to Intermediate 237.3. LC-MS: m/z 255$[M+H]^+$.

[00966] Intermediate 271.1: (1-{(1S,2S)-2-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-cyclohexyl}-piperidin-4-yl)-carbamic acid tert-butyl ester.



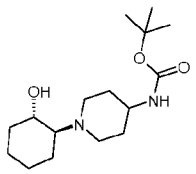
[00967] The title compound (824 mg, 1.04 mmol, 65.5%) as a single diastereomer was obtained as a white solid from Intermediate 148.3 (1.61 g, 3.15 mmol) and Intermediate 271.2 (1.12 g, 3.78 mmol), analogously to Example 240. HPLC: $^{A}t_{Ret}$ = 5.02; LC-MS: m/z 791[M+H]$^{+}$.

[00968] Intermediate 271.2: [1-((1S*,2S*)-2-Amino-cyclohexyl)-piperidin-4-yl]-carbamic acid tert-butyl ester.



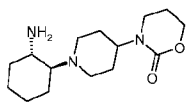
[00969] The title compound (1.14 g, 3.83 mmol, 41.2%) was obtained as a white solid from Intermediate 271.3 (2.64 g, 8.85 mmol), analogously to Intermediate 265.2. LC-MS: m/z 298[M+H]$^{+}$.

[00970] Intermediate 271.3: [1-((1S*,2S*)-2-Hydroxy-cyclohexyl)-piperidin-4-yl]-carbamic acid tert-butyl ester.



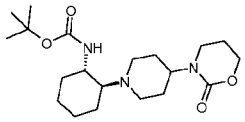
[00971] The title compound (2.75 g, 9.21 mmol, 67.7%) was obtained as a white solid from 7-oxa-bicyclo[4.1.0]heptane (1.90 g, 19.4 mmol) and piperidin-4-yl-carbamic acid tert-butyl ester (2.59 g, 12.93 mmol), analogously to Intermediate 237.3. LC-MS: m/z 299[M+H]$^{+}$.

[00972] Intermediate 273.1: 3-[1-((1S*,2S*)-2-Amino-cyclohexyl)-piperidin-4-yl]-[1,3]oxazinan-2-one 2HCl salt.



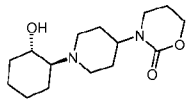
[00973] The title compound (575 mg, 1.81 mmol, quantitative) was obtained as a white solid from Intermediate 273.2 (693 mg, 1.81 mmol), analogously to Example 2. LC-MS: m/z 282[M+H]$^{+}$.

[00974] Intermediate 273.2: {(1S*,2S*)-2-[4-(2-Oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-cyclohexyl}-carbamic acid tert-butyl ester.



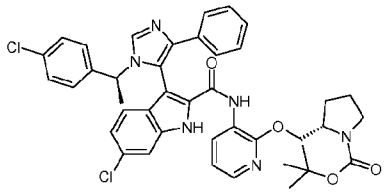
[00975] The title compound (734 mg, 1.92 mmol, 52.1%) was obtained as a white solid from Intermediate 273.3 (990 mg, 3.51 mmol), analogously to Intermediate 237.2. LC-MS: m/z 382[M+H]$^+$.

[00976] Intermediate 273.3: 3-[1-((1S*,2S*)-2-Hydroxy-cyclohexyl)-piperidin-4-yl]-[1,3]oxazinan-2-one.



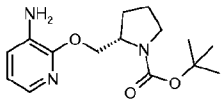
[00977] The title compound (1.10 g, 3.89 mmol, 74.9%) was obtained as a white solid from 7-oxa-bicyclo[4.1.0]heptane (727 mg, 7.41 mmol) and 3,6-dioxa-bicyclo[3.1.0]hexane (910 mg, 4.94 mmol), analogously to Intermediate 237.3. LC-MS: m/z 283[M+H]$^+$.

[00978] Intermediate 274.1: (S)-2-{3-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-pyridin-2-yloxymethyl}-pyrrolidine-1-carboxylic acid tert-butyl ester.



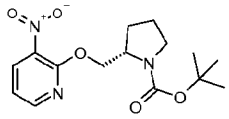
[00979] The title compound (772 mg, 1.02 mmol, 50.8%) was obtained as a slightly yellow solid from Intermediate 1.3 (1.0 g, 1.96 mmol) and Intermediate 274.2 (0.63 g, 2.15 mmol), analogously to Intermediate 239.1. HPLC: $^{A}t_{Ret}$ = 6.03; LC-MS: m/z 751[M+H]$^+$.

[00980] Intermediate 274.2: (S)-2-(3-Amino-pyridin-2-yloxymethyl)-pyrrolidine-1-carboxylic acid tert-butyl ester.



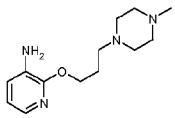
[00981] The title compound (1.02 g, 3.47 mmol, 95%) was obtained as a white solid from Intermediate 274.3 (1.14 g, 3.53 mmol), analogously to Intermediate 239.2. HPLC: $^{A}t_{Ret}$ = 4.35; LC-MS: m/z 294$[M+H]^+$.

[00982] Intermediate 274.3: (S)-2-(3-Nitro-pyridin-2-yloxymethyl)-pyrrolidine-1-carboxylic acid tert-butyl ester.



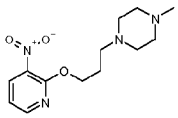
[00983] The title compound (1.14 g, 3.53 mmol, 54.8%) was obtained as a yellow oil from 2-chloro-3-nitro-pyridine (1.0 g, 6.31 mmol) and (S)-2-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (1.39 g, 6.94 mmol), analogously to Intermediate 239.3. HPLC: $^{A}t_{Ret}$ = 5.47; LC-MS: m/z 268$[M+H]^+$.

[00984] Intermediate 275.1: 2-[3-(4-Methyl-piperazin-1-yl)-propoxy]-pyridin-3-ylamine.



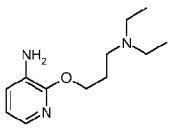
[00985] The title compound (789 mg, 3.15 mmol, quantitative) was obtained as a yellow oil from Intermediate 275.2 (884 mg, 3.15 mmol), analogously to Intermediate 239.2. HPLC: $^{A}t_{Ret}$ = 2.28; LC-MS: m/z 251$[M+H]^+$.

[00986] Intermediate 275.2: 1-Methyl-4-[3-(3-nitro-pyridin-2-yloxy)-propyl]-piperazine.



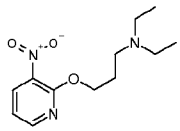
[00987] The title compound (884 mg, 3.15 mmol, 45%) was obtained as a brown oil from 2-chloro-3-nitro-pyridine (1.0 g, 6.31 mmol) and 3-(4-methyl-piperazin-1-yl)-propan-1-ol (1.1 g, 6.94 mmol), analogously to Intermediate 239.3. HPLC: $^{A}t_{Ret}$ = 2.94; LC-MS: m/z 324$[M+H]^+$.

[00988] Intermediate 276.1: 2-(3-Diethylamino-propoxy)-pyridin-3-ylamine.



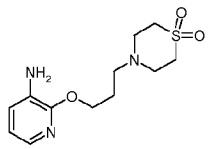
[00989] The title compound (167 mg, 0.74 mmol, 23%) was obtained as a yellow oil from Intermediate 276.2 (807 mg, 3.19 mmol), analogously to Intermediate 239.2. HPLC: $^{A}t_{Ret}$ = 2.79; LC-MS: m/z 224$[M+H]^+$.

[00990] Intermediate 276.2: Diethyl-[3-(3-nitro-pyridin-2-yloxy)-propyl]-amine.



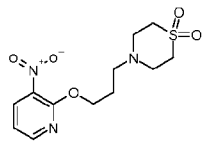
[00991] The title compound (807 mg, 3.19 mmol, 45.5%) was obtained as a brown oil from 2-chloro-3-nitro-pyridine (1.0 g, 6.31 mmol) and 3-diethylamino-propan-1-ol (0.96 g, 6.94 mmol), analogously to Intermediate 239.3. HPLC: $^{A}t_{Ret}$ = 3.60; LC-MS: m/z 254$[M+H]^+$.

[00992] Intermediate 277.1: 4-(3-((3-aminopyridin-2-yl)oxy)propyl)thiomorpholine 1,1-dioxide.



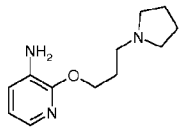
[00993] The title compound (650 mg, 2.27 mmol, 81%) was obtained as a yellow oil from Intermediate 277.2 (800 mg, 2.54 mmol), analogously to Intermediate 239.2. HPLC: $^{A}t_{Ret}$ = 2.43; LC-MS: m/z 286$[M+H]^+$.

[00994] Intermediate 277.2: 4-[3-(3-Nitro-pyridin-2-yloxy)-propyl]-thiomorpholine 1,1-dioxide.



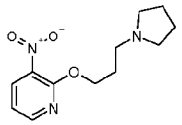
[00995] The title compound (1.44 g, 4.56 mmol, 57.9%) was obtained as a slightly yellow oil from 2-chloro-3-nitro-pyridine (1.0 g, 6.31 mmol) and 3-(1,1-dioxo-thiomorpholin-4-yl)-propan-1-ol (1.34 g, 6.94 mmol), analogously to Intermediate 239.3. HPLC: $^{A}t_{Ret}$ = 3.26; LC-MS: m/z 316$[M+H]^+$.

[00996] Intermediate 278.1: 2-(3-Pyrrolidin-1-yl-propoxy)-pyridin-3-ylamine.



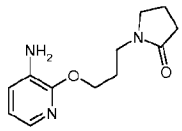
[00997] The title compound (194 mg, 0.87 mmol, 86.8%) was obtained as a yellow oil from Intermediate 278.2 (254 mg, 1.01 mmol), analogously to Intermediate 239.2. HPLC: $^{A}t_{Ret}$ = 2.69; LC-MS: m/z 222$[M+H]^+$.

[00998] Intermediate 278.2 : 3-Nitro-2-(3-pyrrolidin-1-yl-propoxy)-pyridine.



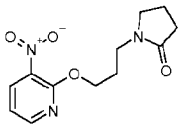
[00999] The title compound (254 mg, 1.01 mmol, 15.2%) was obtained as a yellow oil from 2-chloro-3-nitro-pyridine (1.0 g, 6.31 mmol) and 3-pyrrolidin-1-yl-propan-1-ol (0.81 g, 6.31 mmol), analogously to Intermediate 239.3. HPLC: $^{A}t_{Ret}$ = 3.53; LC-MS: m/z 252$[M+H]^+$.

[001000] Intermediate 279.1: 1-[3-(3-Amino-pyridin-2-yloxy)-propyl]-pyrrolidin-2-one.



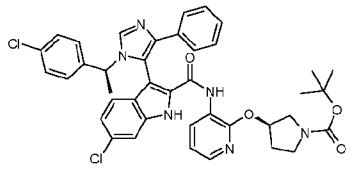
[001001] The title compound (341 mg, 1.45 mmol, 41.7%) was obtained as a yellow oil from Intermediate 279.2 (875 mg, 3.30 mmol), analogously to Intermediate 239.2. HPLC: $^{A}t_{Ret}$ = 3.03; LC-MS: m/z 236 $[M+H]^+$.

[001002] Intermediate 279.2: 1-[3-(3-Nitro-pyridin-2-yloxy)-propyl]-pyrrolidin-2-one.



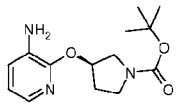
[001003] The title compound (880 mg, 3.31 mmol, 52.6%) was obtained as a yellow oil from 2-chloro-3-nitro-pyridine (1.0 g, 6.31 mmol) and 1-(3-Hydroxy-propyl)-pyrrolidin-2-one (0.99 g, 6.94 mmol), analogously to Intermediate 239.3. HPLC: $^{A}t_{Ret}$ = 4.26; LC-MS: m/z 266 $[M+H]^+$.

[001004] Intermediate 280.1: (R)-3-{3-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-pyridin-2-yloxy}-pyrrolidine-1-carboxylic acid tert-butyl ester.



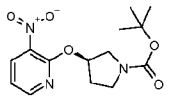
[001005] The title compound (1.84 g, 2.49 mmol, 60.4%) was obtained as a yellow solid from Intermediate 1.3 (2.0 g, 3.92 mmol) and Intermediate 280.2 (1.20 g, 4.31 mmol), analogously to Example 1. HPLC: $^{A}t_{Ret}$ = 5.60; LC-MS: m/z 737 $[M+H]^+$.

[001006] Intermediate 280.2: (R)-3-(3-Amino-pyridin-2-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester.



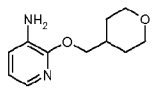
[001007] The title compound (4.19 g, 15.0 mmol, 99.5%) was obtained as a white solid from Intermediate 280.3 (4.66 g, 15.0 mmol), analogously to Intermediate 239.2. HPLC: $^{A}t_{Ret}$ = 4.15; LC-MS: m/z 280$[M+H]^+$.

[001008] Intermediate 280.3: (R)-3-(3-Nitro-pyridin-2-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester.



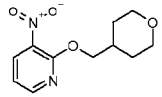
[001009] The title compound (621 mg, 2.00 mmol, 62.4%) was obtained as a yellow oil from 2-chloro-3-nitro-pyridine (500 mg, 3.15 mmol) and (R)-3-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester (650 mg, 3.47 mmol), analogously to Intermediate 239.3. HPLC: $^{A}t_{Ret}$ = 5.21; LC-MS: m/z 310$[M+H]^+$.

[001010] Intermediate 285.1: 2-(Tetrahydro-pyran-4-ylmethoxy)-pyridin-3-ylamine.



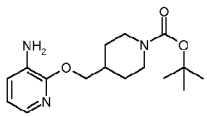
[001011] The title compound (784 mg, 3.76 mmol, 97%) was obtained as a white solid from Intermediate 285.2 (914 mg, 3.84 mmol), analogously to Intermediate 239.2. HPLC: $^{A}t_{Ret}$ = 3.14.

[001012] Intermediate 285.2 : 3-Nitro-2-(tetrahydro-pyran-4-ylmethoxy)-pyridine.



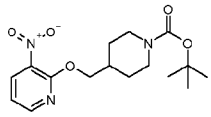
[001013] The title compound (914 mg, 3.84 mmol, 63.7%) was obtained as an orange oil from 2-chloro-3-nitro-pyridine (955 mg, 6.03 mmol) and (tetrahydro-pyran-4-yl)-methanol (700 mg, 6.03 mmol), analogously to Intermediate 239.3. HPLC: $^{A}t_{Ret}$ = 4.75; LC-MS: m/z 239$[M+H]^+$.

[001014] Intermediate 286.1: 4-(3-Amino-pyridin-2-yloxymethyl)-piperidine-1-carboxylic acid tert-butyl ester.



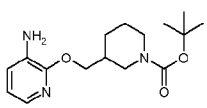
[001015] The title compound (1.22 g, 3.96 mmol, 86%) was obtained as a white solid from Intermediate 286.2 (1.48 g, 4.39 mmol), analogously to Intermediate 239.2. HPLC: $^{A}t_{Ret}$ = 4.34; LC-MS: m/z 308$[M+H]^+$.

[001016] Intermediate 286.2: 4-(3-Nitro-pyridin-2-yloxymethyl)-piperidine-1-carboxylic acid tert-butyl ester.



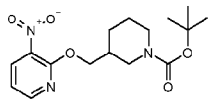
[001017] The title compound (1.48 mg, 4.39 mmol, 68.2%) was obtained as a yellow oil from 2-chloro-3-nitro-pyridine (1.0 g, 6.31 mmol) and 4-hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester (1.54 g, 6.94 mmol), analogously to Intermediate 239.3. HPLC: $^{A}t_{Ret}$ = 5.54; LC-MS: m/z 338$[M+H]^+$.

[001018] Intermediate 288.1: 3-(3-Amino-pyridin-2-yloxymethyl)-piperidine-1-carboxylic acid tert-butyl ester.



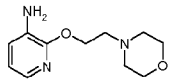
[001019] The title compound (1.06 g, 3.44 mmol, 92%) was obtained as a white solid from Intermediate 288.2 (1.20 g, 3.56 mmol), analogously to Intermediate 239.2. HPLC: $^{A}t_{Ret}$ = 4.42; LC-MS: m/z 308$[M+H]^+$.

[001020] Intermediate 288.2: 3-(3-Nitro-pyridin-2-yloxymethyl)-piperidine-1-carboxylic acid tert-butyl ester.



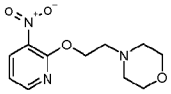
[001021] The title compound (1.21 g, 3.58 mmol, 69.7%) was obtained as a yellow oil from 2-chloro-3-nitro-pyridine (800 mg, 5.05 mmol) and 3-hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester (1.25 g, 5.55 mmol), analogously to Intermediate 239.3. HPLC: $^{A}t_{Ret}$ = 5.57; LC-MS: m/z 338$[M+H]^+$.

[001022] Intermediate 290.1: 2-(2-Morpholin-4-yl-ethoxy)-pyridin-3-ylamine.



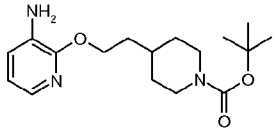
[001023] The title compound (445 mg, 1.99 mmol, 97%) was obtained as a colorless oil from Intermediate 290.2 (519 mg, 2.04 mmol), analogously to Intermediate 239.2. HPLC: $^{A}t_{Ret}$ = 2.50; LC-MS: m/z 224$[M+H]^+$.

[001024] Intermediate 290.2: 4-[2-(3-Nitro-pyridin-2-yloxy)-ethyl]-morpholine.



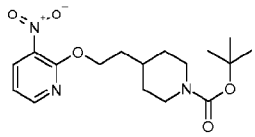
[001025] The title compound (519 mg, 2.04 mmol, 63%) was obtained as a purple oil from 2-chloro-3-nitro-pyridine (500 mg, 3.15 mmol) and 2-morpholin-4-yl-ethanol (455 mg, 3.47 mmol), analogously to Intermediate 239.3. HPLC: $^{A}t_{Ret}$ = 3.10; LC-MS: m/z 253$[M+H]^+$.

[001026] Intermediate 291.1: 4-[2-(3-Amino-pyridin-2-yloxy)-ethyl]-piperidine-1-carboxylic acid tert-butyl ester.



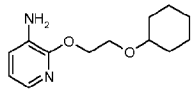
[001027] The title compound (624 mg, 1.94 mmol, 98%) was obtained as a colorless oil from Intermediate 291.2 (690 mg, 1.97 mmol), analogously to Intermediate 239.2. HPLC: $^{A}t_{Ret}$ = 4.47; LC-MS: m/z 322[M+H]$^{+}$.

[001028] Intermediate 291.2: 4-[2-(3-Nitro-pyridin-2-yloxy)-ethyl]-piperidine-1-carboxylic acid tert-butyl ester.



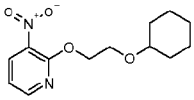
[001029] The title compound (690 mg, 1.97 mmol, 60.4%) was obtained as a yellow oil from 2-chloro-3-nitro-pyridine (500 mg, 3.15 mmol) and 4-(2-hydroxy-ethyl)-piperidine-1-carboxylic acid tert-butyl ester (796 mg, 3.47 mmol), analogously to Intermediate 239.3. HPLC: $^{A}t_{Ret}$ = 5.75; LC-MS: m/z 352[M+H]$^{+}$.

[001030] Intermediate 293.1: 2-(2-Cyclohexyloxy-ethoxy)-pyridin-3-ylamine.



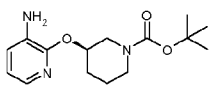
[001031] The title compound (715 mg, 3.02 mmol, 92.5%) was obtained as a colorless oil from Intermediate 293.2 (870 mg, 3.27 mmol), analogously to Intermediate 239.2. HPLC: $^{A}t_{Ret}$ = 3.10; LC-MS: m/z 237[M+H]$^{+}$.

[001032] Intermediate 293.2: 2-(2-Cyclohexyloxy-ethoxy)-3-nitro-pyridine.



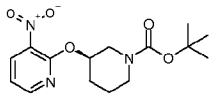
[001033] The title compound (870 mg, 3.27 mmol, 49.2%) was obtained as a slightly yellow oil from 2-chloro-3-nitro-pyridine (1.0 g, 6.31 mmol) and 2-cyclohexyloxy-ethanol (0.91 g, 6.31 mmol), analogously to Intermediate 239.3. HPLC: $^{A}t_{Ret}$ = 5.40; LC-MS: m/z 267[M+H]$^{+}$.

[001034] Intermediate 294.1: (R)-3-(3-Amino-pyridin-2-yloxy)-piperidine-1-carboxylic acid tert-butyl ester.



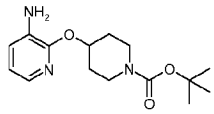
[001035] The title compound (738 mg, 2.51 mmol, 99%) was obtained as a colorless oil from Intermediate 294.2 (820 mg, 2.54 mmol), analogously to Intermediate 239.2. HPLC: $^{A}t_{Ret}$ = 4.28; LC-MS: m/z 294[M+H]$^{+}$.

[001036] Intermediate 294.2: (R)-3-(3-Nitro-pyridin-2-yloxy)-piperidine-1-carboxylic acid tert-butyl ester.



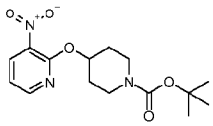
[001037] The title compound (822 mg, 2.54 mmol, 57%) was obtained as a yellow oil from 2-chloro-3-nitro-pyridine (0.7 g, 4.42 mmol) and (R)-3-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (1.03 g, 4.86 mmol), analogously to Intermediate 239.3. HPLC: $^{A}t_{Ret}$ = 5.32; LC-MS: m/z 324[M+H]$^{+}$.

[001038] Intermediate 296.1: 4-(3-Amino-pyridin-2-yloxy)-piperidine-1-carboxylic acid tert-butyl ester.



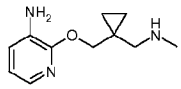
[001039] The title compound (424 mg, 1.44 mmol, 71.6%) was obtained as a white solid from Intermediate 296.2 (620 mg, 1.91 mmol), analogously to Intermediate 239.2. HPLC: $^{A}t_{Ret}$ = 4.21; LC-MS: m/z 294[M+H]$^{+}$.

[001040] Intermediate 296.2: 4-(3-Nitro-pyridin-2-yloxy)-piperidine-1-carboxylic acid tert-butyl ester.



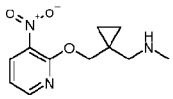
[001041] The title compound (620 mg, 1.91 mmol, 30%) was obtained as a yellow oil from 2-chloro-3-nitro-pyridine (1.0 g, 6.31 mmol) and 4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (1.39 g, 6.94 mmol), analogously to Intermediate 239.3. HPLC: $^{A}t_{Ret}$ = 5.45; LC-MS: m/z 324[M+H]$^{+}$.

[001042] Intermediate 300.1: 2-(1-Methylaminomethyl-cyclopropylmethoxy)-pyridin-3-ylamine.



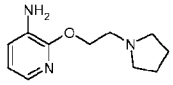
[001043] The title compound (200 mg, 0.96 mmol, 91%) was obtained as a purple solid from Intermediate 300.2 (251 mg, 1.05 mmol), analogously to Intermediate 239.2. HPLC: $^{A}t_{Ret}$ = 2.95; LC-MS: m/z 208$[M+H]^{+}$.

[001044] Intermediate 300.2: Methyl-[1-(3-nitro-pyridin-2-yloxymethyl)-cyclopropylmethyl]-amine.



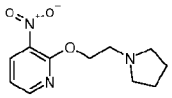
[001045] The title compound (251 mg, 1.05 mmol, 16.7%) was obtained as a slightly yellow oil from 2-chloro-3-nitro-pyridine (1.0 g, 6.31 mmol) and (1-methylaminomethyl-cyclopropyl)-methanol (0.80 g, 6.94 mmol), analogously to Intermediate 239.3. HPLC: $^{A}t_{Ret}$ = 4.38; LC-MS: m/z 238$[M+H]^{+}$.

[001046] Intermediate 301.1: 2-(2-Pyrrolidin-1-yl-ethoxy)-pyridin-3-ylamine.



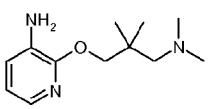
[001047] The title compound (281 mg, 1.35 mmol, 64%) was obtained as a brown oil from Intermediate 301.2 (500 mg, 2.10 mmol), analogously to Intermediate 239.2. HPLC: $^{A}t_{Ret}$ = 2.70.

[001048] Intermediate 301.2: 3-Nitro-2-(2-pyrrolidin-1-yl-ethoxy)-pyridine.



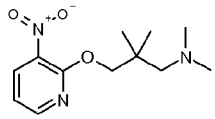
[001049] The title compound (500 mg, 2.10 mmol, 55.7%) was obtained as a yellow oil from 2-chloro-3-nitro-pyridine (600 mg, 3.78 mmol) and 2-pyrrolidin-1-yl-ethanol (479 mg, 4.16 mmol), analogously to Intermediate 239.3. HPLC: $^{A}t_{Ret}$ = 3.27; LC-MS: m/z 238$[M+H]^{+}$.

[001050] Intermediate 302.1 : 2-(3-Dimethylamino-2,2-dimethyl-propoxy)-pyridin-3-ylamine.



[001051] The title compound (315 mg, 1.41 mmol, 95%) was obtained as a brown oil from Intermediate 302.2 (375 mg, 1.48 mmol), analogously to Intermediate 239.2. HPLC: $^{A}t_{Ret}$ = 2.90; LC-MS: m/z 224$[M+H]^+$.

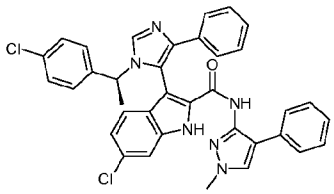
[001052] Intermediate 302.2 : [2,2-Dimethyl-3-(3-nitro-pyridin-2-yloxy)-propyl]-dimethyl-amine.



[001053] The title compound (382 mg, 1.50 mmol, 23%) was obtained as an orange oil from 2-chloro-3-nitro-pyridine (1.0 g, 6.31 mmol) and 3-dimethylamino-2,2-dimethyl-propan-1-ol (0.91 g, 6.94 mmol), analogously to Intermediate 239.3. HPLC: $^{A}t_{Ret}$ = 3.68; LC-MS: m/z 254$[M+H]^+$.

Example 254

6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (1-methyl-4-phenyl-1H-pyrazol-3-yl)-amide

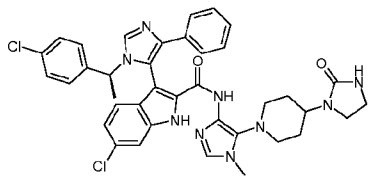


[001054] A mixture of **Intermediate 1.4** (250 mg, 0.52 mmol), 1-Methyl-4-phenyl-1H-pyrazol-3-ylamine (91 mg, 0.52 mmol), HATU (299 mg, 0.78 mmol) and N-methylmorpholine (0.17 ml, 1.57 mmol) in DMF (2 mL) was heated at 50 °C. After 1 h, the reaction mixture was diluted with EtOAc, washed with a saturated solution of $NaHCO_3$. The combined organic phases were washed with water, brine, dried over $MgSO_4$, filtered and solvents were concentrated. The crude product was purified by reversed phase prep-HPLC (eluting with a gradient of MeCN:water + 0.1% TFA). Fractions containing pure material were combined, concentrated and the resulting

aqueous mixture was neutralized with a saturated solution of $NaHCO_3$ followed by extraction with DCM. The organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness to yield the title **Example 254** (96 mg, 0.15 mmol, 29%). HPLC: $^{B}t_{Ret}$ = 6.55; LC-MS: m/z 630.9$[M+H]^+$.

Example 264

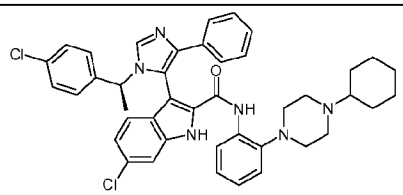
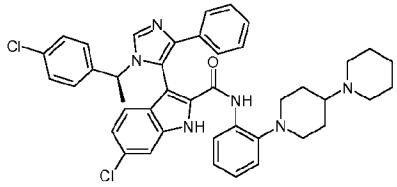
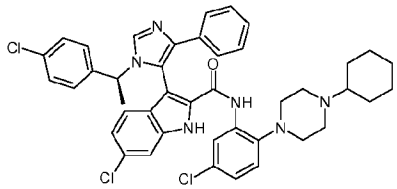
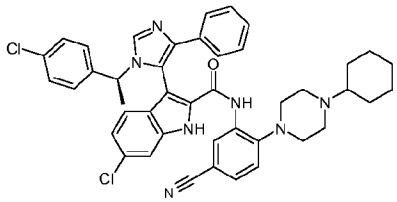
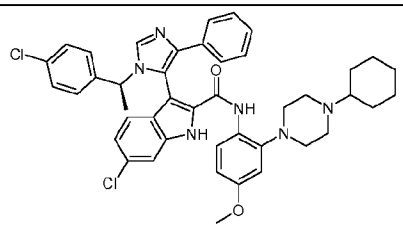
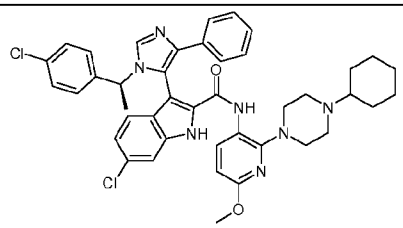
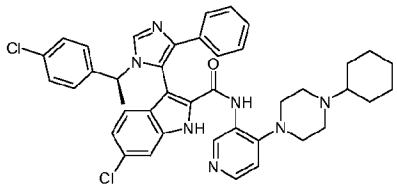
6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {1-methyl-5-[4-(2-oxo-imidazolidin-1-yl)-piperidin-1-yl]-1H-imidazol-4-yl}-amide

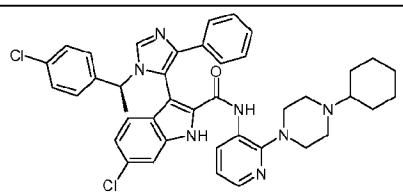
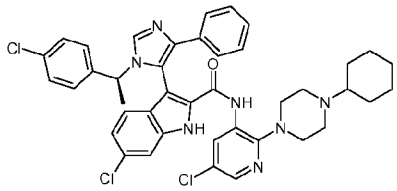
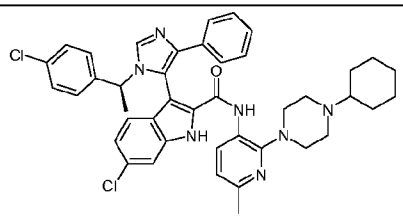
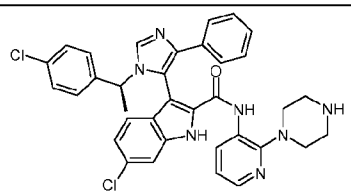
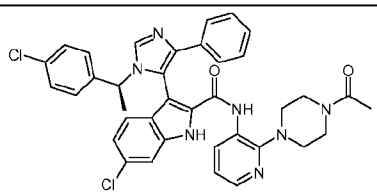
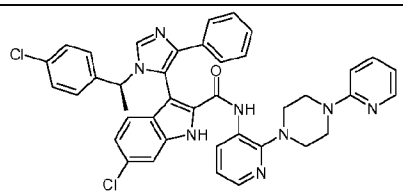
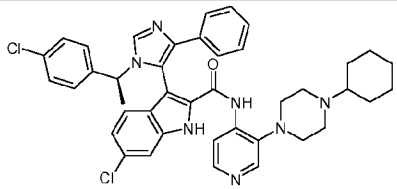
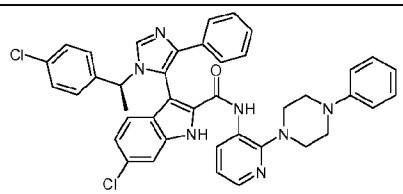


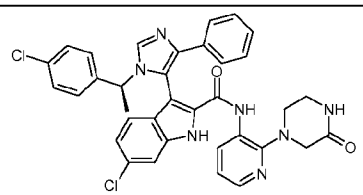
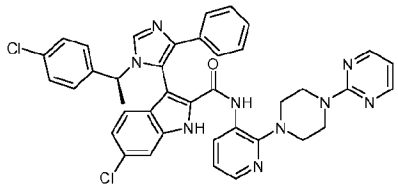
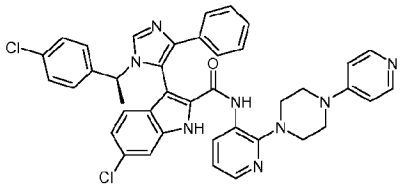
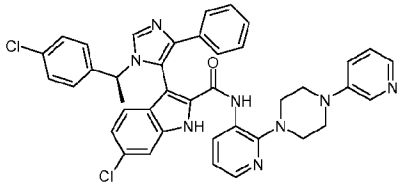
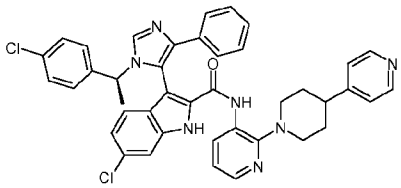
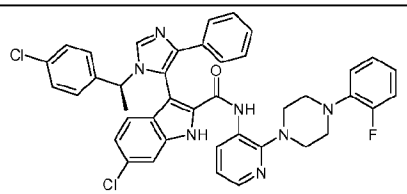
[001055] To a solution of **Intermediate 264.1** (159 mg, 0.60 mmol) in DCM (5 mL) was added drop wise a 1 M hexane solution of Me_2AlCl (1.09 mL, 1.09 mmol) at 0 °C. The resulting suspension was stirred at 0 °C for 30 min. **Intermediate 1.3** (270 mg, 0.54 mmol) was added to the reaction mixture at RT. After 1.5 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ at 0 °C, then poured into vigourously stirring H_2O and immdediately diluted with EtOAc and THF. Large excess Rochelle's salt was added and the mixture was stirred at RT for 1 h. The organic phase was separated, the aqueous phase was extracted twice with a mixture of EtOAc and THF (70:30), washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel column chromatography (eluting with a gradient of DCM:EtOAc = 90:10 to 0:100, then MeOH:EtOAc = 0:100 to 20:80) of the residue afforded the title **Example 264** (40 mg, 0.055 mmol, 10.1%) as a yellow solid. HPLC: AtRet = 4.39; LC-MS: m/z 722.2[M+H]+.

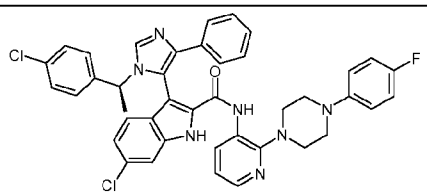
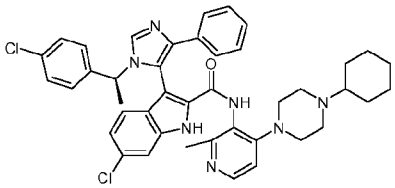
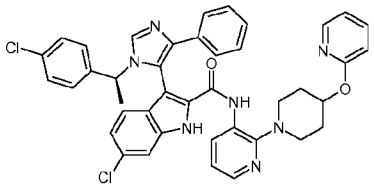
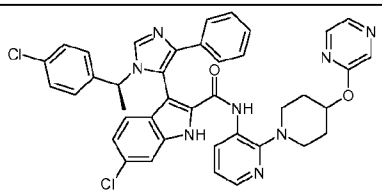
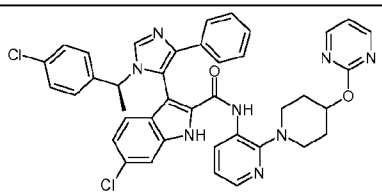
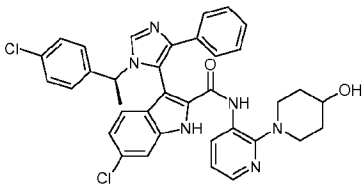
[001056] By repeating the procedures described in the above examples, using appropriate starting materials, the following compounds of Formula I, as identified in Table 1, are obtained.

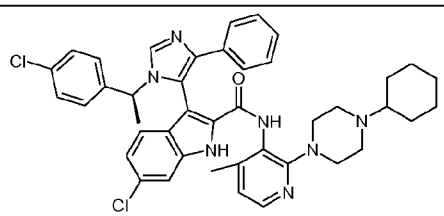
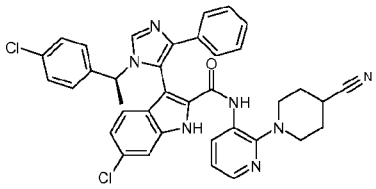
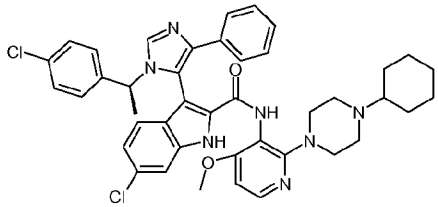
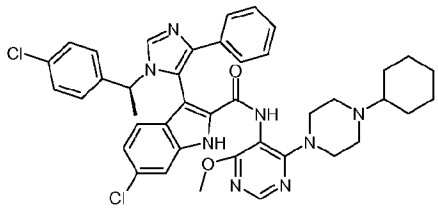
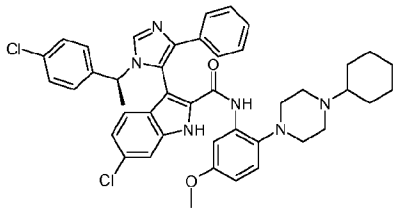
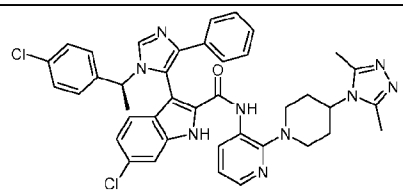
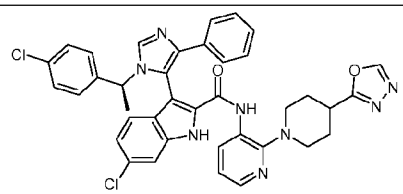
Table 1

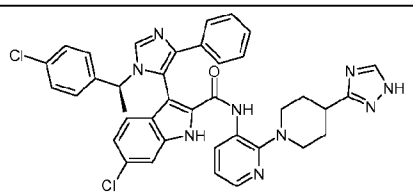
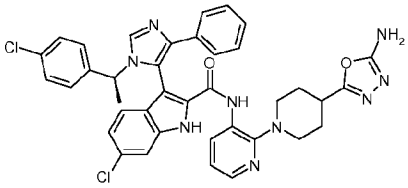
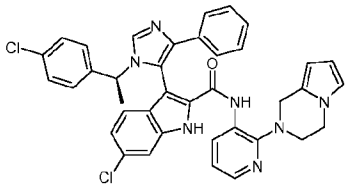
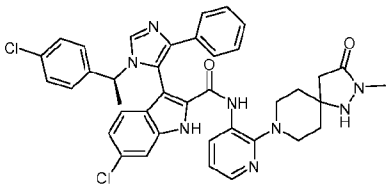
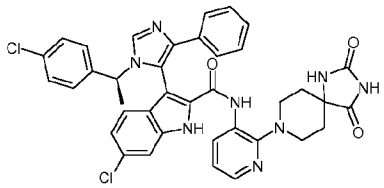
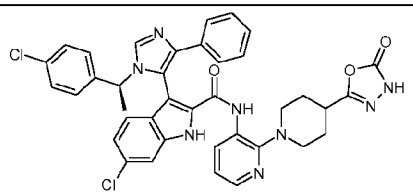
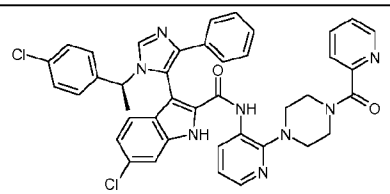
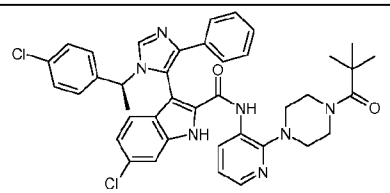
	Structure	Name/HPLC/MS/NMR
4		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-cyclohexyl-piperazin-1-yl)-phenyl]-amide. HPLC: $^{A}t_{Ret}$ = 5.01; LC-MS: m/z 717.2 $[M+H]^+$.
5		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (2-[1,4'] bipiperidinyl-1'-yl-phenyl)-amide. HPLC: $^{A}t_{Ret}$ = 4.93; LC-MS: m/z 717.2 $[M+H]^+$.
6		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [5-chloro-2-(4-cyclohexyl-piperazin-1-yl)-phenyl]-amide. HPLC: $^{A}t_{Ret}$ = 5.15; LC-MS: m/z 753.2 $[M+H]^+$.
7		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [5-cyano-2-(4-cyclohexyl-piperazin-1-yl)-phenyl]-amide. HPLC: $^{A}t_{Ret}$ = 4.99; LC-MS: m/z 742.4 $[M+H]^+$.
8		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-cyclohexyl-piperazin-1-yl)-4-methoxy-phenyl]-amide. HPLC: $^{A}t_{Ret}$ = 5.01; LC-MS: m/z 747.4 $[M+H]^+$.
9		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-cyclohexyl-piperazin-1-yl)-6-methoxy-pyridin-3-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.98; LC-MS: m/z 748.4 $[M+H]^+$.
10		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(4-cyclohexyl-piperazin-1-yl)-pyridin-3-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.40; LC-MS: m/z 717.8 $[M+H]^+$.

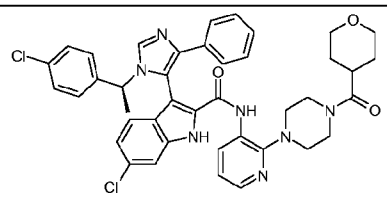
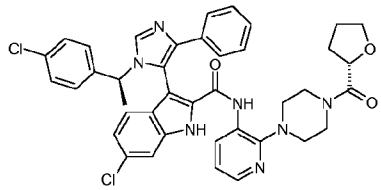
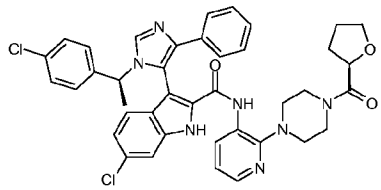
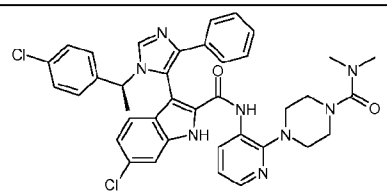
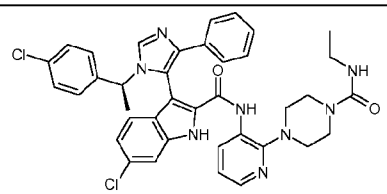
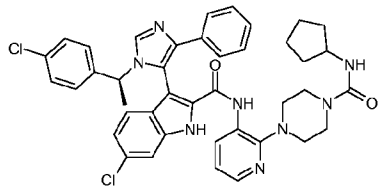
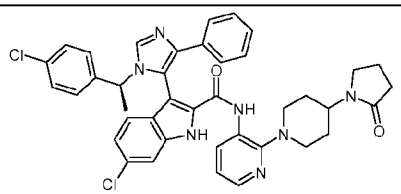
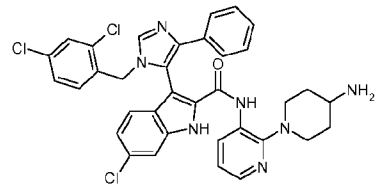
11		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-cyclohexyl-piperazin-1-yl)-pyridin-3-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.88; LC-MS: m/z 718.2 $[M+H]^+$.
12		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [5-chloro-2-(4-cyclohexyl-piperazin-1-yl)-pyridin-3-yl]-amide. HPLC: $^{A}t_{Ret}$ = 5.03; LC-MS: m/z 754.2 $[M+H]^+$.
13		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-cyclohexyl-piperazin-1-yl)-6-methyl-pyridin-3-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.94; LC-MS: m/z 732.3 $[M+H]^+$.
14		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (2-piperazin-1-yl-pyridin-3-yl)-amide HCl salt. HPLC: $^{A}t_{Ret}$ = 4.44; LC-MS: m/z 635.9 $[M+H]^+$.
15		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-acetyl-piperazin-1-yl)-pyridin-3-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.63; LC-MS: m/z 678.1 $[M+H]^+$.
16		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-pyridin-2-yl-piperazin-1-yl)-pyridin-3-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.51; LC-MS: m/z 712.8 $[M+H]^+$.
17		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [3-(4-cyclohexyl-piperazin-1-yl)-pyridin-4-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.56; LC-MS: m/z 717.9 $[M+H]^+$.
18		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-phenyl-piperazin-1-yl)-pyridin-3-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.99; LC-MS: m/z 712.0 $[M+H]^+$.

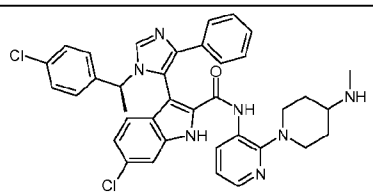
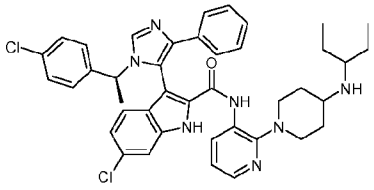
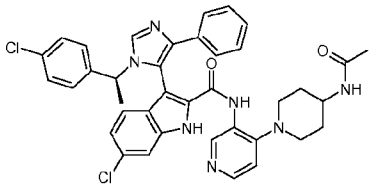
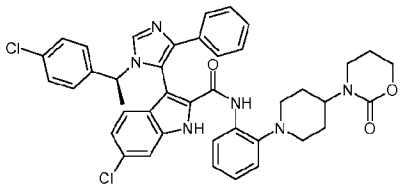
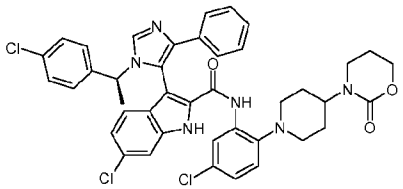
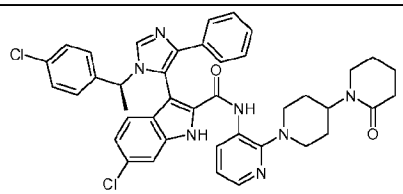
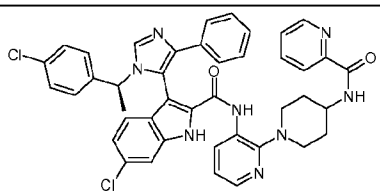
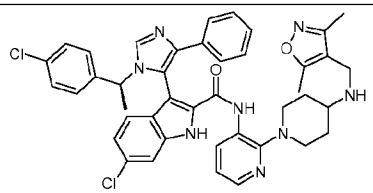
19		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(3-oxo-piperazin-1-yl)-pyridin-3-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.74; LC-MS: m/z 649.8 $[M+H]^+$.
20		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-pyrimidin-2-yl-piperazin-1-yl)-pyridin-3-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.78; LC-MS: m/z 713.9 $[M+H]^+$.
21		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-pyridin-4-yl-piperazin -1-yl)-pyridin-3-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.41; LC-MS: m/z 712.9 $[M+H]^+$.
22		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-pyridin-3-yl-piperazin -1-yl)-pyridin-3-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.43; LC-MS: m/z 712.8 $[M+H]^+$.
23		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (3',4',5',6'-tetrahydro-2'H-[2,1';4',4"]terpyridin-3-yl)-amide. HPLC: $^{A}t_{Ret}$ = 4.32; LC-MS: m/z 711.8 $[M+H]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.28 - 1.40 (m, 2 H), 1.52 (d, *J*=7.06 Hz, 3 H), 1.56 - 1.62 (m, 2 H), 2.30 - 2.44 (m, 2 H), 2.90 (d, *J*=11.71 Hz, 1 H), 2.99 (t, *J*=10.90 Hz, 1 H), 3.10 (d, *J*=11.30 Hz, 1 H), 4.99 - 5.18 (m, 1 H), 6.57 (d, *J*=8.48 Hz, 1 H), 6.65 - 6.73 (m, 2 H), 6.74 - 6.80 (m, 1 H), 6.93 (d, *J*=4.24 Hz, 2 H), 6.98 - 7.13 (m, 5 H), 7.15 - 7.23 (m, 1 H), 7.40 - 7.54 (m, 3 H), 8.08 - 8.15 (m, 1 H), 8.34 (dd, *J*=4.14, 1.72 Hz, 2 H), 8.37 (d, *J*=1.61 Hz, 1 H), 8.52 - 8.63 (m, 2 H), 12.50 (s, 1 H).
24		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {2-[4-(2-fluoro-phenyl)-piperazin-1-yl]-pyridin-3-yl}-amide. HPLC: $^{A}t_{Ret}$ = 5.18; LC-MS: m/z 729.9 $[M+H]^+$.

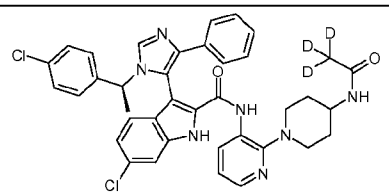
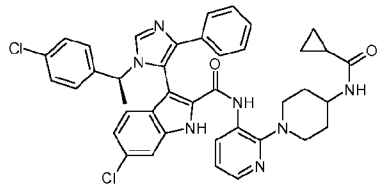
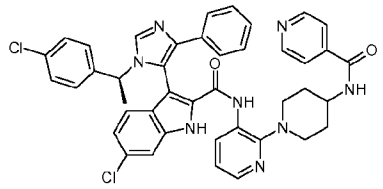
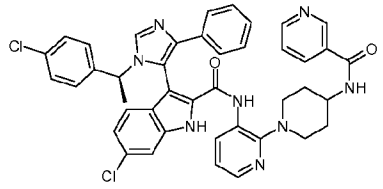
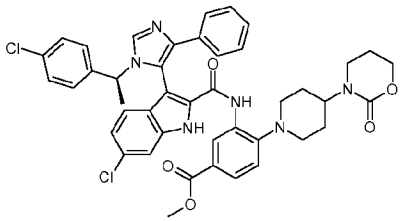
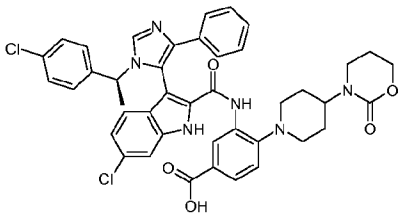
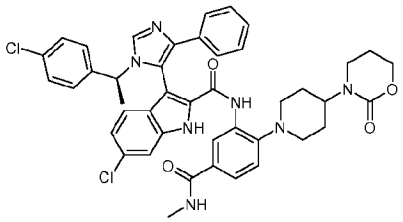
25		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {2-[4-(4-fluoro-phenyl)-piperazin-1-yl]-pyridin-3-yl}-amide. HPLC: $^{A}t_{Ret}$ = 5.06; LC-MS: m/z 729.9 $[M+H]^+$.
26		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(4-cyclohexyl-piperazin-1-yl)-2-methyl-pyridin-3-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.38; LC-MS: m/z 732.0 $[M+H]^+$.
27		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(pyridin-2-yloxy)-3,4,5,6 -tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{B}t_{Ret}$ = 6.21; LC-MS: m/z 728 $[M+H]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.44 – 1.81 (m, 6 H), 1.71 – 1.80 (br s, 1 H), 2.60 – 2.68 (m, 1 H), 2.75 – 2.81 (m, 1 H), 2.84 – 2.93 (m, 1 H), 3.13 – 3.22 (m, 1 H), 4.88 (br. s., 1 H), 5.07 (q, *J*=7.00 Hz, 1 H), 6.62 - 6.79 (m, 4 H), 6.84 (br. d., *J*=8.28, 1 H), 6.88 - 6.96 (m, 1 H), 6.97 - 7.18 (m, 6 H), 7.44 - 7.56 (m, 3 H), 7.61 - 7.72 (m, 1 H), 8.10 (dd, *J*=17.46, 4.54 Hz, 2 H), 8.34 (br. s., 1 H), 8.41 (d, *J*=7.87, 1 H), 8.49 (br. s., 1 H), 12.52 (br. s., 1 H).
28		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(pyrazin-2-yloxy)-3,4,5, 6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.79; LC-MS: m/z 731.2 $[M+H]^+$.
29		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(pyrimidin-2-yloxy)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.75; LC-MS: m/z 730.8 $[M+H]^+$.
30		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (4-hydroxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl)-amide. HPLC: $^{A}t_{Ret}$ = 4.43; LC-MS: m/z 650.9 $[M+H]^+$.

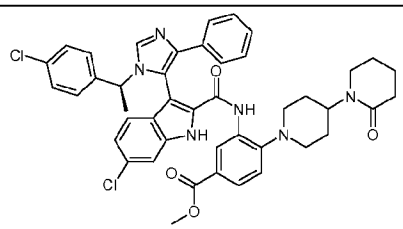
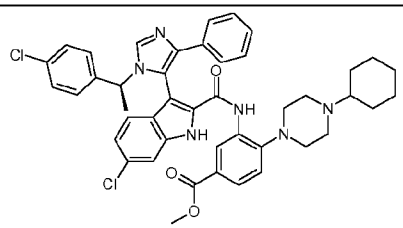
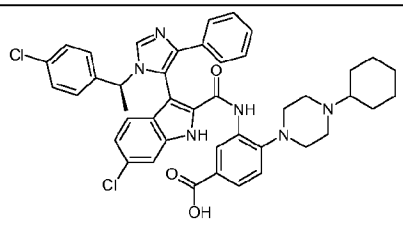
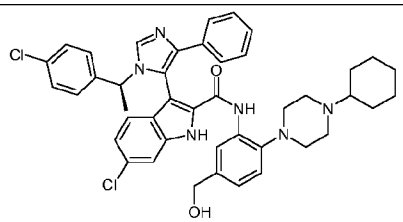
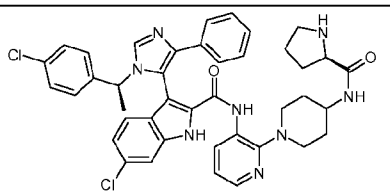
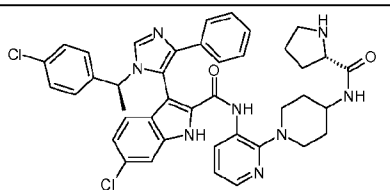
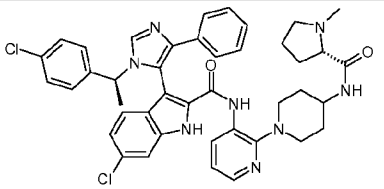
31		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-cyclohexyl-piperazin-1-yl)-4-methyl-pyridin-3-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.73; LC-MS: m/z 732.0 $[M+H]^+$.
32		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (4-cyano-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl)-amide. HPLC: $^{A}t_{Ret}$ = 4.80; LC-MS: m/z 659.9 $[M+H]^+$.
33		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-cyclohexyl-piperazin-1-yl)-4-methoxy-pyridin-3-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.56; LC-MS: m/z 748.0 $[M+H]^+$.
34		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(4-cyclohexyl-piperazin-1-yl)-6-methoxy-pyrimidin-5-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.69; LC-MS: m/z 748.9 $[M+H]^+$.
35		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-cyclohexyl-piperazin-1-yl)-5-methoxy-phenyl]-amide. HPLC: $^{A}t_{Ret}$ = 5.06; LC-MS: m/z 747.3 $[M+H]^+$.
36		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(3,5-dimethyl-[1,2,4] triazol-4-yl)-3,4,5,6-tetrahydro-2H-[1,2'] bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.43; LC-MS: m/z 730.0 $[M+H]^+$.
37		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (4-[1,3,4]oxadiazol-2-yl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl)-amide. HPLC: $^{A}t_{Ret}$ = 4.23; LC-MS: m/z 703.2 $[M+H]^+$.

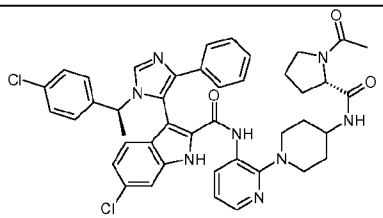
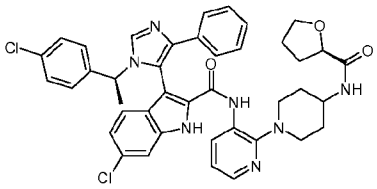
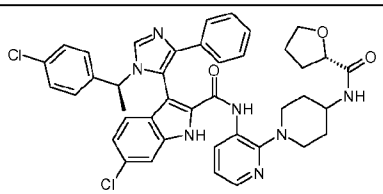
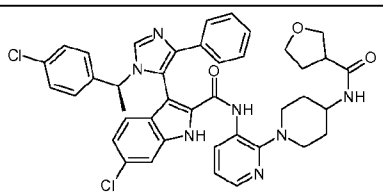
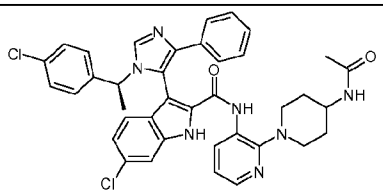
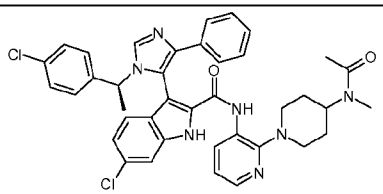
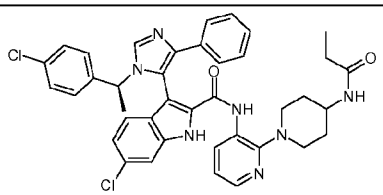
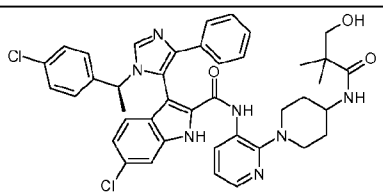
38		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(1H-[1,2,4]triazol-3-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.42; LC-MS: m/z 701.9 $[M+H]^+$.
39		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(5-amino-[1,3,4] oxadiazol-2-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.40; LC-MS: m/z 718.3 $[M+H]^+$.
40		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(3,4-dihydro-1H-pyrrolo [1,2-a]pyrazin-2-yl)-pyridin-3-yl]-amide. HPLC: $^{A}t_{Ret}$ = 5.12; LC-MS: m/z 671.9 $[M+H]^+$.
41		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(2-methyl-3-oxo-1,2,8-triaza-spiro[4.5]dec-8-yl)-pyridin-3-yl]-amide. HPLC: $^{B}t_{Ret}$ = 5.69; LC-MS: m/z 718.8 $[M+H]^+$.
42		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(2,4-dioxo-1,3,8-triaza-spiro[4.5]dec-8-yl)-pyridin-3-yl]-amide. HPLC: $^{B}t_{Ret}$ = 5.73; LC-MS: m/z 718.8 $[M+H]^+$.
43		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(5-oxo-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. LCMS: $^{A}t_{Ret}$ = 1.97; LC-MS: m/z 719.2 $[M+H]^+$.
44		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {2-[4-(pyridine-2-carbonyl) -piperazin-1-yl]-pyridin-3-yl}-amide. HPLC: $^{A}t_{Ret}$ = 4.76; LC-MS: m/z 740.9 $[M+H]^+$.
45		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {2-[4-(2,2-dimethyl-propionyl)-piperazin-1-yl]-pyridin-3-yl}-amide. HPLC: $^{A}t_{Ret}$ = 5.01; LC-MS: m/z 719.9 $[M+H]^+$.

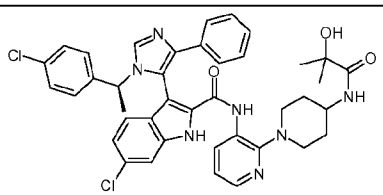
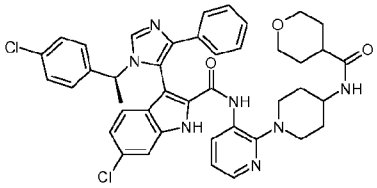
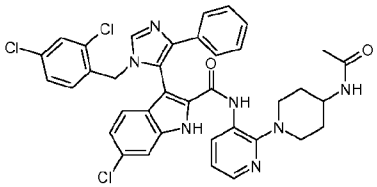
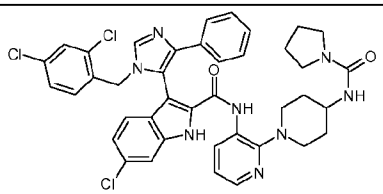
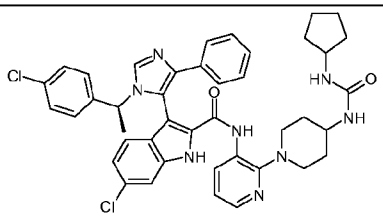
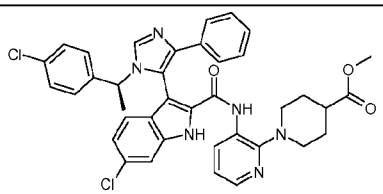
46		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {2-[4-(tetrahydro-pyran-4-carbonyl)-piperazin-1-yl]-pyridin-3-yl}-amide. HPLC: $^{A}t_{Ret}$ = 4.70; LC-MS: m/z 748.3 $[M+H]^+$.
47		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {2-[4-((S)-tetrahydro-furan-2-carbonyl)-piperazin-1-yl]-pyridin-3-yl}-amide. HPLC: $^{A}t_{Ret}$ = 4.74; LC-MS: m/z 734 $[M+H]^+$.
48		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {2-[4-((R)-tetrahydro-furan-2-carbonyl)-piperazin-1-yl]-pyridin-3-yl}-amide. HPLC: $^{A}t_{Ret}$ = 4.73; LC-MS: m/z 733.7 $[M+H]^+$.
49		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-dimethyl-carbamoyl-piperazin-1-yl)-pyridin-3-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.74; LC-MS: m/z 706.9 $[M+H]^+$.
50		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-ethyl-carbamoyl-piperazin-1-yl)-pyridin-3-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.64; LC-MS: m/z 706.9 $[M+H]^+$.
51		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-cyclopentyl-carbamoyl-piperazin-1-yl)-pyridin-3-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.93; LC-MS: m/z 747.2 $[M+H]^+$.
52		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(2-oxo-pyrrolidin-1-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.64; LC-MS: m/z 717.8 $[M+H]^+$.
53		6-Chloro-3-[3-(2,4-dichloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid (4-amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl)-amide. HPLC: $^{A}t_{Ret}$ = 4.30; LC-MS: m/z 672.0 $[M+H]^+$.

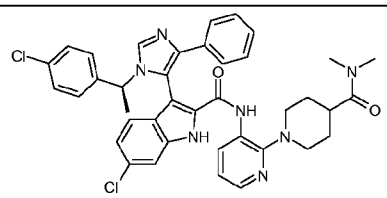
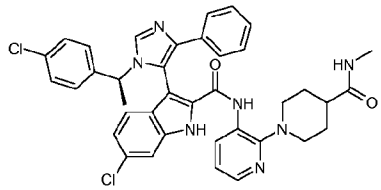
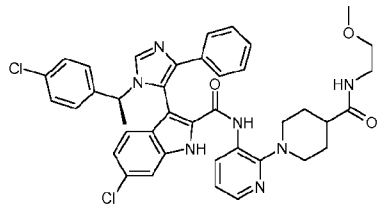
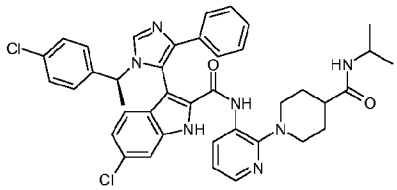
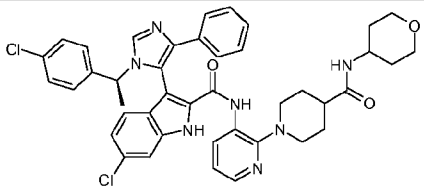
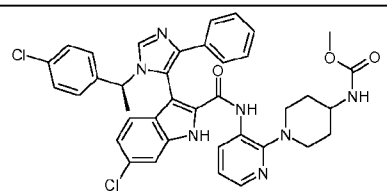
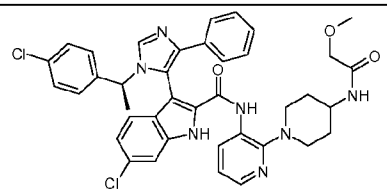
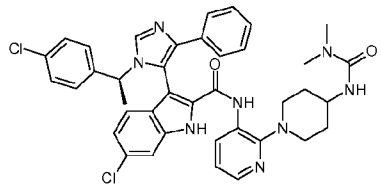
54		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (4-methylamino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl)-amide. HPLC: $^{A}t_{Ret}$ = 4.37; LC-MS: m/z 663.9 $[M+H]^+$.
55		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(1-ethyl-propylamino)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.66; LC-MS: m/z 719.9 $[M+H]^+$.
56		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (4-acetylamino-3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-3'-yl)-amide. HPLC: $^{A}t_{Ret}$ = 4.33; LC-MS: m/z 691.9 $[M+H]^+$.
57		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {2-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-phenyl}-amide. HPLC: $^{A}t_{Ret}$ = 5.12; LC-MS: m/z 733.4 $[M+H]^+$.
58		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {5-chloro-2-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-phenyl}-amide. HPLC: $^{A}t_{Ret}$ = 5.38; LC-MS: m/z 769.0 $[M+H]^+$.
59		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (2-oxo-3,4,5,6,3',4',5',6'-octahydro-2H,2'H-[1,4';1',2'']terpyridin-3''-yl)-amide. HPLC: $^{B}t_{Ret}$ = 5.99; LC-MS: m/z 731.9 $[M+H]^+$.
60		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {4-[(pyridine-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl}-amide. HPLC: $^{A}t_{Ret}$ = 4.77; LC-MS: m/z 755.5 $[M+H]^+$.
61		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {4-[(3,5-dimethyl-isoxazol-4-ylmethyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl}-amide. HPLC: $^{A}t_{Ret}$ = 4.60; LC-MS: m/z 758.9 $[M+H]^+$.

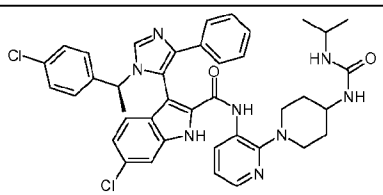
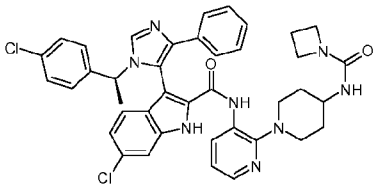
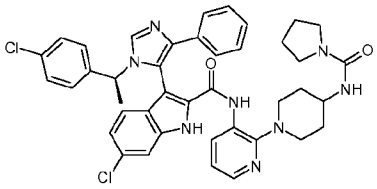
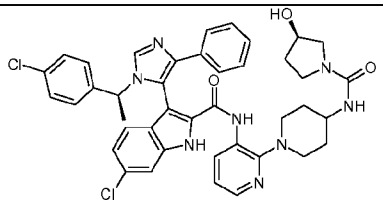
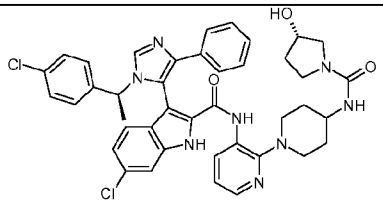
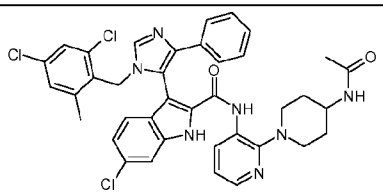
62		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(d_3-methyl-carbonyl-amino)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.49; LC-MS: m/z 695.0 $[M+H]^+$.
63		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(cyclopropane-carbonyl-amino)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.65; LC-MS: m/z 717.8 $[M+H]^+$.
64		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {4-[(pyridine-4-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl}-amide. HPLC: $^{A}t_{Ret}$ = 4.30; LC-MS: m/z 757.0 $[M+H]^+$.
65		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {4-[(pyridine-3-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl}-amide. HPLC: $^{A}t_{Ret}$ = 4.35; LC-MS: m/z 754.9 $[M+H]^+$.
66		3-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-benzoic acid methyl ester. HPLC: $^{A}t_{Ret}$ = 5.27; LC-MS: m/z 791.3 $[M+H]^+$.
67		3-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-benzoic acid. HPLC: $^{A}t_{Ret}$ = 4.92; LC-MS: m/z 777.0 $[M+H]^+$.
68		3-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-benzoic acid methyl amide. HPLC: $^{A}t_{Ret}$ = 4.92; LC-MS: m/z 790.0 $[M+H]^+$.

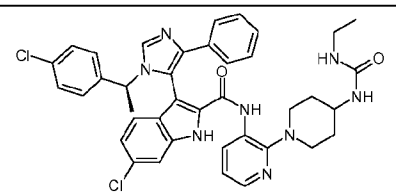
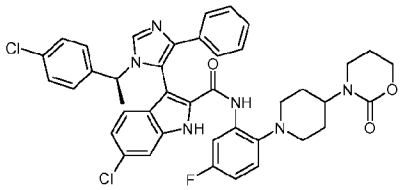
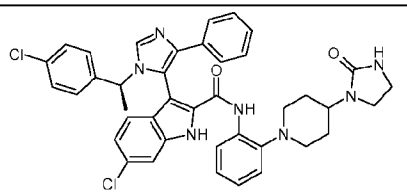
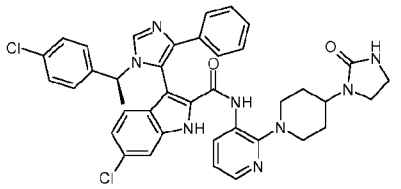
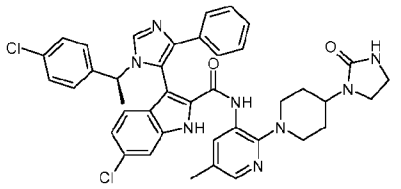
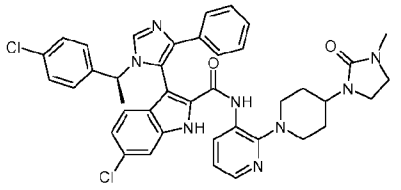
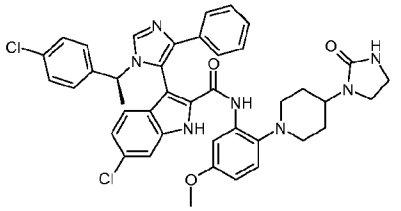
69		3-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-(2-oxo-[1,4']bipiperidinyl-1'-yl)-benzoic acid methyl ester. HPLC: $^{A}t_{Ret}$ = 5.32; LC-MS: m/z 789.3 $[M+H]^+$.
70		3-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-(4-cyclohexyl-piperazin-1-yl)-benzoic acid methyl ester. HPLC: $^{A}t_{Ret}$ = 5.03; LC-MS: m/z 775.3 $[M+H]^+$.
71		3-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-(4-cyclohexyl-piperazin-1-yl)-benzoic acid. HPLC: $^{A}t_{Ret}$ = 4.84; LC-MS: m/z 761.3 $[M+H]^+$.
72		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-cyclohexyl-piperazin-1-yl)-5-hydroxymethyl-phenyl]-amide. HPLC: $^{A}t_{Ret}$ = 4.80; LC-MS: m/z 747.2 $[M+H]^+$.
73		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {4-[((R)-pyrrolidine-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl}-amide. HPLC: $^{A}t_{Ret}$ = 4.27; LC-MS: m/z 746.9 $[M+H]^+$.
74		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {4-[((S)-pyrrolidine-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl}-amide. HPLC: $^{A}t_{Ret}$ = 4.29; LC-MS: m/z 746.9 $[M+H]^+$.
75		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {4-[((S)-1-methyl-pyrrolidine-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl}-amide. HPLC: $^{A}t_{Ret}$ = 4.33; LC-MS: m/z 760.9 $[M+H]^+$.

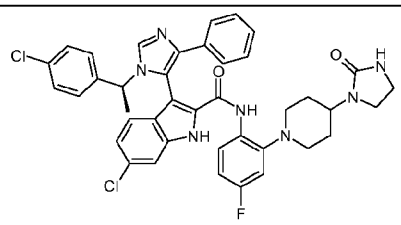
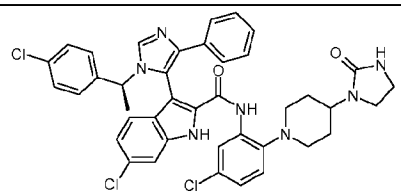
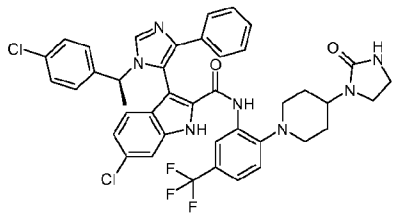
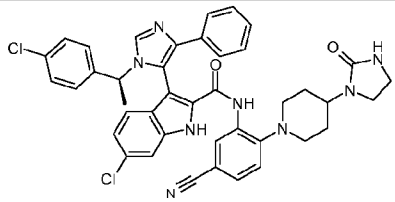
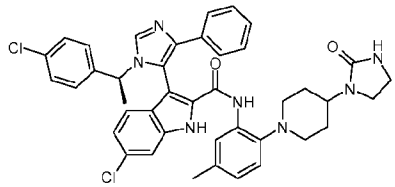
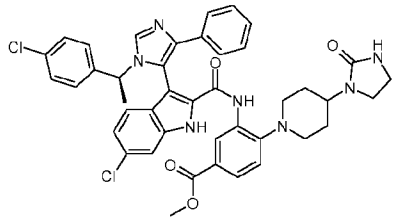
76		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {4-[((S)-1-acetyl-pyrrolidine-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl}-amide. HPLC: $^{A}t_{Ret}$ = 4.56; LC-MS: m/z 788.9 $[M+H]^+$.
77		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {4-[((R)-tetrahydro -furan-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl}-amide. HPLC: $^{A}t_{Ret}$ = 4.64; LC-MS: m/z 748.1 $[M+H]^+$.
78		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {4-[((S)-tetrahydro -furan-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl}-amide. HPLC: $^{A}t_{Ret}$ = 4.65; LC-MS: m/z 747.9 $[M+H]^+$.
79		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {4-[(tetrahydro-furan-3-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl}-amide. HPLC: $^{A}t_{Ret}$ = 4.54; LC-MS: m/z 747.9 $[M+H]^+$.
80		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (4-acetylamino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl)-amide. HPLC: $^{A}t_{Ret}$ = 4.49; LC-MS: m/z 691.9 $[M+H]^+$.
81		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(acetyl-methyl-amino)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.60; LC-MS: m/z 705.9 $[M+H]^+$.
82		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (4-propionylamino -3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl)-amide. HPLC: $^{A}t_{Ret}$ = 4.59; LC-MS: m/z 705.8 $[M+H]^+$.
83		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(3-hydroxy-2,2-dimethyl-propionylamino)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.55; LC-MS: m/z 750.2 $[M+H]^+$.

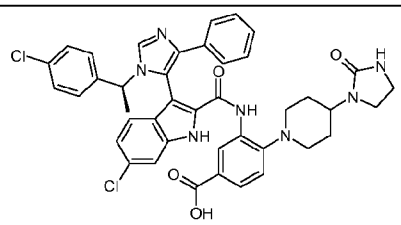
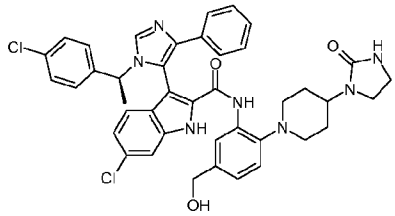
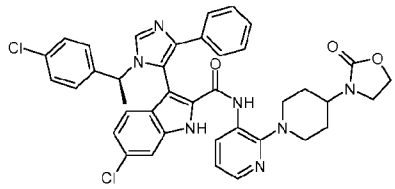
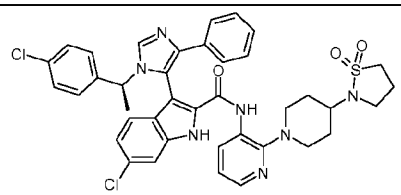
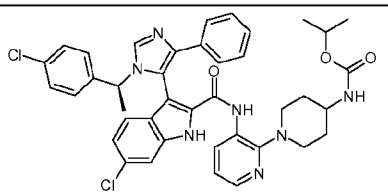
84		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(2-hydroxy-2-methyl-propionylamino)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.51; LC-MS: m/z 737.7 $[M+H]^+$.
85		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {4-[(tetrahydro-pyran-4-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl}-amide. HPLC: $^{A}t_{Ret}$ = 4.55; LC-MS: m/z 762.2 $[M+H]^+$.
86		6-Chloro-3-[3-(2,4-dichloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid (4-acetylamino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl)-amide. HPLC: $^{C}t_{Ret}$ = 5.65; LC-MS: m/z 714.3 $[M+H]^+$. ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.19 - 1.55 (m, 4 H), 1.76 (s, 3 H), 2.52 - 2.65 (m, 2 H), 2.83 (d, *J*=12.92 Hz, 1 H), 3.12 (d, *J*=12.72 Hz, 1 H), 3.41 - 3.49 (m, 1 H), 5.04 (s, 2 H), 6.75 (d, *J*=8.48 Hz, 1 H), 6.91 (s, 1 H), 6.94 (br. s., 2 H), 7.02 - 7.09 (m, 2 H), 7.12 - 7.17 (m, 2 H), 7.22 (d, *J*=1.82 Hz, 1 H), 7.40 (d, *J*=7.47 Hz, 1 H), 7.47 - 7.57 (m, 3 H), 8.00 - 8.05 (m, 1 H), 8.19 - 8.24 (m, 2 H), 8.36 (s, 1 H), 12.46 (s, 1 H).
87		6-Chloro-3-[3-(2,4-dichloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid {4-[(pyrrolidine-1-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl}-amide. HPLC: $^{A}t_{Ret}$ = 4.73; LC-MS: m/z 769.1 $[M+H]^+$.
88		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(3-cyclopentyl-ureido)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.81; LC-MS: m/z 760.9 $[M+H]^+$.
89		3'-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid methyl ester. HPLC: $^{A}t_{Ret}$ = 4.76; LC-MS: m/z 692.8 $[M+H]^+$.

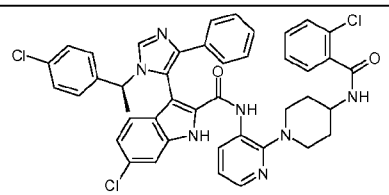
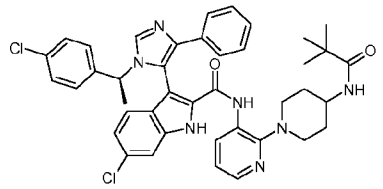
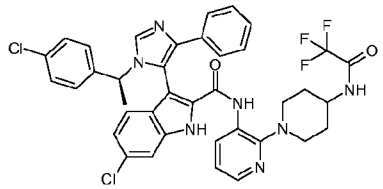
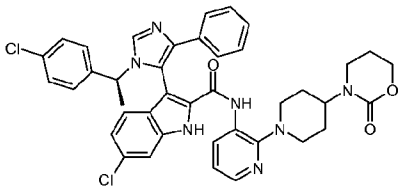
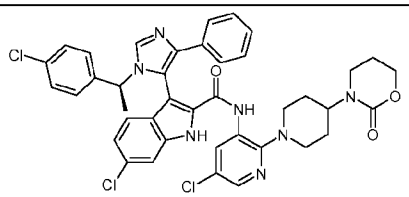
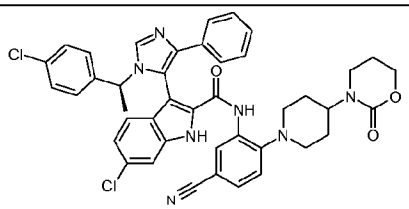
90		3'-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2'] bipyridinyl-4-carboxylic acid dimethylamide. HPLC: $^{A}t_{Ret}$ = 4.63; LC-MS: m/z 706.2 $[M+H]^+$.
91		3'-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid methylamide. HPLC: $^{A}t_{Ret}$ = 4.53; LC-MS: m/z 691.9 $[M+H]^+$.
92		3'-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid (2-methoxy-ethyl)-amide. HPLC: $^{A}t_{Ret}$ = 4.57; LC-MS: m/z 736.7 $[M+H]^+$.
93		3'-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid isopropyl-amide. HPLC: $^{A}t_{Ret}$ = 4.75; LC-MS: m/z 722.0 $[M+H]^+$.
94		3'-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid (tetrahydro -pyran-4-yl)-amide. HPLC: $^{A}t_{Ret}$ = 4.58; LC-MS: m/z 761.9 $[M+H]^+$.
95		{3'-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl}-carbamic acid methyl ester. HPLC: $^{A}t_{Ret}$ = 4.63; LC-MS: m/z 707.9 $[M+H]^+$.
96		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(2-methoxy-acetyl-amino)-3,4,5,6-tetrahydro-2H-[1,2'] bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.57; LC-MS: m/z 721.9 $[M+H]^+$.
97		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(3,3-dimethyl-ureido)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.60; LC-MS: m/z 720.9 $[M+H]^+$.

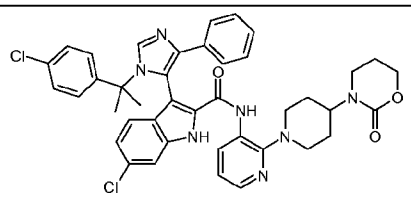
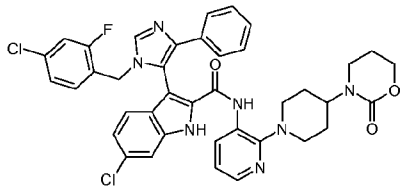
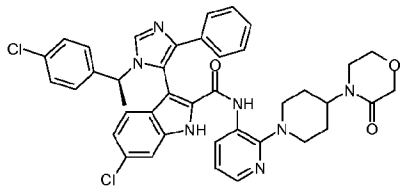
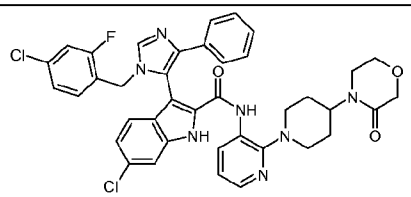
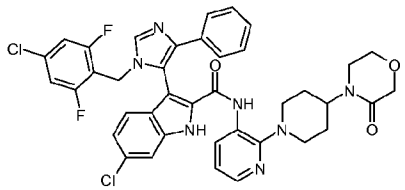
98		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(3-isopropyl-ureido)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.67; LC-MS: m/z 735.1 $[M+H]^+$.
99		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {4-[(azetidine-1-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2'] bipyridinyl-3'-yl}-amide. HPLC: $^{A}t_{Ret}$ = 4.60; LC-MS: m/z 732.9 $[M+H]^+$.
100		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {4-[(pyrrolidine-1-carbonyl) -amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl}-amide. HPLC: $^{A}t_{Ret}$ = 4.69; LC-MS: m/z 747.1 $[M+H]^+$.
101		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {4-[((R)-3-hydroxy-pyrrolidine-1-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl}-amide. HPLC: $^{A}t_{Ret}$ = 4.36; LC-MS: m/z 763.1 $[M+H]^+$.
102		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {4-[((S)-3-hydroxy-pyrrolidine-1-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl}-amide. HPLC: $^{A}t_{Ret}$ = 4.37; LC-MS: m/z 762.9 $[M+H]^+$.
103		6-Chloro-3-[3-(2,4-dichloro-6-methyl-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid (4-acetylamino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl)-amide. HPLC: $^{C}t_{Ret}$ = 5.79; LC-MS: m/z 725.9 $[M+H]^+$. ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.10 - 1.56 (m, 4 H), 1.75 (br. s., 3 H) 1.89 (br. s., 3 H), 2.48 – 2.62 (m, 2 H), 2.80 (d, *J*=11.10 Hz, 1 H), 3.14 (d, *J*=12.11 Hz, 1 H), 3.40 (br. s., 1 H), 4.98 - 5.09 (m, 2 H), 6.98 (br. s., 3 H), 7.02 - 7.17 (m, 5 H), 7.35 (d, *J*=5.45 Hz, 1 H), 7.48 (d, *J*=7.27 Hz, 2 H), 7.55 (br. s., 1 H), 7.88 (br. s., 1 H), 8.04 (br. s., 1 H), 8.29 (d, *J*=7.06 Hz, 1 H), 8.35 (br. s., 1 H), 12.49 (br. s., 1 H).

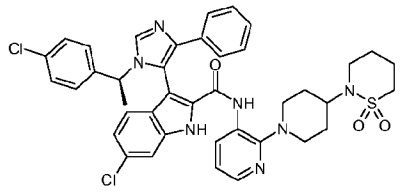
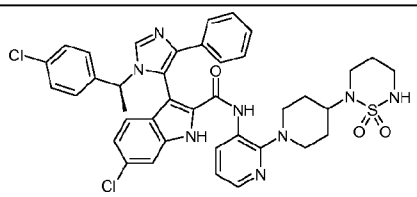
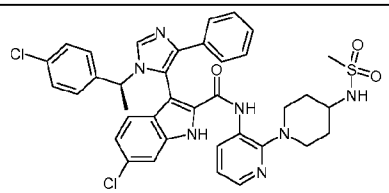
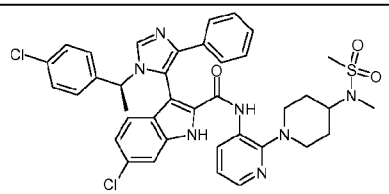
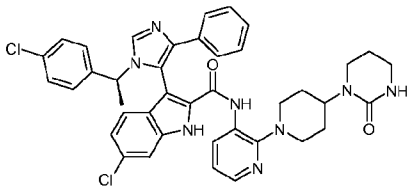
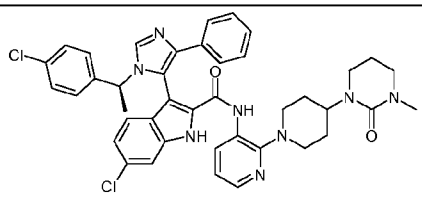
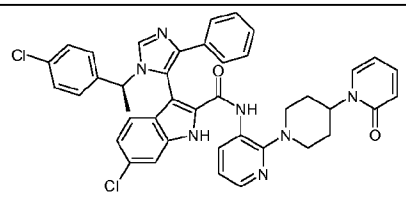
104		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(3-ethyl-ureido) -3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.56; LC-MS: m/z 720.9 $[M+H]^+$.
105		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {5-fluoro-2-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-phenyl}-amide. HPLC: $^{A}t_{Ret}$ = 5.27; LC-MS: m/z 751.4 $[M+H]^+$.
106		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {2-[4-(2-oxo-imidazolidin-1-yl)-piperidin-1-yl]-phenyl}-amide. HPLC: $^{A}t_{Ret}$ = 4.99; LC-MS: m/z 717.9 $[M+H]^+$.
107		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(2-oxo-imidazolidin-1-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.50; LC-MS: m/z 718.8 $[M+H]^+$.
108		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [5'-methyl-4-(2-oxo-imidazolidin-1-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.59; LC-MS: m/z 733.3 $[M+H]^+$.
109		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(3-methyl-2-oxo-imidazolidin-1-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.67; LC-MS: m/z 733.2 $[M+H]^+$.
110		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {5-methoxy-2-[4-(2-oxo-imidazolidin-1-yl)-piperidin-1-yl]-phenyl}-amide. HPLC: $^{A}t_{Ret}$ = 4.97; LC-MS: m/z 748.2 $[M+H]^+$.

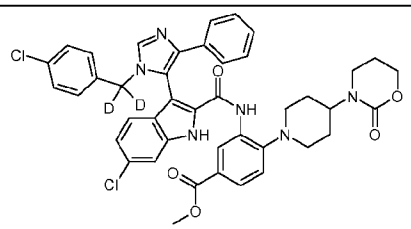
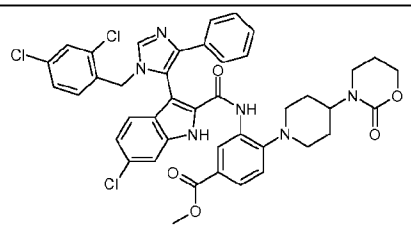
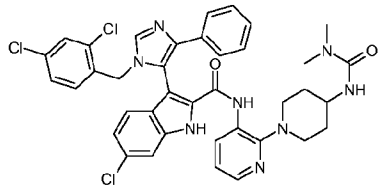
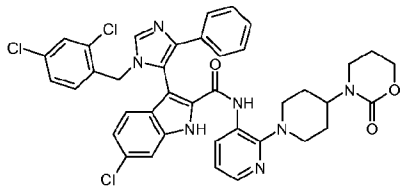
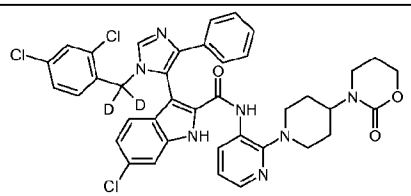
111		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {4-fluoro-2-[4-(2-oxo-imidazolidin-1-yl)-piperidin-1-yl]-phenyl}-amide. HPLC: $^{C}t_{Ret}$ = 6.43; LC-MS: m/z 735.9 $[M+H]^+$. ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.15 – 1.26 (m, 2 H), 1.39 (d, *J*=10.70 Hz, 1 H), 1.46 - 1.56 (m, 4 H), 2.15 - 2.22 (m, 1 H), 2.28 - 2.35 (m, 1 H), 2.62 (d, *J*=9.49 Hz, 1 H), 2.68 - 2.75 (m, 1 H), 2.80 - 2.89 (m, 3 H), 2.96 - 3.04 (m, 1 H), 3.24 (t, *J*=7.57 Hz, 1 H), 5.10 (q, *J*=7.13 Hz, 1 H), 6.11 (s, 1 H), 6.53 (d, *J*=8.68 Hz, 1 H), 6.67 (d, *J*=8.48 Hz, 2 H), 6.75 (dd, *J*=8.58, 1.72 Hz, 1 H), 7.03 - 7.10 (m, 4 H), 7.12 - 7.16 (m, 2 H), 7.19 (dd, *J*=10.50, 2.62 Hz, 1 H), 7.43 - 7.48 (m, 3 H), 8.29 – 8.34 (m, 1 H), 8.56 (s, 1 H), 8.65 (s, 1 H), 12.47 (s, 1 H).
112		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {5-chloro-2-[4-(2-oxo-imidazolidin-1-yl)-piperidin-1-yl]-phenyl}-amide. HPLC: $^{A}t_{Ret}$ = 5.34; LC-MS: m/z 754.1 $[M+H]^+$.
113		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {2-[4-(2-oxo-imidazolidin-1-yl)-piperidin-1-yl]-5-trifluoromethyl-phenyl}-amide. HPLC: $^{A}t_{Ret}$ = 5.37; LC-MS: m/z 786.3 $[M+H]^+$.
114		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {5-cyano-2-[4-(2-oxo-imidazolidin-1-yl-piperidin-1-yl]-phenyl}-amide. HPLC: $^{A}t_{Ret}$ = 5.08; LC-MS: m/z 743.2 $[M+H]^+$.
115		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {5-methyl-2-[4-(2-oxo-imidazolidin-1-yl)-piperidin-1-yl]-phenyl}-amide. HPLC: $^{A}t_{Ret}$ = 5.02; LC-MS: m/z 732.2 $[M+H]^+$.
116		3-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-[4-(2-oxo-imidazolidin-1-yl)-piperidin-1-yl]-benzoic acid methyl ester. HPLC: $^{A}t_{Ret}$ = 5.14; LC-MS: m/z 776.3 $[M+H]^+$.

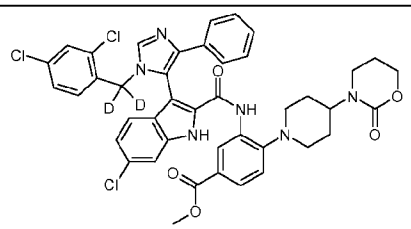
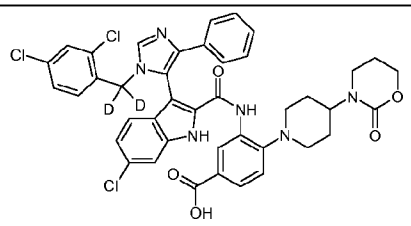
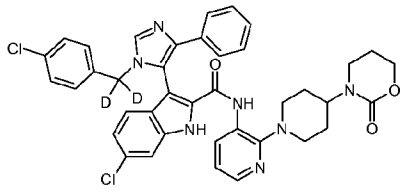
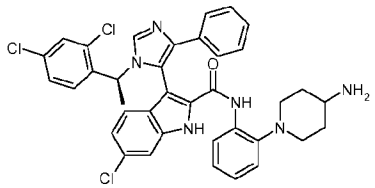
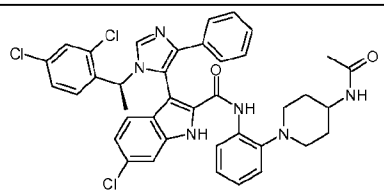
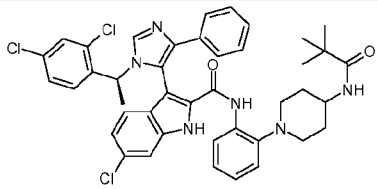
117		3-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-[4-(2-oxo-imidazolidin-1-yl)-piperidin-1-yl]-benzoic acid. HPLC: $^{A}t_{Ret}$ = 4.83; LC-MS: m/z 762.3 $[M+H]^+$.
118		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {5-hydroxymethyl-2-[4-(2-oxo-imidazolidin-1-yl)-piperidin-1-yl]-phenyl}-amide. HPLC: $^{A}t_{Ret}$ = 4.72; LC-MS: m/z 748.2 $[M+H]^+$.
119		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(2-oxo-oxazolidin-3-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.62; LC-MS: m/z 719.8 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.22 - 1.51 (m, 4 H), 1.53 (d, *J*=7.03 Hz, 3 H), 2.38 - 2.47 (m, 1 H), 2.76 - 2.97 (m, 3 H), 3.02 - 3.22 (m, 2 H), 3.31 - 3.43 (m, 1 H), 3.93 - 4.06 (m, 1 H), 4.07 - 4.24 (m, 1 H), 5.09 (q, *J*=7.03 Hz, 1 H), 6.56 (d, *J*=8.59 Hz, 1 H), 6.70 (d, *J*=8.59 Hz, 2 H), 6.77 (dd, *J*=8.59, 1.95 Hz, 1 H), 7.02 - 7.21 (m, 6 H), 7.43 - 7.54 (m, 3 H), 8.09 (dd, *J*=4.88, 1.76 Hz, 1 H), 8.37 (s, 1 H), 8.47 (s, 1 H), 8.54 (dd, *J*=8.20, 1.56 Hz, 1 H), 12.47 (s, 1 H).
120		6-chloro-3-(1-((S)-1-(4-chlorophenyl)ethyl)-4-phenyl-1H-imidazol-5-yl)-N-(2-(4-(1,1-dioxidoisothiazolidin-2-yl)piperidin-1-yl)pyridin-3-yl)-1H-indole-2-carboxamide. HPLC: $^{A}t_{Ret}$ = 4.67; LC-MS: m/z 753.9 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 - 1.51 (m, 2 H), 1.53 (d, *J*=7.03 Hz, 4 H), 1.90 - 1.96 (m, 1 H), 2.02 - 2.14 (m, 1 H), 2.40 - 2.46 (m, 1 H), 2.52 - 2.59 (m, 1 H), 2.73 - 3.23 (m, 8 H), 5.08 (q, *J*=7.03 Hz, 1 H), 6.57 (d, *J*=8.59 Hz, 1 H), 6.70 (d, *J*=8.59 Hz, 2 H), 6.77 (dd, *J*=8.59, 1.95 Hz, 1 H), 7.02 - 7.20 (m, 6 H), 7.43 - 7.50 (m, 3 H), 8.09 (dd, *J*=4.88, 1.76 Hz, 1 H), 8.36 (s, 1 H), 8.48 (s, 1 H), 8.52 (dd, *J*=8.01, 1.37 Hz, 1 H), 12.47 (s, 1 H).
121		{3'-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl}-carbamic acid isopropyl ester. HPLC: $^{A}t_{Ret}$ = 4.86; LC-MS: m/z 736.2 $[M+H]^+$.

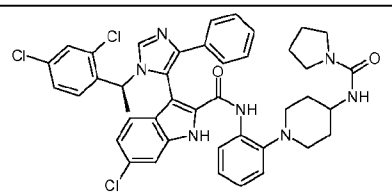
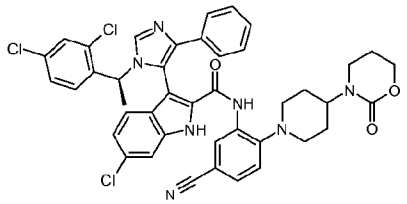
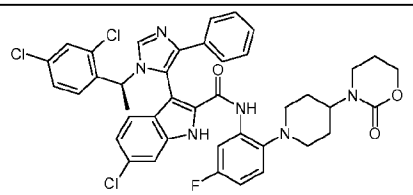
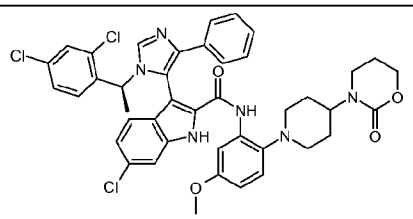
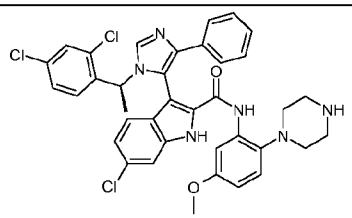
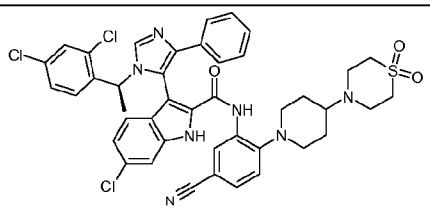
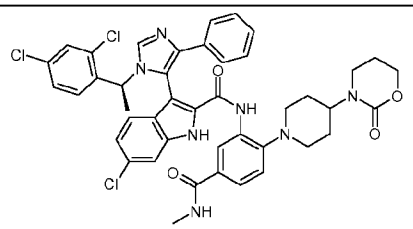
122		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(2-chloro-benzoyl-amino)-3,4,5,6-tetrahydro-2H-[1,2'] bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.87; LC-MS: m/z 787.9 $[M+H]^+$.
123		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(2,2-dimethyl-propionyl-amino)-3,4,5,6-tetrahydro-2H-[1,2'] bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.84; LC-MS: m/z 733.9 $[M+H]^+$.
124		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(2,2,2-trifluoro-acetyl-amino)-3,4,5,6-tetrahydro-2H-[1,2'] bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.85; LC-MS: m/z 745.8 $[M+H]^+$.
125		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(2-oxo-[1,3]oxazinan-3-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{B}t_{Ret}$ = 5.90; LC-MS: m/z 734.4 $[M+H]^+$. ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.14 - 1.46 (m, 3 H), 1.52 (d, *J*=6.26 Hz, 3 H), 1.56 - 1.84 (m, 3 H), 2.39 (t, *J*=10.70 Hz, 2 H), 2.79 - 2.98 (m, 3 H), 3.11 (d, *J*=11.91 Hz, 1 H), 3.73 - 4.10 (m, 3 H), 5.11 (q, *J*=7.00 Hz, 1 H), 6.56 (d, *J*=8.48 Hz, 1 H), 6.70 (d, *J*=8.28 Hz, 2 H), 6.77 (d, *J*=8.28 Hz, 1 H), 7.00 - 7.12 (m, 3 H), 7.12 - 7.23 (m, 3 H), 7.45 (d, *J*=7.87 Hz, 3 H), 8.10 (d, *J*=3.23 Hz, 1 H), 8.40 (br. s., 1 H), 8.49 (br. s., 1 H), 8.60 (d, *J*=8.07 Hz, 1 H), 12.52 (br. s., 1 H).
126		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [5'-chloro-4-(2-oxo-[1,3]oxazinan-3-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 5.27; LC-MS: m/z 770.0 $[M+H]^+$.
127		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {5-cyano-2-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-phenyl}-amide. HPLC: $^{A}t_{Ret}$ = 5.16; LC-MS: m/z 758.3 $[M+H]^+$.

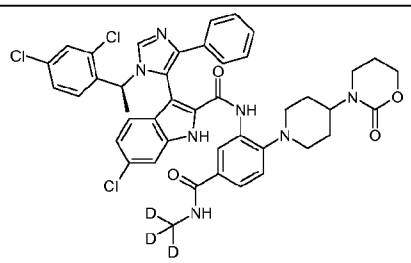
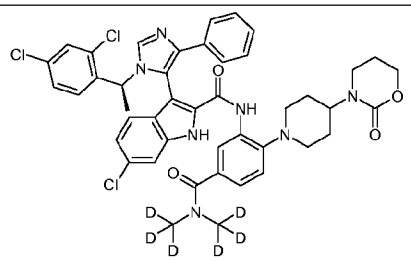
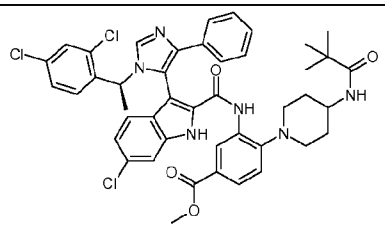
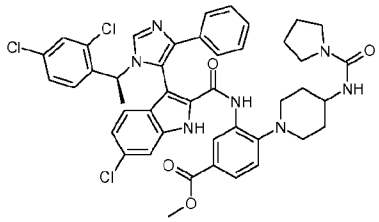
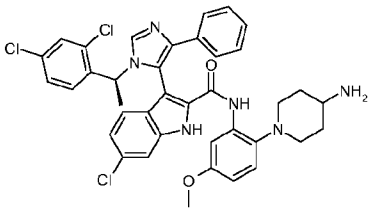
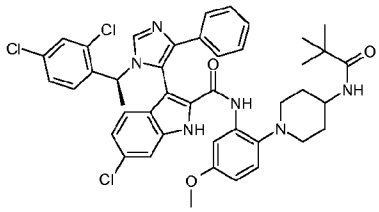
128		6-Chloro-3-{3-[1-(4-chloro-phenyl)-1-methyl-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(2-oxo-[1,3]oxazinan-3-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.62; LC-MS: m/z 748.3 $[M+H]^+$.
129		6-Chloro-3-[3-(4-chloro-2-fluoro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid [4-(2-oxo-[1,3]oxazinan-3-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{B}t_{Ret}$ = 5.78; LC-MS: m/z 737.9 $[M+H]^+$.
130		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(3-oxo-morpholin-4-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.60; LC-MS: m/z 733.9 $[M+H]^+$.
131		6-Chloro-3-[3-(4-chloro-2-fluoro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid [4-(3-oxo-morpholin-4-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{C}t_{Ret}$ = 5.69; LC-MS: m/z 738.2 $[M+H]^+$. ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.13 (d, *J*=10.50 Hz, 1 H), 1.31 (d, *J*=10.50 Hz, 1 H), 1.40 - 1.61 (m, 2 H), 2.37 - 2.47 (m, 1 H), 2.69 (d, *J*=4.64 Hz, 1 H), 2.84 (d, *J*=7.27 Hz, 2 H), 2.97 (d, *J*=4.84 Hz, 1 H), 3.04 (d, *J*=11.50 Hz, 1 H), 3.54 - 3.62 (m, 1 H), 3.68 - 3.77 (m, 1 H), 3.89 - 4.02 (m, 2 H), 4.10 - 4.21 (m, 1 H), 4.97 (s, 2 H), 6.69 - 6.80 (m, 3 H), 6.87 (d, *J*=8.48 Hz, 1 H), 6.96 (d, *J*=9.89 Hz, 1 H), 7.05 - 7.22 (m, 4 H), 7.44 - 7.53 (m, 3 H), 8.07 (d, *J*=4.24 Hz, 1 H), 8.25 (s, 1 H), 8.34 (br. s., 1 H), 8.44 (d, *J*=8.07 Hz, 1 H), 12.46 (s, 1 H).
132		6-Chloro-3-[3-(4-chloro-2,6-difluoro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid [4-(3-oxo-morpholin-4-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{C}t_{Ret}$ = 5.65; LC-MS: m/z 755.9 $[M+H]^+$. ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.13 (d, *J*=10.29 Hz, 1 H), 1.31 (d, *J*=10.70 Hz, 1 H), 1.42 - 1.64 (m, 2 H), 2.39 - 2.48 (m, 1 H), 2.71 - 2.77 (m, 1 H), 2.79 - 2.92 (m, 2 H), 2.97 - 3.12 (m, 2 H), 3.56 - 3.65 (m, 1 H), 3.69 - 3.79 (m, 1 H), 3.90 - 4.02 (m, 2 H), 4.16 (t, *J*=11.91 Hz, 1 H), 4.95 - 5.06 (m, 2 H), 6.67 (d, *J*=8.68 Hz, 1 H), 6.82 (d, *J*=7.67 Hz, 2 H), 6.86 (d, *J*=8.48 Hz, 1 H), 7.06 – 7.10 (m, 1 H), 7.12 – 7.18 (m, *J*=8.27 Hz, 3 H), 7.46 (d, *J*=8.07 Hz, 2 H), 7.50 (s, 1 H), 8.07 (d, *J*=4.24 Hz, 1 H), 8.21 (s,

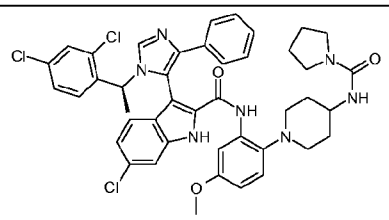
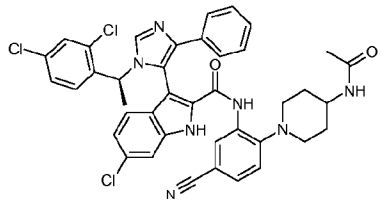
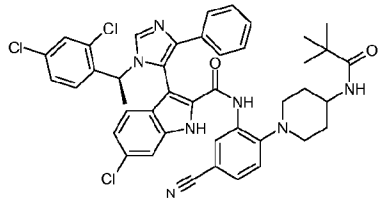
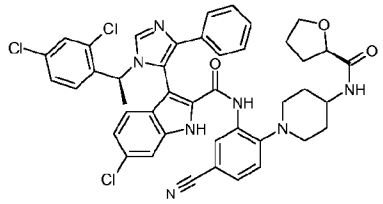
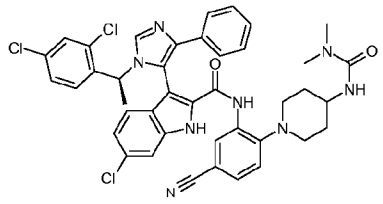
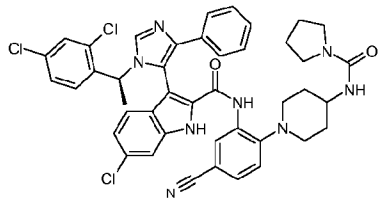
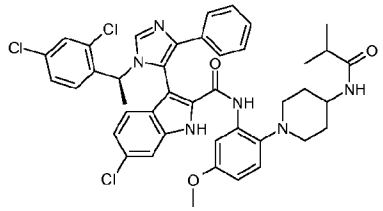
		1 H), 8.40 (s, 1 H), 8.43 (d, *J*=8.07 Hz, 1 H), 12.47 (br s, 1 H).
133		6-chloro-3-(1-((S)-1-(4-chlorophenyl)ethyl)-4-phenyl-1H-imidazol-5-yl)-N-(2-(4-(1,1-dioxido-1,2-thiazinan-2-yl)piperidin-1-yl)pyridin-3-yl)-1H-indole-2-carboxamide. HPLC: $^{A}t_{Ret}$ = 4.79; LC-MS: m/z 767.9 $[M+H]^+$.
134		6-chloro-3-(1-((S)-1-(4-chlorophenyl)ethyl)-4-phenyl-1H-imidazol-5-yl)-N-(2-(4-(1,1-dioxido-1,2,6-thiadiazinan-2-yl)piperidin-1-yl)pyridin-3-yl)-1H-indole-2-carboxamide. HPLC: $^{B}t_{Ret}$ = 6.03; LC-MS: m/z 768.8 $[M+H]^+$.
135		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (4-methane-sulfonyl amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl)-amide. HPLC: $^{A}t_{Ret}$ = 4.57; LC-MS: m/z 727.8 $[M+H]^+$.
136		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(methane-sulfonyl-methyl-amino)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.71; LC-MS: m/z 741.8 $[M+H]^+$.
137		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(2-oxo-tetrahydro-pyrimidin-1-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{B}t_{Ret}$ = 5.79; LC-MS: m/z 733.2 $[M+H]^+$.
138		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(3-methyl-2-oxo-tetrahydro-pyrimidin-1-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.76; LC-MS: m/z 747.2 $[M+H]^+$.
139		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (2-oxo-3',4',5',6'-tetrahydro-2H,2'H-[1,4';1',2'']terpyridin-3''-yl)-amide. HPLC: $^{B}t_{Ret}$ = 6.00; LC-MS: m/z 728 $[M+H]^+$.

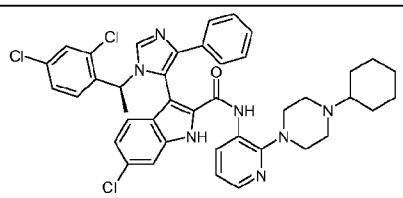
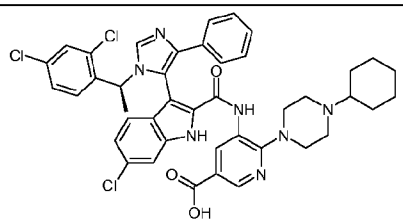
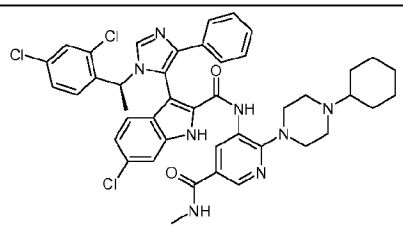
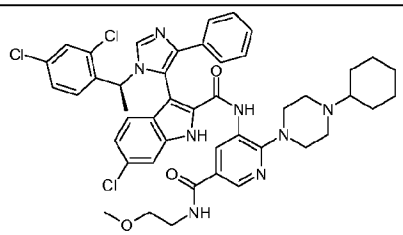
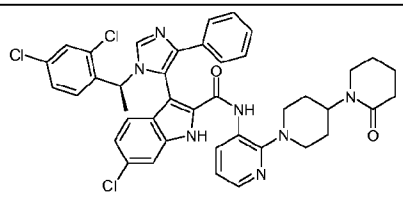
140		3-({6-Chloro-3-[3-(4-chloro-phenyl-d_2-methyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carbonyl}-amino)-4-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-benzoic acid methyl ester. HPLC: $^{A}t_{Ret}$ = 5.14; LC-MS: m/z 781.2 $[M+H]^+$.
141		3-({6-Chloro-3-[3-(2,4-dichloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carbonyl}-amino)-4-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-benzoic acid methyl ester. HPLC: $^{A}t_{Ret}$ = 5.25; LC-MS: m/z 813.0 $[M+H]^+$.
142		6-Chloro-3-[3-(2,4-dichloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid [4-(3,3-dimethyl-ureido)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.60; LC-MS: m/z 743.0 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20 – 1.47 (m, 4 H), 2.51 - 2.63 (m, 2 H), 2.75 (s, 6 H), 2.81 – 2.88 (m, 1 H), 3.06 - 3.15 (m, 1 H), 3.31 – 3.39 (m, 1 H), 4.95 - 5.10 (m, 2 H), 5.51 (d, *J*=7.42 Hz, 1 H), 6.74 (d, *J*=8.20 Hz, 1 H), 6.84 - 6.96 (m, 3 H), 7.00 - 7.17 (m, 4 H), 7.19 (d, *J*=2.34 Hz, 1 H), 7.47 (dd, *J*=8.40, 1.37 Hz, 2 H), 7.53 (d, *J*=1.56 Hz, 1 H), 8.01 (dd, *J*=4.88, 1.76 Hz, 1 H), 8.21 - 8.26 (m, 2 H), 8.30 (s, 1 H), 12.41 (s, 1 H).
143		6-Chloro-3-[3-(2,4-dichloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid [4-(2-oxo-[1,3]oxazinan-3-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.65; LC-MS: m/z 753.8 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.15 - 1.23 (m, 1 H), 1.33 - 1.86 (m, 5 H), 2.37 – 2.48 (m, 1 H), 2.59 - 2.69 (m, 1 H), 2.75 - 2.94 (m, 3 H), 3.08 (d, *J*=12.50 Hz, 1 H), 3.81 (t, *J*=11.52 Hz, 1 H), 3.95 - 4.10 (m, 2 H), 4.96 - 5.12 (m, 2 H), 6.73 (dd, *J*=16.21, 8.40 Hz, 2 H), 6.86 (dd, *J*=8.98, 1.56 Hz, 1 H), 6.92 (dd, *J*=8.20, 1.95 Hz, 1 H), 7.04 - 7.23 (m, 5 H), 7.44 - 7.52 (m, 3 H), 8.06 (dd, *J*=4.69, 1.95 Hz, 1 H), 8.20 (s, 1 H), 8.33 - 8.44 (m, 2 H), 12.41 (s, 1 H).
144		6-Chloro-3-[3-(2,4-dichloro-phenyl-d_2-methyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid [4-(2-oxo-[1,3]oxazinan-3-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.64; LC-MS: m/z 758.2 $[M+H]^+$.

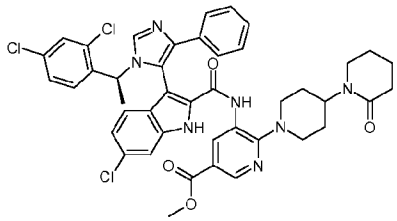
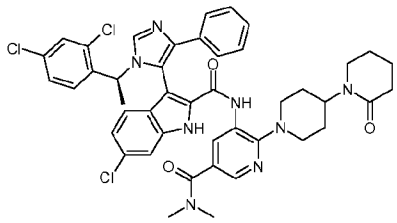
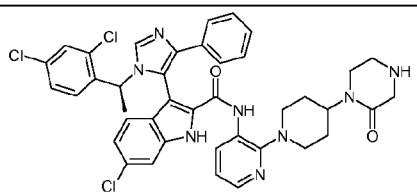
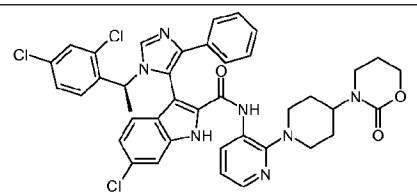
145		3-({6-Chloro-3-[3-(2,4-dichloro-phenyl-d_2-methyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carbonyl}-amino)-4-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-benzoic acid methyl ester. HPLC: $^{A}t_{Ret}$ = 5.24; LC-MS: m/z 815.2 $[M+H]^+$.
146		3-({6-Chloro-3-[3-(2,4-dichloro-phenyl-d_2-methyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carbonyl}-amino)-4-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-benzoic acid. HPLC: $^{A}t_{Ret}$ = 4.95; LC-MS: m/z 801.3 $[M+H]^+$.
147		6-Chloro-3-[3-(4-chloro-phenyl-d_2-methyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid [4-(2-oxo-[1,3]oxazinan-3-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.56; LC-MS: m/z 720.1 $[M+H]^+$.
148		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-amino-piperidin-1-yl)-phenyl]-amide. HPLC: $^{A}t_{Ret}$ = 4.61; LC-MS: m/z 685.0 $[M+H]^+$.
149		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-acetylamino-piperidin-1-yl)-phenyl]-amide. HPLC: $^{A}t_{Ret}$ = 5.10; LC-MS: m/z 727.0 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.07 - 1.32 (m, 2 H), 1.37 - 1.61 (m, 5 H), 1.75 (s, 3 H), 2.34 - 2.45 (m, 1 H), 2.53 - 2.62 (m, 2 H), 2.77 - 2.88 (m, 1 H), 3.33 - 3.42 (m, 1 H), 5.53 (q, *J*=7.29 Hz, 1 H), 6.41 (d, *J*=8.59 Hz, 1 H), 6.69 (dd, *J*=8.40, 1.76 Hz, 1 H), 6.84 (d, *J*=8.20 Hz, 2 H), 7.00 (d, *J*=2.34 Hz, 1 H), 7.03 - 7.17 (m, 6 H), 7.22 (dd, *J*=7.61, 1.76 Hz, 1 H), 7.43 (d, *J*=1.56 Hz, 1 H), 7.47 - 7.56 (m, 2 H), 8.08 (dd, *J*=7.81, 1.95 Hz, 1 H), 8.39 (s, 1 H), 8.78 (s, 1 H), 12.40 (s, 1 H).
150		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {2-[4-(2,2-dimethyl-propionylamino)-piperidin-1-yl]-phenyl}-amide. HPLC: $^{A}t_{Ret}$ = 5.44; LC-MS: m/z 767.3 $[M+H]^+$.

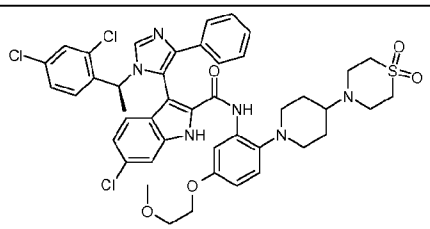
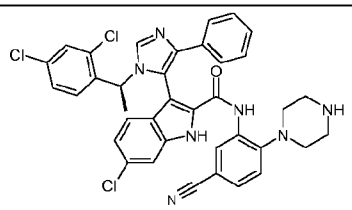
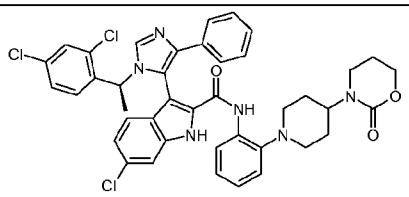
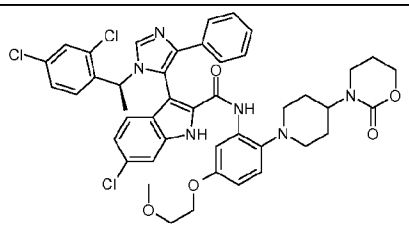
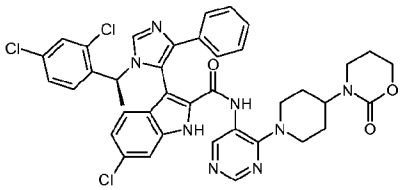
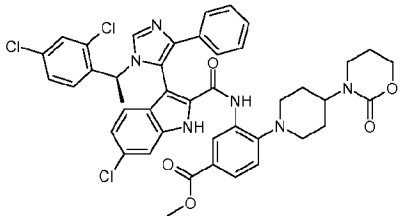
151		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (2-{4-[(pyrrolidine -1-carbonyl)-amino]-piperidin-1-yl}-phenyl)-amide. HPLC: $^{A}t_{Ret}$ = 5.31; LC-MS: m/z 782.2 $[M+H]^+$.
152		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {5-cyano-2-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-phenyl}-amide. HPLC: $^{A}t_{Ret}$ = 5.22; LC-MS: m/z 794.0 $[M+H]^+$.
153		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {5-fluoro-2-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-phenyl}-amide. HPLC: $^{A}t_{Ret}$ = 5.36; LC-MS: m/z 787.0 $[M+H]^+$.
154		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {5-methoxy-2-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-phenyl}-amide. HPLC: $^{A}t_{Ret}$ = 5.15; LC-MS: m/z 799.0 $[M+H]^+$.
155		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (5-methoxy-2-piperazin-1-yl-phenyl)-amide. HPLC: $^{A}t_{Ret}$ = 4.55; LC-MS: m/z 701$[M+H]^+$.
156		6-chloro-N-(5-cyano-2-(4-(1,1-dioxidothiomorpholino)piperidin-1-yl)phenyl)-3-(1-((S)-1-(2,4-dichlorophenyl)ethyl)-4-phenyl-1H-imidazol-5-yl)-1H-indole-2-carboxamide. HPLC: $^{A}t_{Ret}$ = 4.80; LC-MS: m/z 828.0 $[M+H]^+$.
157		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {5-methyl-carbamoyl-2-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-phenyl}-amide. HPLC: $^{A}t_{Ret}$ = 4.97; LC-MS: m/z 826.0 $[M+H]^+$.

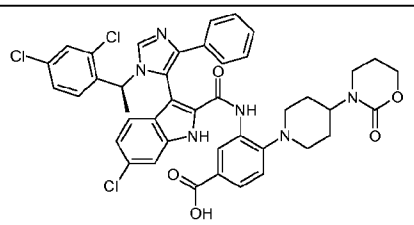
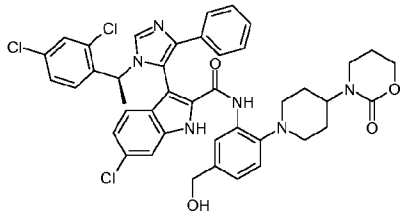
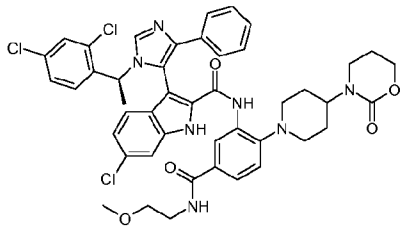
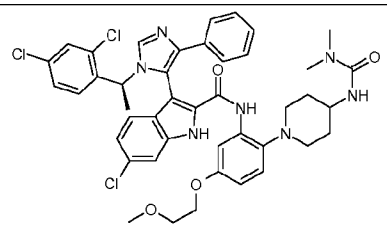
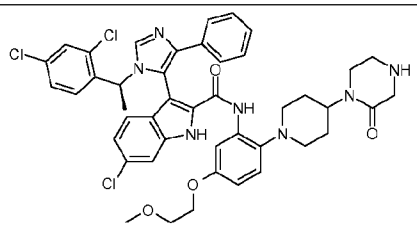
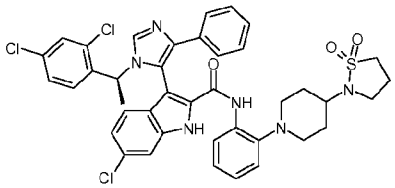
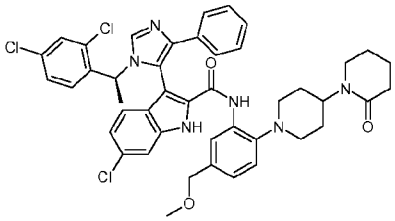
158		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {5-d_3-methyl-carbamoyl-2-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-phenyl}-amide. HPLC: $^{A}t_{Ret}$ = 4.87; LC-MS: m/z 829.4 $[M+H]^+$.
159		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {5-d_3-dimethyl-carbamoyl-2-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-phenyl}-amide. HPLC: $^{A}t_{Ret}$ = 4.94; LC-MS: m/z 846.4 $[M+H]^+$.
160		3-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-[4-(2,2-dimethyl-propionylamino)-piperidin-1-yl]-benzoic acid methyl ester. HPLC: $^{A}t_{Ret}$ = 5.45; LC-MS: m/z 827.0 $[M+H]^+$.
161		3-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-{4-[(pyrrolidine-1-carbonyl)-amino]-piperidin-1-yl}-benzoic acid methyl ester. HPLC: $^{A}t_{Ret}$ = 5.45; LC-MS: m/z 840.0 $[M+H]^+$.
162		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-amino-piperidin-1-yl)-5-methoxy-phenyl]-amide. HPLC: $^{A}t_{Ret}$ = 4.63; LC-MS: m/z 713.1 $[M+H]^+$.
163		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {2-[4-(2,2-dimethyl-propionylamino)-piperidin-1-yl]-5-methoxy-phenyl}-amide. HPLC: $^{A}t_{Ret}$ = 5.37; LC-MS: m/z 799.0 $[M+H]^+$.

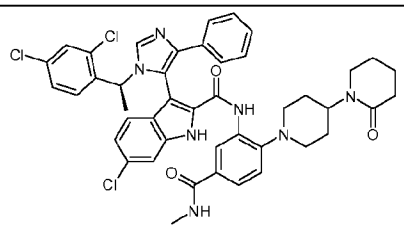
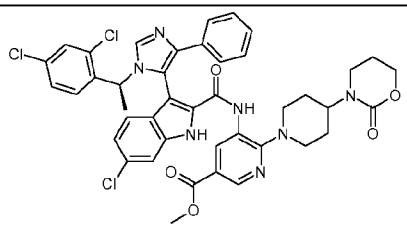
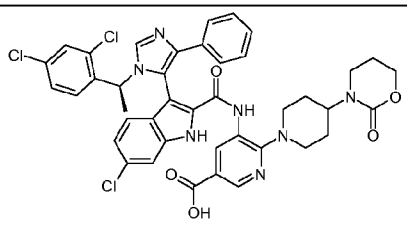
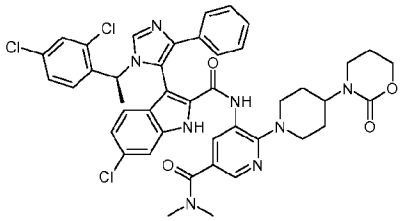
164		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (5-methoxy-2-{4-[(pyrrolidine-1-carbonyl)-amino]-piperidin-1-yl}-phenyl)-amide. HPLC: $^{A}t_{Ret}$ = 5.24; LC-MS: m/z 810.3 $[M+H]^+$.
165		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-acetylamino-piperidin-1-yl)-5-cyano-phenyl]-amide. HPLC: $^{A}t_{Ret}$ = 5.14; LC-MS: m/z 752.0 $[M+H]^+$.
166		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {5-cyano-2-[4-(2,2-dimethyl-propionylamino)-piperidin-1-yl]-phenyl}-amide. HPLC: $^{A}t_{Ret}$ = 5.39; LC-MS: m/z 794.4 $[M+H]^+$.
167		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (5-cyano-2-{4-[((R)-tetrahydro-furan-2-carbonyl)-amino]-piperidin-1-yl}-phenyl)-amide. HPLC: $^{A}t_{Ret}$ = 5.28; LC-MS: m/z 808.2 $[M+H]^+$.
168		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {5-cyano-2-[4-(3,3-dimethyl-ureido)piperidin-1-yl]-phenyl}-amide. HPLC: $^{A}t_{Ret}$ = 5.17; LC-MS: m/z 781.0 $[M+H]^+$.
169		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (5-cyano-2-{4-[(pyrrolidine-1-carbonyl)-amino]-piperidin-1-yl}-phenyl)-amide. HPLC: $^{A}t_{Ret}$ = 5.38; LC-MS: m/z 807.0 $[M+H]^+$.
170		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-isobutyrylamino-piperidin-1-yl)-5-methoxy-phenyl]-amide. HPLC: $^{A}t_{Ret}$ = 5.23; LC-MS: m/z 785.3 $[M+H]^+$.

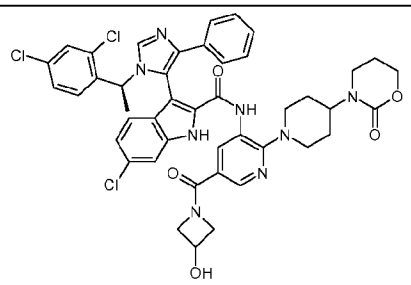
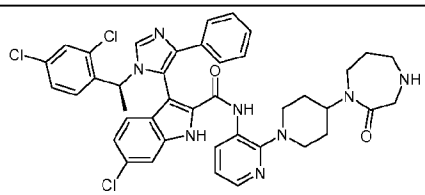
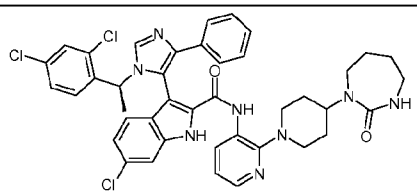
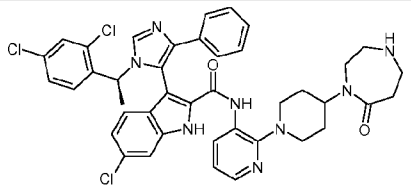
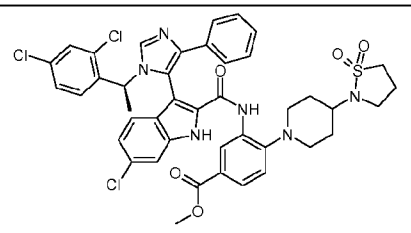
171		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-cyclohexyl-piperazin-1-yl)-pyridin-3-yl]-amide. HPLC: $^{C}t_{Ret}$ = 6.47; LC-MS: m/z 754.2 $[M+H]^+$. ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 0.69 - 1.12 (m, 5 H), 1.38 - 1.66 (m, 8 H), 1.84 (t, *J*=10.80 Hz, 1 H), 2.25 (br. s., 4 H), 2.60 - 2.68 (m, 2 H), 2.88 - 3.01 (m, 2 H), 5.50 (q, *J*=7.20 Hz, 1 H), 6.37 (d, *J*=8.48 Hz, 1 H), 6.68 (d, *J*=8.68 Hz, 1 H), 6.79 (d, *J*=8.48 Hz, 1 H), 7.00 - 7.08 (m, 2 H), 7.09 - 7.18 (m, 4 H), 7.43 (s, 1 H), 7.47 (d, *J*=8.07 Hz, 2 H), 8.09 (d, *J*=4.64 Hz, 1 H), 8.29 (d, *J*=7.87 Hz, 1 H), 8.40 (s, 1 H), 8.61 (s, 1 H), 12.38 (br s, 1 H).
172		5-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-6-(4-cyclohexyl-piperazin-1-yl)-nicotinic acid. HPLC: $^{A}t_{Ret}$ = 4.67; LC-MS: m/z 798.0 $[M+H]^+$.
173		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-cyclohexyl-piperazin-1-yl)-5methylcarbamoyl-pyridin-3-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.70; LC-MS: m/z 811.0 $[M+H]^+$.
174		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-cyclohexyl-piperazin-1-yl)-5-(2-methoxy-ethylcarbamoyl)-pyridin-3-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.70; LC-MS: m/z 855.3 $[M+H]^+$.
175		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (2-oxo-3,4,5,6,3',4',5',6'-octahydro-2H,2'H-[1,4';1',2'']terpyridin-3''-yl)-amide. HPLC: $^{C}t_{Ret}$ = 6.14; LC-MS: m/z 768.2 $[M+H]^+$. ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.12 (d, 1 H), 1.32 (d, *J*=11.30 Hz, 1 H), 1.35 - 1.69 (m, 9 H), 2.04 - 2.20 (m, 2 H), 2.35 - 2.48 (m, 2 H), 2.74 - 2.86 (m, 1 H), 2.86 - 3.01 (m, 2 H), 3.17 (d, *J*=11.30 Hz, 1 H), 4.22 (t, *J*=11.91 Hz, 1 H), 5.50 (q, *J*=7.00 Hz, 1 H), 6.34 (d, *J*=8.68 Hz, 1 H), 6.66 (d, *J*=8.48 Hz, 1 H), 6.78 (d, *J*=8.48 Hz, 1 H), 7.03 (d, *J*=2.02 Hz, 1 H), 7.08 (t, *J*=7.16 Hz, 1 H), 7.11 - 7.21 (m, 4 H), 7.41 (s, 1 H), 7.46 (d, *J*=7.87 Hz, 2 H), 8.11 (d,

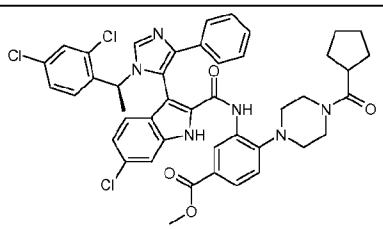
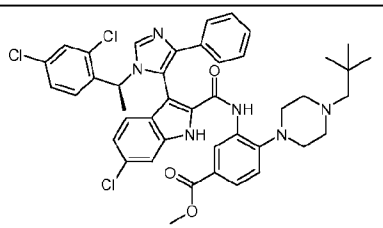
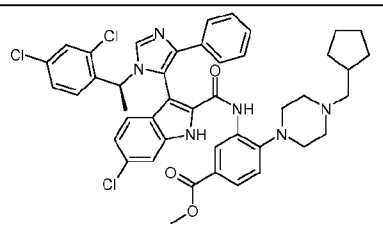
		J=3.83 Hz, 1 H), 8.43 - 8.54 (m, 2 H), 8.61 (s, 1 H), 12.41 (s, 1 H).
176		3''-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-2-oxo-3,4,5,6,3',4',5',6'-octahydro-2H,2'H-[1,4';1',2'']terpyridine-5''-carboxylic acid methyl ester. HPLC: $^{A}t_{Ret}$ = 5.18; LC-MS: m/z 826.3 $[M+H]^+$.
177		3''-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-2-oxo-3,4,5,6,3',4',5',6'-octahydro-2H,2'H-[1,4';1',2'']terpyridine-5''-carboxylic acid dimethylamide. HPLC: $^{C}t_{Ret}$ = 6.11; LC-MS: m/z 841.3 $[M+H]^+$. ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.14 - 1.20 (m, 1 H), 1.32 (d, *J*=11.71 Hz, 1 H), 1.40 - 1.68 (m, 9 H), 2.06 - 2.20 (m, 2 H), 2.48 - 2.63 (m, 2 H), 2.79 - 2.91 (m, 2 H), 3.00 (s, 6 H), 3.18 (d, *J*=11.50 Hz, 1 H), 3.35 - 3.42 (m, 1 H), 4.26 (t, *J*=12.21 Hz, 1 H), 5.50 (q, *J*=7.00 Hz, 1 H), 6.35 (d, *J*=8.68 Hz, 1 H), 6.67 (d, *J*=8.48 Hz, 1 H), 6.80 (d, *J*=8.48 Hz, 1 H), 7.02 (d, *J*=2.02 Hz, 1 H), 7.05 - 7.09 (m, 1 H), 7.10 - 7.19 (m, 3 H), 7.40 - 7.48 (m, 3 H), 8.18 (s, 1 H), 8.39 (s, 1 H), 8.47 (s, 1 H), 8.67 (s, 1 H), 12.39 (s, 1 H).
178		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(2-oxo-piperazin-1-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{A}t_{Ret}$ = 4.17; LC-MS: m/z 769.0 $[M+H]^+$.
179		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(2-oxo-[1,3]oxazinan-3-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{B}t_{Ret}$ = 5.92; LC-MS: m/z 767.8 $[M+H]^+$. ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.12 - 1.48 (m, 3 H), 1.52 (d, *J*=6.86 Hz, 3 H), 1.58 - 1.84 (m, 3 H), 2.37 - 2.61 (m, 2 H), 2.81 - 3.03 (m, 3 H), 3.18 (d, *J*=11.50 Hz, 1 H), 3.84 (t, *J*=12.11 Hz, 1 H), 3.94 - 4.11 (m, 2 H), 5.50 (q, *J*=6.80 Hz, 1 H), 6.35 (d, *J*=8.48 Hz, 1 H), 6.67 (d, *J*=8.28 Hz, 1 H), 6.79 (d, *J*=8.48 Hz, 1 H), 7.03 (d, *J*=1.82 Hz, 1 H), 7.08 (t, *J*=7.17 Hz, 1 H), 7.12 - 7.23 (m, 4 H), 7.41 (s, 1 H), 7.46 (d, *J*=7.87 Hz, 2 H), 8.11 (d, *J*=3.83 Hz, 1 H), 8.45 - 8.54 (m, 2 H), 8.60 (br. s., 1 H), 12.42 (s, 1 H).

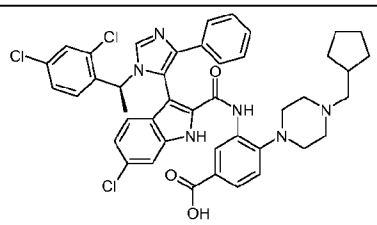
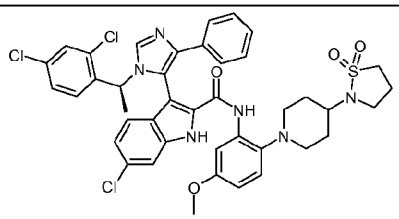
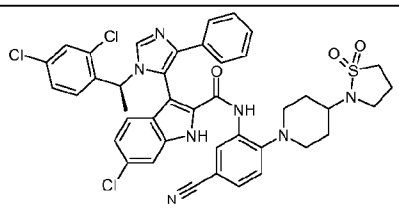
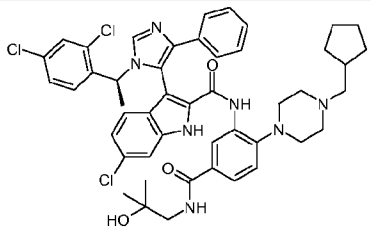
180		6-chloro-3-(1-((S)-1-(2,4-dichlorophenyl)ethyl)-4-phenyl-1H-imidazol-5-yl)-N-(2-(4-(1,1-dioxidothiomorpholino)piperidin-1-yl)-5-(2-methoxyethoxy)phenyl)-1H-indole-2-carboxamide. HPLC: $^{B}t_{Ret}$ = 6.19; LC-MS: m/z 877.4 $[M+H]^+$.
181		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (5-cyano-2-piperazin-1-yl-phenyl)-amide. HPLC: $^{A}t_{Ret}$ = 4.52; LC-MS: m/z 694 $[M+H]^+$.
182		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {2-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-phenyl}-amide. HPLC: $^{A}t_{Ret}$ = 5.20; LC-MS: m/z 769.2 $[M+H]^+$.
183		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {5-(2-methoxy-ethoxy)-2-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-phenyl}-amide. HPLC: $^{D}t_{Ret}$ = 1.38; LC-MS: m/z 843.4 $[M+H]^+$.
184		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {4-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-pyrimidin-5-yl}-amide. HPLC: $^{E}t_{Ret}$ = 1.37; LC-MS: m/z 771.0 $[M+H]^+$. ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.30 - 1.55 (m, 4 H), 1.72 (d, *J*=7.06 Hz, 3 H), 1.76 - 1.82 (m, 2 H),2.67 - 2.79 (m, 2 H), 2.84 - 2.99 (m, 2 H), 3.95 - 4.09 (m, 3 H), 4.28 - 4.36 (m, 2 H), 5.62 (q, *J*=6.66 Hz, 1 H), 6.33 (d, *J*=8.68 Hz, 1 H), 6.67 (dd, *J*=8.48, 1.41 Hz, 1 H), 6.91 (d, *J*=8.48 Hz, 1 H), 6.98 (d, *J*=1.82 Hz, 1 H), 7.04 (t, 1 H), 7.09 (t, *J*=7.57 Hz, 2 H), 7.20 (dd, *J*=8.38, 1.92 Hz, 1 H), 7.38 (d, *J*=7.47 Hz, 2 H), 7.50 (d, *J*=1.21 Hz, 1 H), 8.16 (s, 1 H), 8.35 (s, 1 H), 8.46 (s, 1 H), 9.56 (s, 1 H), 12.20 (s, 1 H).
185		3-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-benzoic acid methyl ester. HPLC: $^{A}t_{Ret}$ = 5.27; LC-MS: m/z 827.0 $[M+H]^+$.

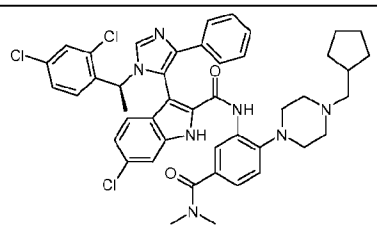
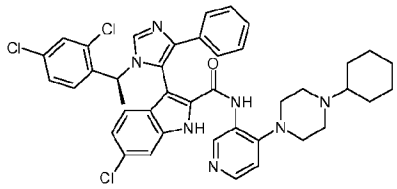
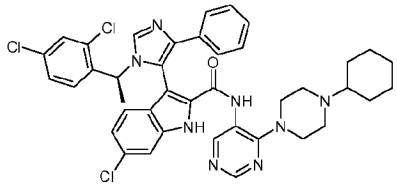
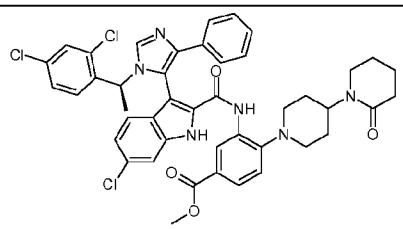
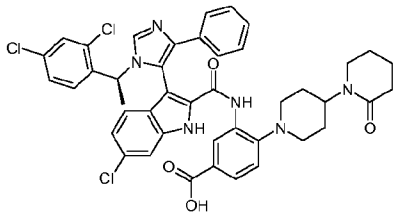
186		3-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-benzoic acid. HPLC: $^{A}t_{Ret}$ = 4.96; LC-MS: m/z 813.0 $[M+H]^+$.
187		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {5-hydroxymethyl-2-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-phenyl}-amide. HPLC: $^{A}t_{Ret}$ = 4.81; LC-MS: m/z 799.0 $[M+H]^+$.
188		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {5-(2-methoxy-ethylcarbamoyl)-2-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-phenyl}-amide. HPLC: $^{A}t_{Ret}$ = 4.91; LC-MS: m/z 870.0 $[M+H]^+$.
189		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-[4-(3,3-dimethyl-ureido)-piperidin-1-yl]-5-(2-methoxy-ethoxy)-phenyl]-amide. HPLC: $^{B}t_{Ret}$ = 6.43; LC-MS: m/z 830.4 $[M+H]^+$.
190		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {5-(2-methoxy-ethoxy)-2-[4-(2-oxo-piperazin-1-yl)-piperidin-1-yl]-phenyl}-amide. HPLC: $^{A}t_{Ret}$ = 4.54; LC-MS: m/z 842.0 $[M+H]^+$.
191		6-chloro-3-(1-((S)-1-(2,4-dichlorophenyl)ethyl)-4-phenyl-1H-imidazol-5-yl)-N-(2-(4-(1,1-dioxidoisothiazolidin-2-yl)piperidin-1-yl)phenyl)-1H-indole-2-carboxamide. HPLC: $^{A}t_{Ret}$ = 5.24; LC-MS: m/z 789.0 $[M+H]^+$.
192		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [5-methoxymethyl-2-(2-oxo-[1,4']bipiperidinyl-1'-yl)-phenyl]-amide. HPLC: $^{C}t_{Ret}$ = 6.77; LC-MS: m/z 811.4 $[M+H]^+$. ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.12 – 1.68 (m, 11 H), 2.04 - 2.23 (m, 3 H), 2.33 (t, *J*=11.30 Hz,

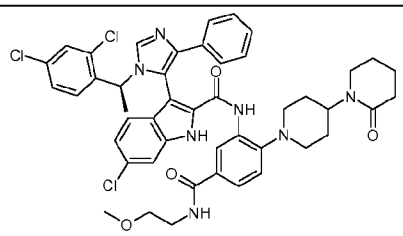
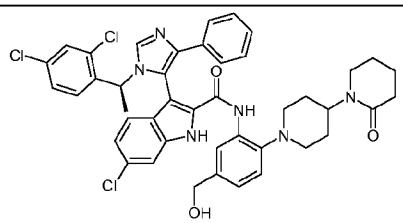
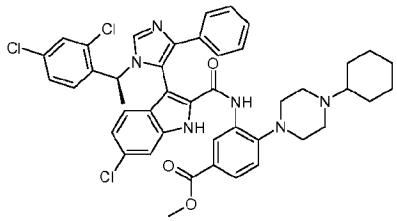
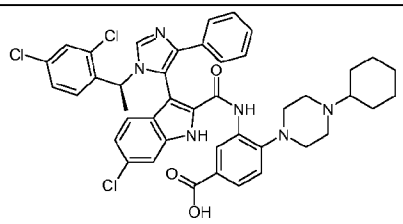
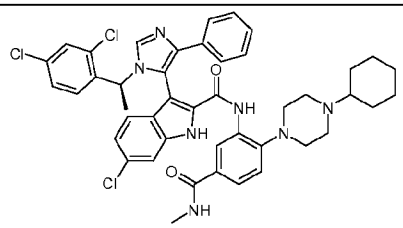
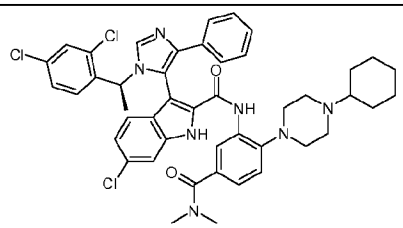
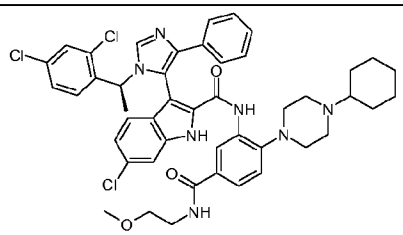
		1 H), 2.57 - 2.67 (m, 2 H) 2.83 (d, *J*=11.50 Hz, 1 H), 2.91 (t, *J*=11.20 Hz, 1 H), 3.30 (s, 3 H), 4.21 (t, *J*=12.01 Hz, 1 H), 4.41 (s, 2 H), 5.55 (q, *J*=7.13 Hz, 1 H), 6.31 (d, *J*=8.68 Hz, 1 H), 6.64 (d, *J*=8.68 Hz, 1 H), 6.75 (d, *J*=8.48 Hz, 1 H), 7.04 - 7.11 (m, 3 H), 7.12 - 7.19 (m, 3 H), 7.31 (d, *J*=8.07 Hz, 1 H), 7.38 (s, 1 H), 7.46 (d, *J*=8.07 Hz, 2 H), 8.26 (s, 1 H), 8.45 (s, 1 H), 8.87 (s, 1 H), 12.34 (s, 1 H).
193		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [5-methyl-carbamoyl-2-(2-oxo-[1,4']bipiperidinyl-1'-yl)-phenyl]-amide. HPLC: $^{A}t_{Ret}$ = 5.03; LC-MS: m/z 824.0 $[M+H]^+$.
194		3'-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-(2-oxo-[1,3]oxazinan-3-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid methyl ester. HPLC: $^{A}t_{Ret}$ = 5.00; LC-MS: m/z 828.4 $[M+H]^+$.
195		3'-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-(2-oxo-[1,3]oxazinan-3-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid. HPLC: $^{A}t_{Ret}$ = 4.70; LC-MS: m/z 814.0 $[M+H]^+$.
196		3'-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-(2-oxo-[1,3]oxazinan-3-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid dimethyl amide. HPLC: $^{C}t_{Ret}$ = 6.13; LC-MS: m/z 841.4 $[M+H]^+$. ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.21 - 1.31 (m, 1 H), 1.39 - 1.71 (m, 7 H), 1.76 - 1.83 (m, 1 H), 2.47 – 2.56 (m, 1 H), 2.60 – 2.67 (m, 1 H), 2.84 - 2.95 (m, 2 H), 3.00 (s, 6 H), 3.15 – 3.22 (m, 1 H), 3.35 – 3.41 (m, 1 H), 3.87 (t, *J*=12.01 Hz, 1 H), 3.95 - 4.11 (m, 2 H), 5.51 (q, *J*=6.93 Hz, 1 H), 6.36 (d, *J*=8.68 Hz, 1 H), 6.68 (d, *J*=8.68 Hz, 1 H), 6.80 (d, *J*=8.48 Hz, 1 H), 7.02 (d, *J*=2.22 Hz, 1 H), 7.04 - 7.10 (m, 1 H), 7.10 - 7.19 (m, 3 H), 7.40 - 7.51 (m, 3 H), 8.18 (s, 1 H), 8.40 (s, 1 H), 8.47 (s, 1 H), 8.66 (s, 1 H), 12.40 (s, 1 H).

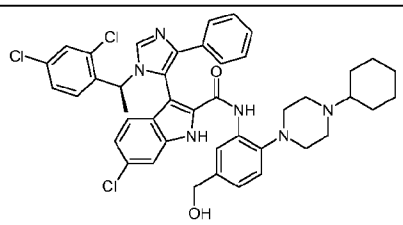
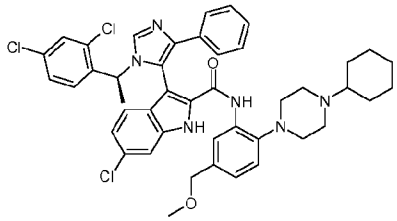
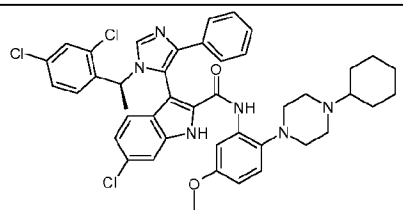
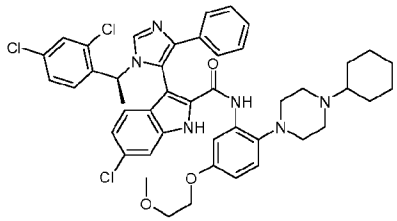
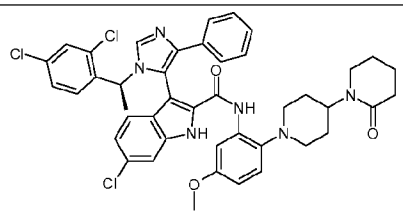
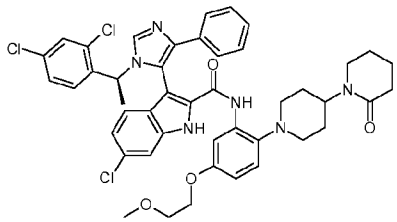
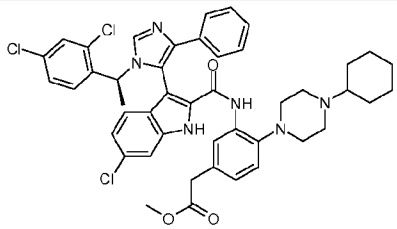
197		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [5'-(3-hydroxy-azetidine-1-carbonyl)-4-(2-oxo-[1,3]oxazinan-3-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{C}t_{Ret}$ = 5.92; LC-MS: m/z 869.4 $[M+H]^+$.
198		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(2-oxo-[1,4]diazepan-1-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{E}t_{Ret}$ = 1.03; LC-MS: m/z 783.4 $[M+H]^+$. ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.09 – 1.62 (m, 9 H), 2.81 – 3.41 (m, 10 H), 4.11 - 4.23 (m, 1 H), 5.47 - 5.53 (m, 1 H), 6.35 (d, *J*=8.68 Hz, 1 H), 6.67 (d, *J*=8.48 Hz, 1 H), 6.82 (d, *J*=8.48 Hz, 1 H), 7.01 (s, 1 H), 7.08 (d, *J*=7.47 Hz, 1 H), 7.11 - 7.19 (m, 4 H), 7.42 (s, 1 H), 7.45 (d, *J*=7.87 Hz, 2 H), 8.08 - 8.15 (m, 1 H), 8.46 (d, *J*=7.47 Hz, 1 H), 8.49 (s, 1 H), 8.66 (s, 1 H), 12.41 (s, 1 H).
199		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(2-oxo-[1,3]diazepan-1-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{B}t_{Ret}$ = 6.04; LC-MS: m/z 783.4 $[M+H]^+$.
200		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(7-oxo-[1,4]diazepan-1-yl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl]-amide. HPLC: $^{E}t_{Ret}$ = 1.05; LC-MS: m/z 781.3 $[M+H]^+$. ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.57 - 1.76 (m, 3 H) 1.84 (d, *J*=6.66 Hz, 3 H) 1.88 - 1.95 (m, 1 H) 2.90 - 3.74 (m, 12 H) 3.84 - 3.96 (m, 1 H) 5.72 - 5.84 (m, 1 H) 6.55 (d, *J*=8.68 Hz, 1 H) 6.77 (dd, *J*=8.68, 1.61 Hz, 1 H) 6.97 (s, 1 H) 7.07 - 7.12 (m, 1 H) 7.15 (s, 2 H) 7.22 - 7.37 (m, 5 H) 7.52 (s, 1 H) 8.01 (d, *J*=6.86 Hz, 1 H) 8.12 (d, *J*=4.84 Hz, 1 H) 8.66 - 8.86 (m, 1 H) 9.78 (s, 1 H) 9.88 - 9.96 (m, 1 H) 13.00 - 13.08 (m, 1 H)
201		methyl 3-(6-chloro-3-(1-((S)-1-(2,4-dichlorophenyl)ethyl)-4-phenyl-1H-imidazol-5-yl)-1H-indole-2-carboxamido)-4-(4-(1,1-dioxidoisothiazolidin-2-yl)piperidin-1-yl)benzoate. HPLC: $^{A}t_{Ret}$ = 5.29; LC-MS: m/z 847.0 $[M+H]^+$.

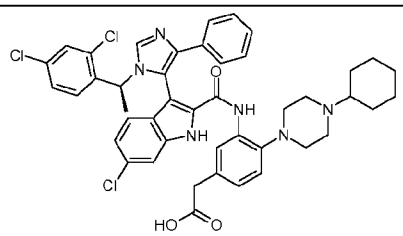
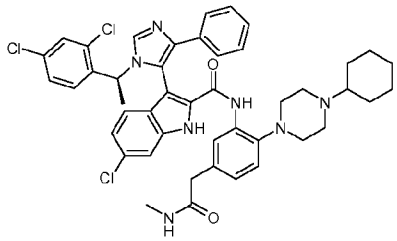
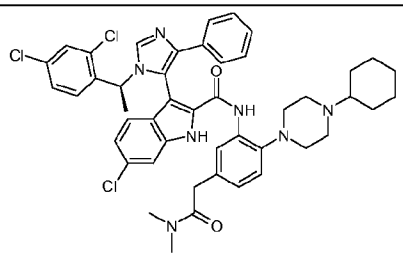
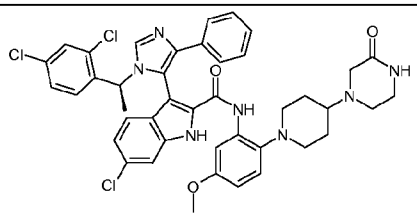
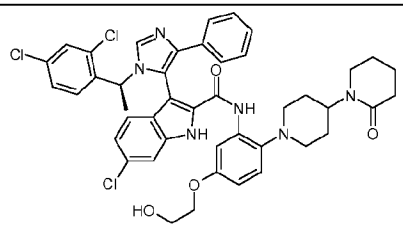
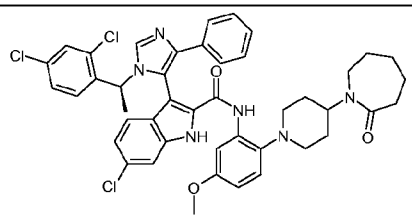
202		3-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-(4-cyclopentanecarbonyl-piperazin-1-yl)-benzoic acid methyl ester. HPLC: $^{E}t_{Ret}$ = 1.38; LC-MS: m/z 825.4 $[M+H]^+$. ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.32 - 1.86 (m, 7 H), 2.38 - 2.78 (m, 7 H), 2.90 - 3.03 (m, 2 H), 3.16 - 3.29 (m, 4 H), 3.86 (s, 3 H), 5.47 (q, *J*=7.33 Hz, 1 H), 6.45 (d, *J*=8.48 Hz, 1 H), 6.73 (d, *J*=8.48 Hz, 1 H), 6.82 (d, *J*=8.48 Hz, 1 H), 6.96 - 7.06 (m, 2 H), 7.09 (t, *J*=7.57 Hz, 2 H), 7.16 (dd, *J*=8.48, 2.22 Hz, 1 H), 7.31 (d, *J*=8.48 Hz, 1 H), 7.47 (s, 1 H), 7.51 (d, *J*=7.87 Hz, 2 H), 7.72 (d, *J*=8.48 Hz, 1 H), 8.42 (s, 1 H), 8.67 (s, 1 H), 8.72 (s, 1 H), 12.43 (s, 1 H).
203		3-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-[4-(2,2-dimethyl-propyl)-piperazin-1-yl]-benzoic acid methyl ester. HPLC: t_{Ret} = 1.13; LC-MS: m/z 799.3 $[M+H]^+$. ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 0.71 (s, 9 H), 1.42 (d, *J*=13.93 Hz, 1 H), 1.53 (d, *J*=7.06 Hz, 3 H), 1.70 (d, *J*=13.93 Hz, 1 H), 2.12 - 2.27 (m, 4 H), 2.44 - 2.54 (m, 2 H), 2.77 - 2.88 (m, 2 H), 3.85 (s, 3 H), 5.49 (q, *J*=7.06 Hz, 1 H), 6.43 (d, *J*=8.48 Hz, 1 H), 6.72 (dd, *J*=8.58, 1.72 Hz, 1 H), 6.81 (d, *J*=8.48 Hz, 1 H), 7.04 - 7.09 (m, 2 H), 7.11 - 7.19 (m, 3 H), 7.27 (d, *J*=8.48 Hz, 1 H), 7.46 (d, *J*=1.61 Hz, 1 H), 7.53 (d, *J*=7.47 Hz, 2 H), 7.72 (dd, *J*=8.38, 1.92 Hz, 1 H), 8.38 (s, 1 H), 8.61 (d, *J*=1.82 Hz, 1 H), 8.64 (s, 1 H), 12.40 (s, 1 H).
204		3-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-(4-cyclopentylmethyl-piperazin-1-yl)-benzoic acid methyl ester. HPLC: t_{Ret} = 1.33; LC-MS: m/z 807.6 $[M+H]^+$. ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 0.87 - 2.37 (m, 12 H), 2.58 - 3.55 (m, 10 H), 3.88 (s, 3 H), 5.51 (br. s., 1 H), 6.40 (d, *J*=7.47 Hz, 1 H), 6.70 (d, 1 H) 6.79 (br. s., 1 H), 7.04 (d, *J*=2.02 Hz, 1 H), 7.13 (dd, *J*=8.48, 1.82 Hz, 1 H), 7.17 (d, *J*=6.46 Hz, 1 H), 7.22 (t, *J*=7.37 Hz, 2 H), 7.35 (d, *J*=8.48 Hz, 1 H), 7.44 (s, 1 H), 7.56 (d, 2 H), 7.78 (dd, *J*=8.28, 1.61 Hz, 1 H), 8.31 - 8.98 (m, 2 H), 9.97 (br. s., 1 H), 12.58 (br. s., 1 H).

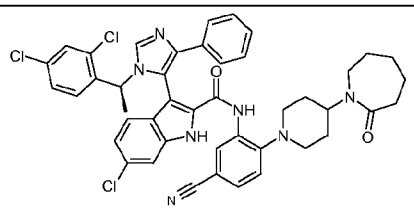
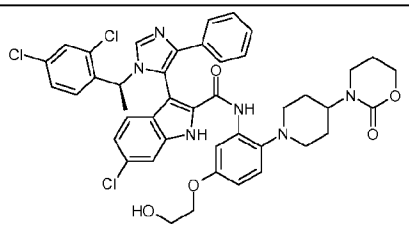
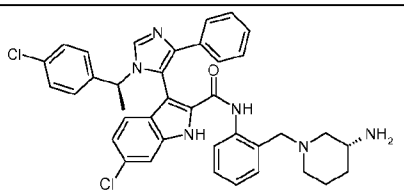
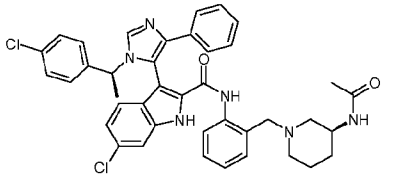
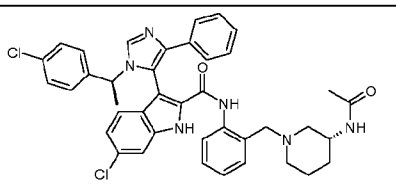
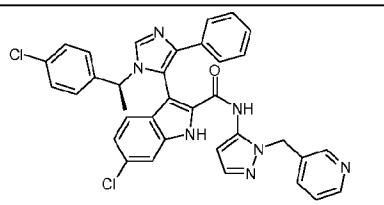
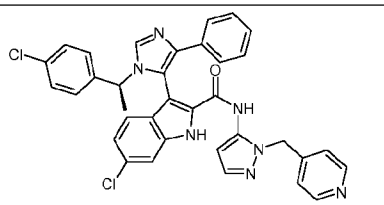
205		3-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-(4-cyclopentylmethyl-piperazin-1-yl)-benzoic acid. HPLC: t_{Ret} = 1.45; LC-MS: m/z 797.3 $[M+H]^+$ ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 0.89 - 1.16 (m, 4 H), 1.36 - 1.77 (m, 8 H), 1.97 - 2.20 (m, 4 H), 2.47 (br. s., 2 H), 2.82 (br. s., 2 H), 3.60 (t, *J*=6.56 Hz, 2 H), 5.50 (q, *J*=7.13 Hz, 1 H), 6.40 (d, *J*=8.68 Hz, 1 H), 6.70 (dd, *J*=8.58, 1.72 Hz, 1 H), 6.78 (d, *J*=8.48 Hz, 1 H), 7.01 - 7.09 (m, 2 H), 7.10 - 7.18 (m, 3 H), 7.26 (d, *J*=8.48 Hz, 1 H), 7.44 (d, *J*=1.61 Hz, 1 H), 7.52 (d, *J*=7.67 Hz, 2 H), 7.70 (dd, *J*=8.28, 1.82 Hz, 1 H), 8.39 (s, 1 H), 8.60 - 8.72 (m, 2 H), 12.40 (s, 1 H), 12.90 (br s, 1H).
206		6-chloro-3-(1-((S)-1-(2,4-dichlorophenyl)ethyl)-4-phenyl-1H-imidazol-5-yl)-N-(2-(4-(1,1-dioxidoisothiazolidin-2-yl)piperidin-1-yl)-5-methoxyphenyl)-1H-indole-2-carboxamide. HPLC: $^A t_{Ret}$ = 5.20; LC-MS: m/z 819.3 $[M+H]^+$.
207		6-chloro-N-(5-cyano-2-(4-(1,1-dioxidoisothiazolidin-2-yl)piperidin-1-yl)phenyl)-3-(1-((S)-1-(2,4-dichlorophenyl)ethyl)-4-phenyl-1H-imidazol-5-yl)-1H-indole-2-carboxamide. HPLC: $^A t_{Ret}$ = 5.23; LC-MS: m/z 814.1 $[M+H]^+$.
208		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-cyclopentyl-methyl-piperazin-1-yl)-5-(2-hydroxy-2-methyl-propylcarbamoyl)-phenyl]-amide. HPLC: t_{Ret} = 1.34; LC-MS: m/z 868.5 $[M+H]^+$. ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 0.94 - 1.10 (m, 8 H), 1.31 - 1.78 (m, 12 H), 2.02 - 2.17 (m, 4 H), 2.35 - 2.48 (m, 2 H), 2.72 - 2.85 (m, 2 H), 3.18 - 3.39 (m, 2 H), 4.58 (s, 1 H), 5.47 - 5.55 (m, 1 H), 6.39 (d, *J*=8.68 Hz, 1 H), 6.70 (dd, *J*=8.68, 1.61 Hz, 1 H), 6.80 (d, *J*=8.48 Hz, 1 H), 7.00 - 7.09 (m, 2 H), 7.09 - 7.20 (m, 3 H), 7.25 (d, *J*=8.28 Hz, 1 H), 7.44 (s, 1 H), 7.51 (d, *J*=7.67 Hz, 2 H), 7.64 (d, *J*=8.48 Hz, 1 H), 8.18 (t, *J*=5.65 Hz, 1 H), 8.39 (s, 1 H), 8.53 (s, 1 H), 8.71 (s, 1 H), 12.41 (s, 1 H).

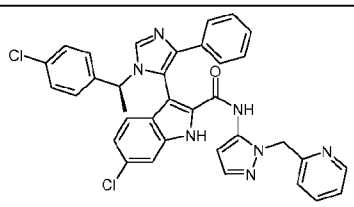
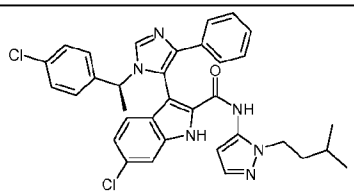
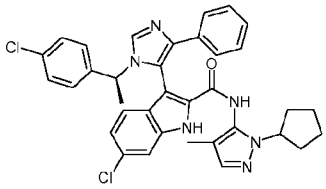
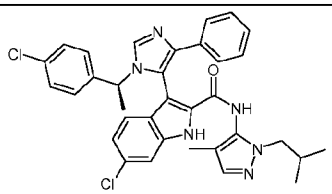
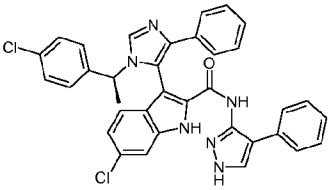
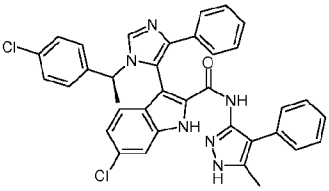
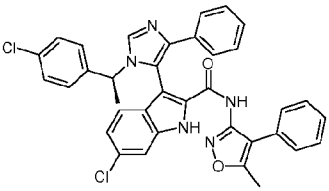
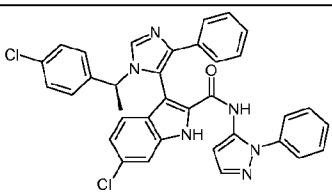
209		3-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-(4-cyclopentylmethyl-piperazin-1-yl)-benzoic acid dimethyl amide. HPLC: t_{Ret} = 1.38; LC-MS: m/z 824.4 $[M+H]^+$. ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 0.90 - 1.06 (m, 2 H), 1.20 - 1.59 (m, 10 H), 1.63 - 1.75 (m, 2 H), 2.06 – 2.13 (m, 4 H), 2.40 (br. s., 2 H), 2.77 (br. s., 2 H), 2.96 (br. s., 6 H), 5.49 (q, *J*=7.00 Hz, 1 H), 6.42 (d, *J*=8.48 Hz, 1 H), 6.70 (d, *J*=8.88 Hz, 1 H), 6.77 (d, *J*=8.48 Hz, 1 H), 7.02 - 7.08 (m, 2 H), 7.09 - 7.18 (m, 4 H), 7.24 (d, *J*=8.07 Hz, 1 H), 7.42 (s, 1 H), 7.53 (d, *J*=7.67 Hz, 2 H), 8.13 (s, 1 H), 8.39 (s, 1 H), 8.70 (s, 1 H), 12.42 (s, 1 H).
210		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(4-cyclohexyl-piperazin-1-yl)-pyridin-3-yl]-amide. HPLC: $^C t_{Ret}$ = 6.02; LC-MS: m/z 754.4 $[M+H]^+$.
211		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [4-(4-cyclohexyl-piperazin-1-yl)-pyrimidin-5-yl]-amide. HPLC: t_{Ret} = 1.44; LC-MS: m/z 753.0 $[M+H]^+$. ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 0.95 - 1.68 (m, 10 H), 1.74 (d, *J*=6.86 Hz, 3 H), 2.00 - 2.07 (m, 1 H), 2.20 – 2.27 (m, 4 H), 3.30 – 3.52 (m, 4 H), 5.61 - 5.69 (m, 1 H), 6.32 (d, *J*=8.68 Hz, 1 H), 6.66 (d, *J*=9.08 Hz, 1 H), 6.92 (d, *J*=8.48 Hz, 1 H), 6.99 (s, 1 H), 7.02 – 7.05 (m, 1 H), 7.09 (t, *J*=7.67 Hz, 2 H), 7.21 (d, 1 H), 7.39 (d, *J*=7.67 Hz, 2 H), 7.50 (s, 1 H), 8.03 - 8.15 (m, 1 H), 8.35 (s, 1 H), 8.44 (s, 1 H), 9.60 (s, 1 H), 12.21 (br s, 1 H).
212		3-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-(2-oxo-[1,4']bipiperidinyl-1'-yl)-benzoic acid methyl ester. HPLC: $^A t_{Ret}$ = 5.47; LC-MS: m/z 825.2 $[M+H]^+$.
213		3-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-(2-oxo-[1,4']bipiperidinyl-1'-yl)-benzoic acid. HPLC: $^A t_{Ret}$ = 5.13; LC-MS: m/z 811.3 $[M+H]^+$.

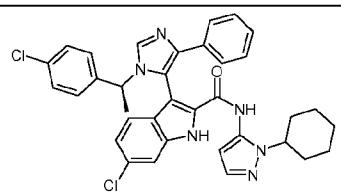
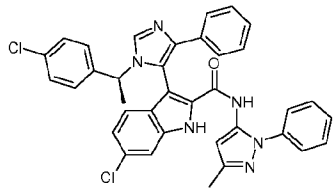
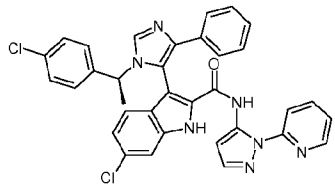
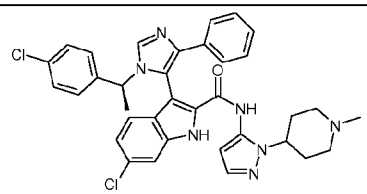
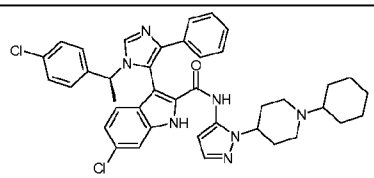
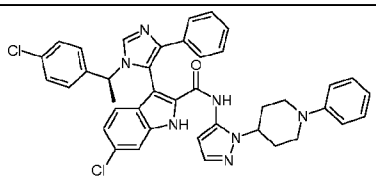
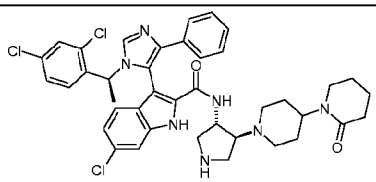
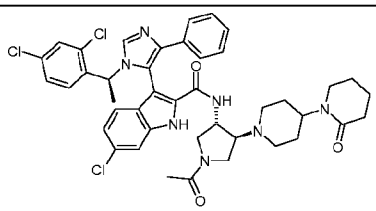
214		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [5-(2-methoxy-ethylcarbamoyl)-2-(2-oxo-[1,4']bipiperidinyl-1'-yl)-phenyl]-amide. HPLC: $^{A}t_{Ret}$ = 5.09; LC-MS: m/z 868.2 $[M+H]^+$.
215		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [5-hydroxymethyl-2-(2-oxo-[1,4']bipiperidinyl-1'-yl)-phenyl]-amide. HPLC: $^{A}t_{Ret}$ = 4.95; LC-MS: m/z 797.0 $[M+H]^+$.
216		3-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-(4-cyclohexyl-piperazin-1-yl)-benzoic acid methyl ester. HPLC: $^{A}t_{Ret}$ = 5.05; LC-MS: m/z 811.2 $[M+H]^+$.
217		3-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-(4-cyclohexyl-piperazin-1-yl)-benzoic acid. HPLC: $^{A}t_{Ret}$ = 4.846; LC-MS: m/z 797.3 $[M+H]^+$.
218		3-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-(4-cyclohexyl-piperazin-1-yl)-benzoic acid methyl amide. HPLC: $^{A}t_{Ret}$ = 4.84; LC-MS: m/z 808.2 $[M+H]^+$.
219		3-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-(4-cyclohexyl-piperazin-1-yl)-benzoic acid dimethyl amide. HPLC: $^{A}t_{Ret}$ = 4.79; LC-MS: m/z 824.3 $[M+H]^+$.
220		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-cyclohexyl-piperazin-1-yl)-5-(2-methoxy-ethylcarbamoyl)-phenyl]-amide. HPLC: $^{A}t_{Ret}$ = 4.77; LC-MS: m/z 854.4 $[M+H]^+$.

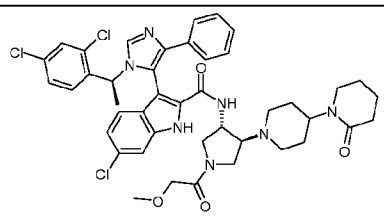
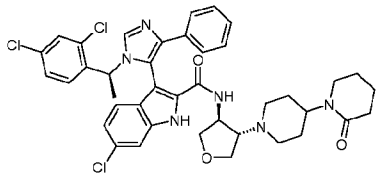
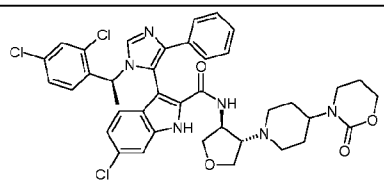
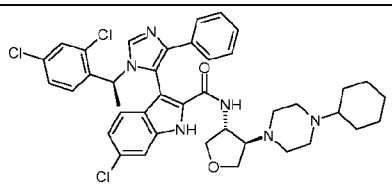
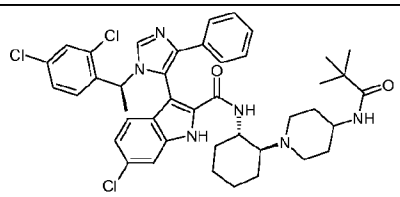
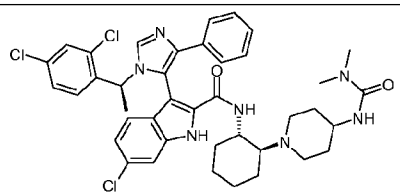
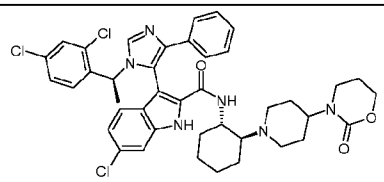
221		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-cyclohexyl-piperazin-1-yl)-5-hydroxymethyl-phenyl]-amide. HPLC: $^{A}t_{Ret}$ = 4.75; LC-MS: m/z 783.4 $[M+H]^+$.
222		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-cyclohexyl-piperazin-1-yl)-5-methoxymethyl-phenyl]-amide. HPLC: $^{C}t_{Ret}$ = 6.77; LC-MS: m/z 797.4 $[M+H]^+$.
223		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-cyclohexyl-piperazin-1-yl)-5-methoxy-phenyl]-amide. HPLC: $^{A}t_{Ret}$ = 5.10; LC-MS: m/z 783.3 $[M+H]^+$.
224		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(4-cyclohexyl-piperazin-1-yl)-5-(2-methoxy-ethoxy)-phenyl]-amide. HPLC: $^{B}t_{Ret}$ = 6.48; LC-MS: m/z 827.4 $[M+H]^+$.
225		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [5-methoxy-2-(2-oxo-[1,4']bipiperidinyl-1'-yl)-phenyl]-amide. HPLC: $^{A}t_{Ret}$ = 5.32; LC-MS: m/z 797.0 $[M+H]^+$.
226		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [5-(2-methoxy-ethoxy)-2-(2-oxo-[1,4']bipiperidinyl-1'-yl)-phenyl]-amide. HPLC: $^{D}t_{Ret}$ = 1.48; LC-MS: m/z 841.4 $[M+H]^+$.
227		[3-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-(4-cyclohexyl-piperazin-1-yl)-phenyl]-acetic acid methyl ester. HPLC: $^{A}t_{Ret}$ = 4.98; LC-MS: m/z 825.4 $[M+H]^+$.

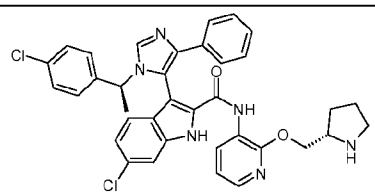
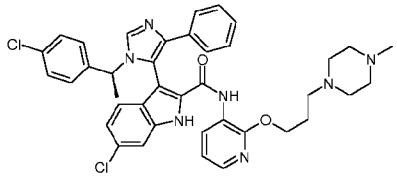
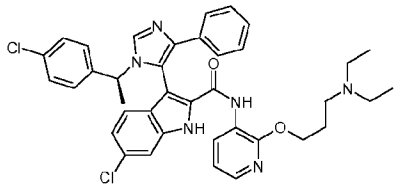
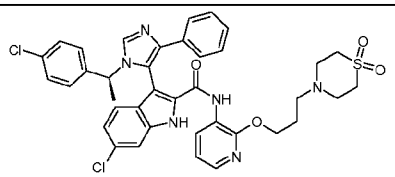
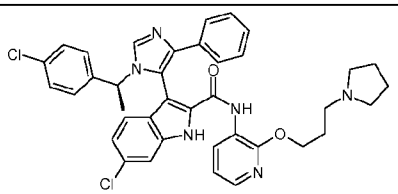
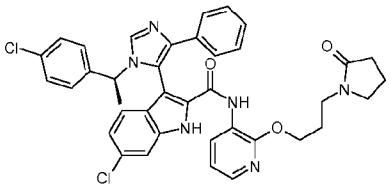
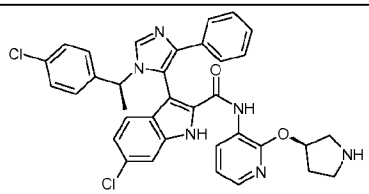
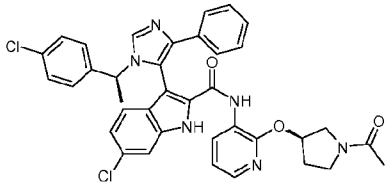
228		[3-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-(4-cyclohexyl-piperazin-1-yl)-phenyl]-acetic acid. HPLC: $^{A}t_{Ret}$ = 4.78; LC-MS: m/z 811.3 $[M+H]^+$.
229		[3-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-(4-cyclohexyl-piperazin-1-yl)-phenyl]-acetic acid methyl amide. HPLC: $^{A}t_{Ret}$ = 4.75; LC-MS: m/z 824.5 $[M+H]^+$.
230		[3-[(6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-4-(4-cyclohexyl-piperazin-1-yl)-phenyl]-acetic acid dimethyl amide. HPLC: $^{A}t_{Ret}$ = 4.85; LC-MS: m/z 838.3 $[M+H]^+$
231		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {5-methoxy-2-[4-(3-oxo-piperazin-1-yl)-piperidin-1-yl]-phenyl}-amide. HPLC: $^{A}t_{Ret}$ = 4.64; LC-MS: m/z 798.0 $[M+H]^+$.
232		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [5-(2-hydroxy-ethoxy)-2-(2-oxo-[1,4']bipiperidinyl-1'-yl)-phenyl]-amide. HPLC: $^{D}t_{Ret}$ = 1.40; LC-MS: m/z 827.4 $[M+H]^+$.
233		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {5-methoxy-2-[4-(2-oxo-azepan-1-yl)-piperidin-1-yl]-phenyl}-amide. HPLC: $^{B}t_{Ret}$ = 6.83; LC-MS: m/z 811.2 $[M+H]^+$.

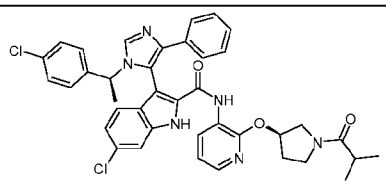
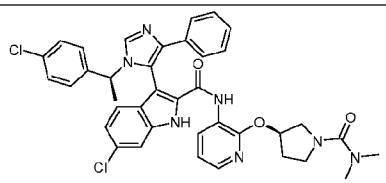
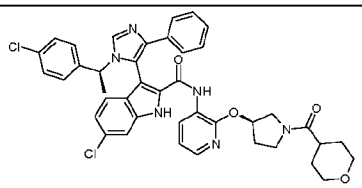
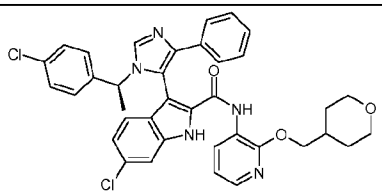
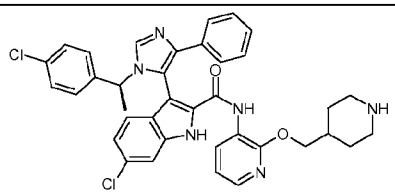
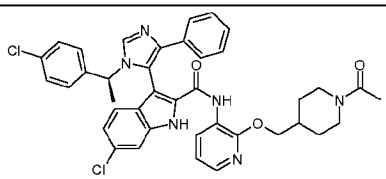
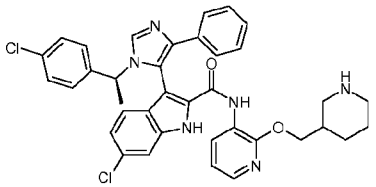
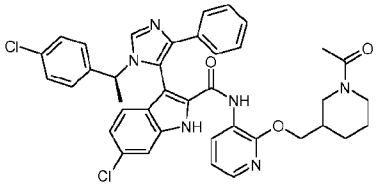
234		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {5-cyano-2-[4-(2-oxo-azepan-1-yl)-piperidin-1-yl]-phenyl}-amide. HPLC: $^{B}t_{Ret}$ = 6.90; LC-MS: m/z 806.4 $[M+H]^+$.
235		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {5-(2-hydroxy-ethoxy)-2-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-phenyl}-amide. HPLC: $^{D}t_{Ret}$ = 1.32; LC-MS: m/z 829.4 $[M+H]^+$.
244		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-((R)-3-amino-piperidin-1-ylmethyl)-phenyl]-amide. HPLC: AtRet = 4.35; LC-MS: m/z 663.3[M+H]+.
245		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-((S)-3-acetylamino-piperidin-1-ylmethyl)-phenyl]-amide. HPLC: AtRet = 4.57; LC-MS: m/z 705.2[M+H]+.
246		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-((R)-3-acetylamino-piperidin-1-ylmethyl) -phenyl]-amide. HPLC: AtRet = 4.57; LC-MS: m/z 705.3[M+H]+.
247		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (2-pyridin-3-ylmethyl-2H-pyrazol-3-yl)-amide. HPLC: BtRet = 5.62; LC-MS: m/z 631.9[M+H]+.
248		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (2-pyridin-4-ylmethyl-2H-pyrazol-3-yl)-amide. HPLC: BtRet = 5.57; LC-MS: m/z 631.9[M+H]+.

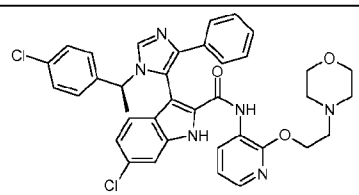
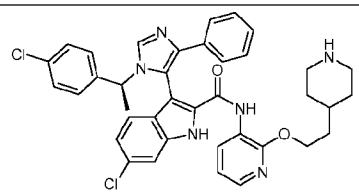
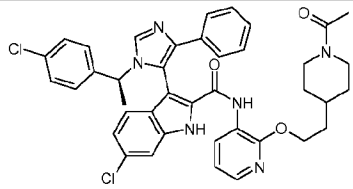
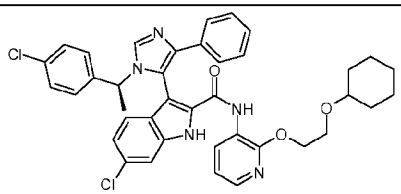
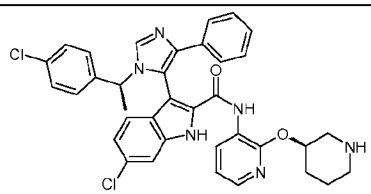
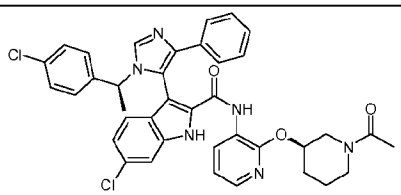
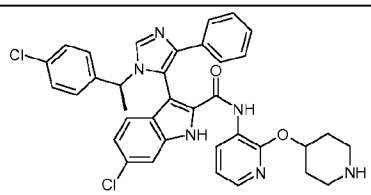
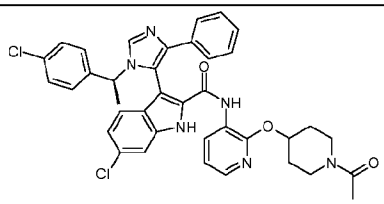
249		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (2-pyridin-2-ylmethyl-2H-pyrazol-3-yl)-amide. HPLC: BtRet = 5.96; LC-MS: m/z 631.9[M+H]+.
250		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(3-methyl-butyl)-2H-pyrazol-3-yl]-amide. HPLC: BtRet = 6.67; LC-MS: m/z 611M+H]+.
251		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (2-cyclopentyl-4-methyl-2H-pyrazol-3-yl)-amide. HPLC: BtRet = 6.66; LC-MS: m/z 622.9[M+H]+.
252		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (2-isobutyl-4-methyl-2H-pyrazol-3-yl)-amide. HPLC: BtRet = 6.56; LC-MS: m/z 610.8[M+H]+.
253		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (4-phenyl-1H-pyrazol-3-yl)-amide. HPLC: CtRet = 6.50; LC-MS: m/z 616.8[M+H]+.
255		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (5-methyl-4-phenyl-1H-pyrazol-3-yl)-amide. HPLC: CtRet = 6.52; LC-MS: m/z 630.8[M+H]+.
256		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (5-methyl-4-phenyl-isoxazol-3-yl)-amide. HPLC: AtRet = 5.24; LC-MS: m/z 631.8[M+H]+.
257		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (2-phenyl-2H-pyrazol-3-yl)-amide. HPLC: CtRet = 6.46; LC-MS: m/z 617[M+H]+.

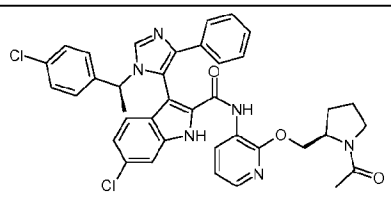
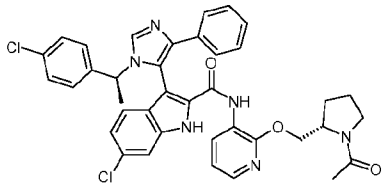
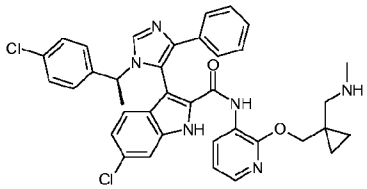
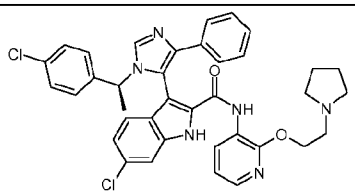
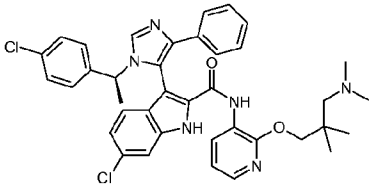
258		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (2-cyclohexyl-2H-pyrazol-3-yl)-amide. HPLC: BtRet = 6.71; LC-MS: m/z 623[M+H]+.
259		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (5-methyl-2-phenyl-2H-pyrazol-3-yl)-amide. HPLC: BtRet = 6.49; LC-MS: m/z 630.9[M+H]+.
260		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (2-pyridin-2-yl-2H-pyrazol-3-yl)-amide. HPLC: BtRet = 6.76; LC-MS: m/z 617.9[M+H]+.
261		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(1-methyl-piperidin-4-yl)-2H-pyrazol-3-yl]-amide. HPLC: BtRet = 5.63; LC-MS: m/z 638[M+H]+.
262		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(1-cyclohexyl-piperidin-4-yl)-2H-pyrazol-3-yl]-amide. HPLC: BtRet = 6.12; LC-MS: m/z 705.9[M+H]+.
263		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(1-phenyl-piperidin-4-yl)-2H-pyrazol-3-yl]-amide. HPLC: BtRet = 6.00; LC-MS: m/z 699.9[M+H]+.
265		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [(3S*,4S*)-4-(2-oxo-[1,4'] bipiperidinyl-1'-yl)-pyrrolidin-3-yl]-amide. HPLC: AtRet = 4.30; LC-MS: m/z 760[M+H]+.
266		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [(3S*,4S*)-1-acetyl-4-(2-oxo-[1,4']bipiperidinyl-1'-yl)-pyrrolidin-3-yl]-amide. HPLC: AtRet = 4.40; LC-MS: m/z 802.2[M+H]+.

267		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [(3S*,4S*)-1-(2-methoxy-acetyl)-4-(2-oxo-[1,4']bipiperidinyl-1'-yl)-pyrrolidin-3-yl]-amide. HPLC: AtRet = 4.40; LC-MS: m/z 832.3[M+H]+.
268		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [(3S*,4S*)-4-(2-oxo-[1,4'] bipiperidinyl-1'-yl)-tetrahydro-furan-3-yl]-amide. HPLC: AtRet = 4.45; LC-MS: m/z 761.3[M+H]+.
269		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {(3S*,4S*)-4-[4-(2-oxo-[1,3] oxazinan-3-yl)-piperidin-1-yl]-tetrahydro-furan-3-yl}-amide. HPLC: AtRet = 4.43; LC-MS: m/z 763[M+H]+.
270		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [(3R*,4R*)-4-(4-cyclohexyl-piperazin-1-yl)-tetrahydro-furan-3-yl]-amide. HPLC: AtRet = 4.62; LC-MS: m/z 747.2[M+H]+.
271		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {(1S,2S)-2-[4-(2,2-dimethyl-propionylamino)-piperidin-1-yl]-cyclohexyl}-amide. HPLC: AtRet = 4.91; LC-MS: m/z 775.3[M+H]+.
272		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {(1S,2S)-2-[4-(3,3-dimethyl-ureido)-piperidin-1-yl]-cyclohexyl}-amide. HPLC: AtRet = 4.66; LC-MS: m/z 762.2[M+H]+.
273		6-Chloro-3-{3-[(S)-1-(2,4-dichloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {(1S,2S)-2-[4-(2-oxo-[1,3]oxazinan-3-yl)-piperidin-1-yl]-cyclohexyl}-amide. HPLC: AtRet = 4.68; LC-MS: m/z 773.2[M+H]+.

274		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-((S)-1-pyrrolidin-2-ylmethoxy)-pyridin-3-yl]-amide HPLC: AtRet = 4.74; LC-MS: m/z 651.2[M+H]+.
275		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {2-[3-(4-methyl-piperazin-1-yl)-propoxy]-pyridin-3-yl}-amide. HPLC: AtRet = 4.48; LC-MS: m/z 708[M+H]+.
276		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(3-diethylamino -propoxy)-pyridin-3-yl]-amide. HPLC: AtRet = 4.83; LC-MS: m/z 681.3[M+H]+.
277		6-chloro-3-(1-((S)-1-(4-chlorophenyl)ethyl)-4-phenyl-1H-imidazol-5-yl)-N-(2-(3-(1,1-dioxidothiomorpholino)propoxy)pyridin-3-yl)-1H-indole-2-carboxamide. HPLC: AtRet = 4.76; LC-MS: m/z 743.3[M+H]+.
278		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(3-pyrrolidin-1-yl-propoxy)-pyridin-3-yl]-amide. HPLC: AtRet = 4.83; LC-MS: m/z 679[M+H]+.
279		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {2-[3-(2-oxo-pyrrolidin-1-yl)-propoxy]-pyridin-3-yl}-amide. HPLC: AtRet = 5.67; LC-MS: m/z 693[M+H]+.
280		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-((R)-pyrrolidin-3-yloxy)-pyridin-3-yl]-amide. HPLC: AtRet = 4.62; LC-MS: m/z 638.7[M+H]+.
281		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-((R)-1-acetyl-pyrrolidin-3-yloxy)-pyridin-3-yl]-amide. HPLC: AtRet = 5.05; LC-MS: m/z 678.9[M+H]+.

282		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-((R)-1-isobutyryl-pyrrolidin-3-yloxy)-pyridin-3-yl]-amide. HPLC: AtRet = 5.25; LC-MS: m/z 706.9[M+H]+.
283		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-((R)-1-dimethylcarbamoyl-pyrrolidin-3-yloxy)-pyridin-3-yl]-amide. HPLC: AtRet = 5.49; LC-MS: m/z 707.9[M+H]+.
284		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {2-[(R)-1-(tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yloxy]-pyridin-3-yl}-amide. HPLC: AtRet = 5.07; LC-MS: m/z 748.9[M+H]+.
285		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(tetrahydro-pyran-4-ylmethoxy)-pyridin-3-yl]-amide. HPLC: AtRet = 5.34; LC-MS: m/z 666.2[M+H]+
286		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(piperidin-4-ylmethoxy)-pyridin-3-yl]-amide. HPLC: AtRet = 4.66; LC-MS: m/z 664.9[M+H]+.
287		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(1-acetyl-piperidin-4-ylmethoxy)-pyridin-3-yl]-amide. HPLC: AtRet = 5.21; LC-MS: m/z 706.9[M+H]+.
288		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(piperidin-3-ylmethoxy)-pyridin-3-yl]-amide. HPLC: AtRet = 4.68; LC-MS: m/z 664.9[M+H]+.
289		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(1-acetyl-piperidin-3-ylmethoxy)-pyridin-3-yl]-amide. HPLC: AtRet = 5.50; LC-MS: m/z 706.9[M+H]+.

290		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(2-morpholin-4-yl-ethoxy)-pyridin-3-yl]-amide. HPLC: AtRet = 4.71; LC-MS: m/z 681.2[M+H]+.
291		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(2-piperidin-4-yl-ethoxy)-pyridin-3-yl]-amide. HPLC: AtRet = 4.69; LC-MS: m/z 679.2[M+H]+.
292		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {2-[2-(1-acetyl-piperidin-4-yl)-ethoxy]-pyridin-3-yl}-amide. HPLC: AtRet = 5.30; LC-MS: m/z 721.2[M+H]+.
293		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(2-cyclohexyloxy-ethoxy)-pyridin-3-yl]-amide. HPLC: AtRet = 5.95; LC-MS: m/z 694.3[M+H]+.
294		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-((R)-piperidin-3-yloxy)-pyridin-3-yl]-amide. HPLC: AtRet = 4.64; LC-MS: m/z 650.9[M+H]+.
295		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-((R)-1-acetyl-piperidin-3-yloxy)-pyridin-3-yl]-amide. HPLC: AtRet = 5.56; LC-MS: m/z 692.9[M+H]+.
296		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(piperidin-4-yloxy)-pyridin-3-yl]-amide. HPLC: AtRet = 4.63; LC-MS: m/z 650.9[M+H]+.
297		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(1-acetyl-piperidin-4-yloxy)-pyridin-3-yl]-amide. HPLC: AtRet = 5.15; LC-MS: m/z 692.9[M+H]+.

298		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-((R)-1-acetyl-pyrrolidin-2-ylmethoxy)-pyridin-3-yl]-amide. HPLC: AtRet = 5.77; LC-MS: m/z 692.9[M+H]+.
299		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-((S)-1-acetyl-pyrrolidin-2-ylmethoxy)-pyridin-3-yl]-amide. HPLC: AtRet = 5.82; LC-MS: m/z 692.9[M+H]+.
300		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(1-methylaminomethyl-cyclopropyl-methoxy)-pyridin-3-yl]-amide. HPLC: AtRet = 4.67; LC-MS: m/z 665[M+H]+.
301		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(2-pyrrolidin-1-yl-ethoxy)-pyridin-3-yl]-amide. HPLC: AtRet = 4.81; LC-MS: m/z 665.2[M+H]+.
302		6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid [2-(3-dimethylamino-2,2-dimethyl-propoxy) -pyridin-3-yl]-amide. HPLC: AtRet = 4.69; LC-MS: m/z 681.3[M+H]+.

[001057] Compounds of the present invention are assayed to evaluate their capacity to inhibit the interaction between p53 and HDM2 and HDM4.

Example 395

Time Resolved Fluorescence Energy Transfer (TR-FRET) Assay

[001058] The test is performed in white 1536w microtiterplates (Greiner Bio-One GmbH, Frickenhausen, Germany) in a total volume of 3.1µl by combining 100nl of compounds diluted in 90% DMSO/10% H_2O (3.2% final DMSO concentration) with 2µl Europium labeled streptavidin (final concentration 2.5nM) in reaction buffer (PBS, 125mM NaCl, 0.001% Novexin

(consists of carbohydrate polymers (Novexin polymers), designed to increase the solubility and stability of proteins; Novexin Ltd., Cambridgeshire, United Kingdom), Gelatin 0.01%, 0.2% Pluronic (block copolymer from ethylenoxide and propyleneoxide, BASF, Ludwigshafen, Germany), 1 mM DTT), followed by the addition of 0.5µl MDM4-Bio diluted in assay buffer (final concentration 10nM). Allow the solution to pre-incubate for 15 minutes at room temperature, followed by addition of 0.5µl Cy5-p53 peptide in assay buffer (final concentration 20nM). Incubate at room temperature for 10 minutes prior to reading the plate. For measurement of samples, an Analyst GT multimode microplate reader (Molecular Devices) with the following settings is used: Dichroic mirror 380nm, Excitation 330nm, Emission Donor 615nm and Emission Acceptor 665nm. IC50 values are calculated by curve fitting using XLfit. If not specified, reagents are purchased from Sigma Chemical Co, St. Louis, MO, USA.

[001059] Compounds described in the present invention preferably display inhibition of p53-HDM4 interaction at IC50s of 0.005 to 100 µM, e.g. from 10 nM to 50 µM.

Example 396

Cellular proliferation assay in SJSA-1 and SAOS-2 cells based on YO-PRO®-1 iodide staining

[001060] The effect of PPI (protein-protein interaction) inhibitors on cell growth of p53 wild-type or mutant cells is assessed in a proliferation assay based on YO-PRO®-1 iodide staining (J Immunol Methods. 1995;185(2):249-58). The principal of this assay is the use of the DNA-intercalating dye YO-PRO®-1 iodide which upon binding to DNA emits a strong fluorescence signal. In addition, the dye is membrane-impermeant and thus, apoptotic cells can be distinguished from the viable cell population during the same assay. In the absence of cell permeabilization, the dye is only entering into cells that are beginning to undergo apoptosis. After treatment of the cells with a lysis buffer, the total cell number can be estimated.

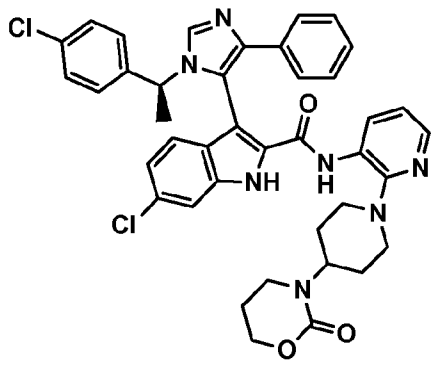
[001061] To test PPI inhibitors on cell growth, SJSA-1 cells (p53 wild-type cells) and SAOS-2 cells (p53 null cells) are plated out into 96-well micro-titer plates and treated with decreasing concentrations of the compounds. After a 72 hour incubation period, 2.5 µM YO-PRO®-1 iodide is directly added to the cells and a first read-out is performed using a standard fluorescence plate reader (filter setting 485/530 nm) revealing the relative number of apoptotic

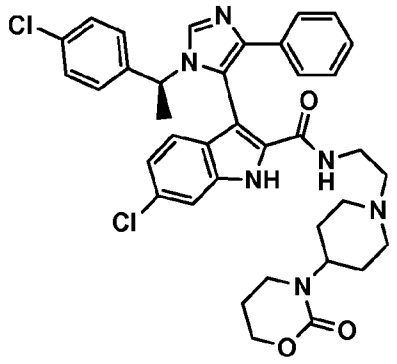
cells. Subsequently, cells are permeabilized by directly adding lysis buffer containing the detergent NP40, EDTA and EGTA to obtain final concentrations of 0.01 % and 5 mM, respectively. After complete permeabilization, the total cell number is quantified during a second read using the fluorescence plate reader with the same settings.

[001062] Compounds of the invention have a more restrained structural confirmation with the R_4 ring that is directly attached to –NH– of the amide bond in Formula I compared with compounds that do not have a ring directly attached at this position. Surprisingly, the increased rigidity offers an enthalpically suitable binding mode allowing compounds of the invention to stay in the p53 binding pocket of MDM2/4 with a longer residence time, offering a ten fold shift in potency. For example, compare example 125 (in table 2) and it's equivalent without a R_4 ring attached to the amide bond of formula I in the cellular proliferation assay of example 396: IC_{50} of Example 125 is 70nM compared with an IC_{50} of 820nM for the equivalent without a R_4 ring attached to the amide bond of formula I.

[001063] Table 2 shows a comparison of Example 125 with a compound without an R_4 ring structure attached to the amide bond of formula I.

Table 2

	Example 125 (70nM)

	820nM

[001064] MDM2 and MDM4 inhibitory activity of representative compounds of the present invention are displayed in Table 3.

Table 3

Example	IC_{50} (μM) of p53-HDM2 inhibition (TR-FRET) Assay	IC_{50} (μM) of p53-HDM4 inhibition (TR-FRET) Assay
1	0.0196	-
2	0.0079	5.3521
3	0.0066	14.9854
4	0.0013	1.3626
5	0.0012	0.6552
6	0.0098	11.9448
7	0.0019	1.8675
8	0.0036	2.2155
9	0.0047	4.2243
10	0.0016	0.7495
11	0.0019	0.7864
12	0.0084	7.6978
13	0.002	2.2503
14	0.0105	10.2282
15	0.0216	37.3327

16	0.0095	44.8055
17	0.0016	0.7147
18	0.0238	35.3561
19	0.0139	-
20	0.0345	24.959
21	0.0041	5.1877
22	0.0043	12.7157
23	0.0378	83.0901
24	0.0274	-
25	0.2725	-
26	0.0077	4.7811
27	0.0693	84.1919
28	0.0741	-
29	0.0129	-
30	0.0541	76.0799
31	0.0135	7.1293
32	0.0657	99.8589
33	0.0058	2.6762
34	0.0449	23.8869
35	0.0022	1.7826
36	0.0088	10.9638
37	0.0243	28.7601
38	0.0817	-
39	0.0171	19.7784
40	0.1065	27.3036
41	0.0041	9.8707
42	0.0229	-
43	0.0501	48.6857
44	0.00215	7.0512
45	0.0143	-
46	0.0022	8.7206
47	0.0045	5.9695
48	0.0169	38.3342

49	0.0054	13.6277
50	0.0066	28.7785
51	0.0074	22.4153
52	0.0042	2.1139
53	0.0402	9.284
54	0.012	8.4837
55	0.0042	4.9801
56	0.0026	3.183
57	0.0016	2.297
58	0.0061	8.368
59	0.0025	1.5475
60	0.0109	-
61	0.0165	17.9524
62	0.006	10.0544
63	0.0094	11.0743
64	0.0098	39.0965
65	0.00315	6.7347
66	0.0021	3.55705
67	0.0009	0.1433
68	0.0014	0.6773
69	0.003	14.7814
70	0.00255	7.82735
71	0.0011	0.2689333
72	0.0012	0.7853
73	0.007	7.4236
74	0.0026	1.7943
75	0.0027	4.1029
76	0.0033	4.9677
77	0.0024	5.3659
78	0.0037	10.4649
79	0.0043	10.2395
80	0.0037	4.2081
81	0.0062	10.6232

82	0.0033	5.0919
83	0.0053	11.5489
84	0.0139	47.1658
85	0.0082	18.4619
86	0.0165	31.0178
87	0.0065	10.3503
88	0.0355	28.3408
89	0.0207	-
90	0.0359	-
91	0.0119	23.554
92	0.0068	22.0678
93	0.0133	38.8624
94	0.031	62.932
95	0.00625	22.9659
96	0.0052	10.3739
97	0.0012	2.8284
98	0.0135	32.4451
99	0.0026	8.1557
100	0.0023	4.0721
101	0.0054	9.4547
102	0.0034	9.3514
103	0.0566	22.4594
104	0.0032	7.3212
105	0.0029	6.7683
106	0.0046	5.5376
107	0.003	2.2595
108	0.0056	6.2468
109	0.0021	1.6555
110	0.0032	7.013
111	0.0054	6.445
112	0.0102	17.858
113	0.0244	29.3333
114	0.0047	4.5872

115	0.0038	10.1333
116	0.0065	13.3689
117	0.0006	0.1818
118	0.0021	2.0405
119	0.0048	3.4917
120	0.00505	7.29925
121	0.0315	94.779
122	0.0146	50.2973
123	0.00255	7.3502
124	0.0521	-
125	0.00114	0.9031
126	0.0061	8.3423
127	0.0031	2.6146
128	0.0089	8.2954
129	0.0093	6.3073
130	0.0014	0.7142
131	0.0052	2.2206
132	0.0195	5.1915
133	0.016	24.3772
134	0.0054	12.2978
135	0.0245	-
136	0.0277	22.8849
137	0.0014	1.5033
138	0.0013	0.8724
139	0.0027	3.8652
140	0.0122	15.3662
141	0.0108	33.0132
142	0.0036	5.7556
143	0.0027	2.21
144	0.0034	2.1009
145	0.0079	20.1001
146	0.0012	0.142
147	0.0082	2.1893

148	0.0059	6.4744
149	0.0021	7.284
150	0.0027	38.384
151	0.0017	4.935
152	0.00138	1.4084
153	0.0035	4.8951
154	0.0013	2.0974
155	0.0047	7.0192
156	0.0132	16.3211
157	0.00105	0.35905
158	0.0033	0.8739
159	0.0014	0.2912
160	0.0045	81.638
161	0.0023	26.155
162	0.011	6.505
163	0.0131	24.948
164	0.0023	9.528
165	0.0152	25.5461
166	0.0027	-
167	0.002	4.0263
168	0.002	3.3362
169	0.0095	15.5104
170	0.007	25.5565
171	0.0012	0.7796
172	0.0012	0.1192
173	0.0017	0.8322
174	0.0013	0.62
175	0.0025	1.8731
176	0.001	1.3988
177	0.0038	0.5614
178	0.00143	1.509
179	0.0585	13.5423
180	0.0108	68.2968

181	0.0078	5.6603
182	0.0016	2.0008
183	0.00106	1.30705
184	0.0012	1.1999
185	0.00125	2.44575
186	0.00135	0.0866
187	0.0022	0.6631
188	0.0008	0.3949
189	0.0041	5.1816
190	0.0017	4.0894
191	0.0049	17.3387
192	0.0038	2.7065
193	0.001	0.6831
194	0.0009	1.2018
195	0.0016	0.1424
196	0.0042	0.5676
197	0.0015	0.3388
198	0.0025	1.6673
199	0.0014	1.7543
200	0.0142	6.027
201	0.0034	22.3768
202	0.004	-
203	0.0156	-
204	0.0017	7.0281
205	0.001	0.1364
206	0.0043	29.3974
207	0.0206	35.0061
208	0.0012	0.6333
209	0.0045	2.2933
210	0.0012	0.4692
211	0.0024	2.5094
212	0.0022	4.9461
213	0.0005	0.0581

214	0.0012	0.7161
215	0.0018	0.6859
216	0.00156	2.4129
217	0.0007	0.0904667
218	0.0016	0.742975
219	0.001	0.49565
220	0.0019	1.0707
221	0.0013	0.3577
222	0.004	1.8345
223	0.0009	0.8257
224	0.00375	1.49705
225	0.0014	3.3866
226	0.0022	2.263
227	0.0007	0.3418
228	0.0015	0.1453
229	0.0009	0.20825
230	0.0019	0.42605
231	0.0024	9.8447
232	0.0017	0.8293
233	0.0042	23.7757
234	0.0025	2.2639
235	0.0007	0.6537
236	0.0304	27.0171
237	0.0028	0.2197
238	0.0459	8.5809
239	0.0249	11.6274
240	0.056	24.4271
241	0.021	11.2833
242	0.0345	9.957
243	0.0064	3.5406
244	0.0183	8.222
245	0.0044	15.0763
246	0.0184	27.6645

247	0.0126	28.2071
248	0.0175	25.3694
249	0.0184	59.8177
250	0.0594	41.4504
251	0.0572	-
252	0.0264	89.2776
253	0.0506	49.904
254	0.0665	69.3179
255	0.0407	55.0038
256	0.0591	-
257	0.0356	58.9575
258	0.0405	72.7447
259	0.0323	31.5241
260	0.0836	-
261	0.0031	4.5227
262	0.0012	1.3373
263	0.0377	24.6066
264	0.01	9.5177
265	0.0057	1.452
266	0.0024	1.371
267	0.0018	0.9542
268	0.0133	18.7039
269	0.0083	16.2193
270	0.0044	2.9445
271	0.0031	5.6361
272	0.0014	1.103
273	0.0019	0.4261
274	0.017	7.2962
275	0.0117	19.2021
276	0.0021	6.2627
277	0.0165	27.8609
278	0.0018	2.3628
279	0.0034	20.7641

280	0.01085	7.82335
281	0.0098	33.5987
282	0.0069	29.4975
283	0.005	48.1132
284	0.0076	-
285	0.113	48.3358
286	0.0095	5.4911
287	0.0246	49.8024
288	0.0114	9.427
289	0.0293	30.7852
290	0.0199	78.682
291	0.0052	4.816
292	0.0215	-
293	0.0623	-
294	0.0206	14.6143
295	0.0213	47.8266
296	0.0195	20.8873
297	0.0149	42.2865
298	0.0205	20.5186
299	0.0257	-
300	0.0241	72.2638
301	0.0045	4.707
302	0.0136	10.579

Example 397

Tablets comprising compounds of the formula I

[001065] Tablets, comprising, as active ingredient, 100 mg of any one of the compounds of formula I of Examples 1 to 394 are prepared with the following composition, following standard procedures:

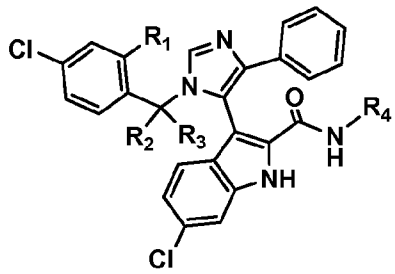
Active Ingredient 100 mg

crystalline lactose	240 mg
Avicel	80 mg
PVPPXL	20 mg
Aerosil	2 mg
magnesium stearate	5 mg
	---
	447 mg

[001066] Manufacture: The active ingredient is mixed with the carrier materials and compressed by means of a tabletting machine (Korsch EKO, Stempeldurchmesser 10 mm). Avicel® is microcrystalline cellulose (FMC, Philadelphia, USA). PVPPXL is polyvinylpoly-pyrrolidone, cross-linked (BASF, Germany). Aerosil® is silicium dioxide (Degussa, Germany).

CLAIMS

1. A compound of Formula I:



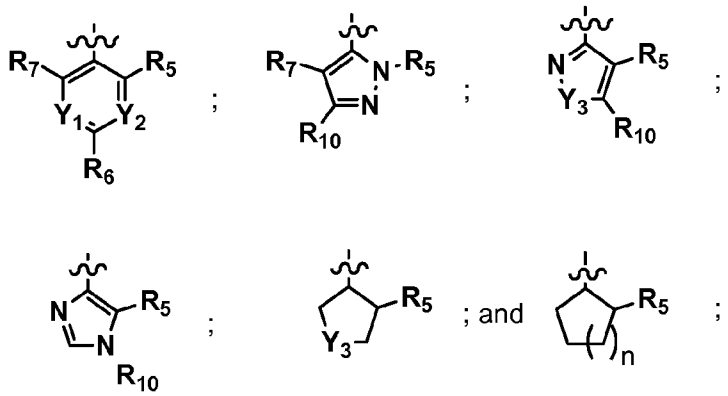
in which:

R_1 is selected from hydrogen and chloro;

R_2 is selected from hydrogen, deuterium and methyl;

R_3 is selected from hydrogen and deuterium;

R_4 is selected from:



wherein:

n is selected from 1 and 2;

R_5 is selected from methyl, phenyl, piperidinyl, piperazinyl, 3-oxopiperazin-1-yl, 3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl, 2,4-dioxo-1,3,8-triazaspiro[4.5]decan-8-yl, 3-oxo-1,2,8-triazaspiro[4.5]decan-8-yl, pyrrolidin-1-ylmethyl, piperidin-1-ylmethyl, benzyl, pyridin-4-ylmethyl, pyridin-3-ylmethyl, pyridin-2-ylmethyl, isopentyl, cyclopentyl, cyclohexyl, cyclohexyl-methyl, isobutyl, benzyloxy, pyrrolidin-2-ylmethoxy, 3-(piperazin-1-yl)propoxy, 3-(1,1-dioxidothiomorpholino)propoxy, 3-(diethylamino)propoxy, 3-(pyrrolidin-1-yl)propoxy, 3-

(piperidin-1-yl)propoxy, 3-(azepan-1-yl)propoxy, 3-(2-oxopyrrolidin-1-yl)propoxy, pyrrolidin-3-yloxy, 3-(piperazin-1-yl)propoxy, (tetrahydro-2H-pyran-4-yl)methoxy, piperidin-4-ylmethoxy, piperidin-3-ylmethoxy, morpholino-ethoxy, piperidin-4-ylethoxy, 2-(tert-butoxy)ethoxy, 2-isobutoxyethoxy, 2-(2,2,2-trifluoroethoxy)ethoxy, phenoxy-ethoxy, piperidin-3-yloxy, piperidin-4-yloxy, cyclohexyloxy, cyclopropyl-methoxy, 2-amino-ethoxy, pyrrolidinyl-ethoxy, 3-amino-propoxy, and 3-(dimethylamino)-2,2-dimethylpropoxy;

wherein said phenyl, piperidinyl, piperazinyl, 3-oxopiperazin-1-yl, 3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl, 2,4-dioxo-1,3,8-triazaspiro[4.5]decan-8-yl, 3-oxo-1,2,8-triazaspiro[4.5]decan-8-yl, pyrrolidin-1-ylmethyl, piperidin-1-ylmethyl, benzyl, pyridin-4-ylmethyl, pyridin-3-ylmethyl, pyridin-2-ylmethyl, cyclopentyl, cyclohexyl, cyclohexyl-, benzyloxy, pyrrolidin-2-ylmethoxy, 3-(piperazin-1-yl)propoxy, 3-(1,1-dioxidothiomorpholino)propoxy, 3-(pyrrolidin-1-yl)propoxy, 3-(piperidin-1-yl)propoxy, 3-(azepan-1-yl)propoxy, 3-(2-oxopyrrolidin-1-yl)propoxy, pyrrolidin-3-yloxy, 3-(piperazin-1-yl)propoxy, (tetrahydro-2H-pyran-4-yl)methoxy, piperidin-4-ylmethoxy, piperidin-3-ylmethoxy, morpholino-ethoxy, piperidin-4-ylethoxy, 2-(tert-butoxy)ethoxy, phenoxy-ethoxy, piperidin-3-yloxy, piperidin-4-yloxy, cyclohexyloxy, cyclopropyl-methoxy, pyrrolidinyl-ethoxy, 2-amino-ethoxy, 3-amino-propoxy, or 3-(dimethylamino)-2,2-dimethylpropoxy of R_5 can be unsubstituted or substituted with 1 to 2 groups selected from $-NR_{13}C(O)OR_{14}$, $-NR_{13}S(O)_{0-2}R_{14}$, $-NR_{13}C(O)X_1OR_{14}$, $-NR_{13}C(O)OX_1OR_{14}$, $-NR_{13}C(O)NR_{13}R_{14}$, $-NR_{13}R_{14}$, $-X_1NR_{13}R_{14}$, $-NR_{13}C(O)R_{14}$, $-C(O)R_{14}$, $-C(O)OR_{14}$, $-C(O)NR_{13}R_{14}$, $-C(O)OX_1OR_{14}$, $C(O)NR_{13}X_1OR_{14}$, $-OR_{14}$, $-X_1R_{14}$, $-X_1OR_{14}$, $-NR_{13}X_1R_{14}$, hydroxyl, cyano, branched or unbranched C_{1-6}alkyl, piperidinyl, cyclohexyl, pyridinyl, piperazinyl, phenyl, pyrimidinyl, 4H-1,2,4-triazol-4-yl, 1,3,4-oxadiazol-2-yl, 1H-1,2,4-triazol-3-yl, 5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl, tetrahydro-2H-pyran-4-yl, 2-oxopyrrolidin-1-yl, 2-oxo-1,3-oxazinan-3-yl, 2-oxopiperidin-1-yl, isoxazol-4-yl, 2-oxoimidazolidin-1-yl, 2-oxooxazolidin-3-yl, 1,1-dioxidoisothiazolidin-2-yl, 3-oxomorpholino, 1,1-dioxido-1,2-thiazinan-2-yl, 1,1-dioxido-1,2,6-thiadiazinan-2-yl, 2-oxotetrahydropyrimidin-1(2H)-yl, 2-oxo-1,3-oxazinan-3-yl, 2-oxopiperidin-1-yl, 2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl, 1,1-dioxidothiomorpholino, 2-oxo-1,4-diazepan-1-yl, 7-oxo-1,4-diazepan-1-yl and 2-oxoazepan-1-yl; wherein R_{13} at each occurrence is independently selected from hydrogen, methyl and ethyl; and R_{14} at each occurrence is independently selected from hydrogen, branched or unbranched C_{1-6}alkyl, branched or unbranched hydroxy-substituted-C_{1-6}alkyl, branched or unbranched halo-substituted-C_{1-6}alkyl, phenyl, pyridinyl, pyrazinyl, pyrimidinyl,

tetrahydrofuranyl, cyclopentyl, trideuterated-methyl, cyclopropyl, pyrrolidinyl, tetrahydro-2H-pyran-4-yl, azetidin-1-yl and cyclobutyl; wherein each R_{14} can be optionally further substituted with halo, hydroxy, $-X_1OR_{15}$, $-C(O)OR_{15}$ and $-C(O)R_{15}$; wherein R_{15} at each occurrence is independently selected from hydrogen and branched or unbranched C_{1-6}alkyl;

wherein said piperidinyl, cyclohexyl, pyridinyl, piperazinyl, phenyl, pyrimidinyl, 4H-1,2,4-triazol-4-yl, 1,3,4-oxadiazol-2-yl, 1H-1,2,4-triazol-3-yl, 5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl, tetrahydro-2H-pyran-4-yl, tetrahydrofuranyl, 2-oxopyrrolidin-1-yl, 2-oxo-1,3-oxazinan-3-yl, 2-oxopiperidin-1-yl, isoxazol-4-yl, 2-oxoimidazolidin-1-yl, 2-oxooxazolidin-3-yl, 1,1-dioxidoisothiazolidin-2-yl, 3-oxomorpholino, 1,1-dioxido-1,2-thiazinan-2-yl, 1,1-dioxido-1,2,6-thiadiazinan-2-yl, 2-oxotetrahydropyrimidin-1(2H)-yl, 2-oxo-1,3-oxazinan-3-yl, 2-oxopiperidin-1-yl, 2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl, 2-oxo-1,4-diazepan-1-yl, 7-oxo-1,4-diazepan-1-yl and 2-oxoazepan-1-yl substituents of R_5 can be optionally further substituted by 1 to 3 groups selected from halo, C_{1-4}alkyl, amino, tetrahydrofuranyl and hydroxy-substituted-C_{1-4}alkyl;

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

R_7 is selected from hydrogen, C_{1-4}alkyl and C_{1-4}alkoxy;

Y_1 and Y_2 are independently selected from CR_8 and N; wherein

R_8 is selected from hydrogen, halo, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, $-OX_1OR_{9a}$, $-X_1OR_{9a}$, $-C(O)OR_{9a}$, $-X_1C(O)OR_{9a}$, $-C(O)NR_{9a}R_{9b}$, $-X_1C(O)NR_{9a}R_{9b}$ and $-C(O)NR_{9a}X_1OR_{9b}$; wherein

X_1 is at each occurrence is independently selected from branched or unbranched C_{1-6}alkylene;

R_{9a} and R_{9b} are independently selected from hydrogen, C_{1-4}alkyl, deutorated-C_{1-4}alkyl, halo-substituted-C_{1-4}alkyl and hydroxy-substituted-C_{1-4}alkyl; or R_{9a} and R_{9b} together with the nitrogen to which they are both attached form a 4-7 member saturated ring containing up to 2 heteroatoms selected from N, O and S; wherein said ring formed by R_{9a} and R_{9b} can be unsubstituted or substituted with a group selected from hydroxyl and C_{1-4}alkyl;

R_{10} is selected from hydrogen and C_{1-4}alkyl;

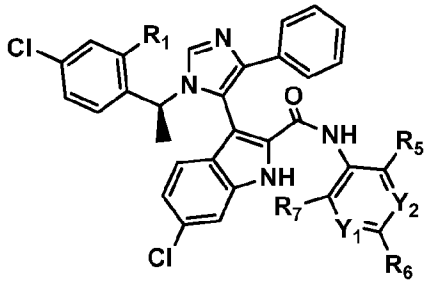
Y_3 is selected from NR_{11} and O;

R_{11} is selected from hydrogen, C_{1-4}alkyl, $-S(O)_{0-2}R_{12}$, $-C(O)X_2OR_{12}$ and $-C(O)R_{12}$; wherein

R_{12} is selected from hydrogen and C_{1-4}alkyl;

or the pharmaceutically acceptable salts thereof.

2. The compound of claim 1, of Formula Ia:



Ia

in which:

R_1 is selected from hydrogen and chloro;

Y_1 and Y_2 are independently selected from CR_8 and N;

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

R_5 is selected from methyl, piperidinyl, piperazinyl, 3-oxopiperazin-1-yl, 3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl, 3-oxo-1,2,8-triazaspiro[4.5]decan-8-yl, 2,4-dioxo-1,3,8-triazaspiro[4.5]decan-8-yl, pyrrolidin-1-ylmethyl, piperidin-1-ylmethyl, pyrrolidin-2-ylmethoxy, 3-(piperazin-1-yl)propoxy, 3-(1,1-dioxidothiomorpholino)propoxy, 3-(diethylamino)propoxy, 3-(azepan-1-yl)propoxy, 3-(2-oxopyrrolidin-1-yl)propoxy, pyrrolidin-3-yloxy, 3-(piperazin-1-yl)propoxy, (tetrahydro-2H-pyran-4-yl)methoxy, piperidin-4-ylmethoxy, piperidin-3-ylmethoxy, 2-(tert-butoxy)ethoxy, 2-isobutoxyethoxy, 2-(2,2,2-trifluoroethoxy)ethoxy, phenoxy-ethoxy, piperidin-3-yloxy, piperidin-4-yloxy, cyclohexyloxy, cyclopropyl-methoxy, 2-amino-ethoxy, pyrrolidinyl-ethoxy, 3-amino-propoxy, and 3-(dimethylamino)-2,2-dimethylpropoxy; wherein said piperidinyl, piperazinyl, 3-oxopiperazin-1-yl, 3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl, 3-oxo-1,2,8-triazaspiro[4.5]decan-8-yl, 2,4-dioxo-1,3,8-triazaspiro[4.5]decan-8-yl, pyrrolidin-1-ylmethyl, piperidin-1-ylmethyl, pyrrolidin-2-ylmethoxy, 3-(piperazin-1-yl)propoxy, 3-(1,1-dioxidothiomorpholino)propoxy, 3-(diethylamino)propoxy, 3-(azepan-1-yl)propoxy, 3-(2-oxopyrrolidin-1-yl)propoxy, pyrrolidin-3-yloxy, 3-(piperazin-1-yl)propoxy, (tetrahydro-2H-pyran-4-yl)methoxy, piperidin-4-ylmethoxy, piperidin-3-ylmethoxy, 2-(tert-butoxy)ethoxy, 2-isobutoxyethoxy, 2-(2,2,2-trifluoroethoxy)ethoxy, phenoxy-ethoxy, piperidin-3-yloxy, piperidin-4-yloxy, cyclohexyloxy, cyclopropyl-methoxy, 2-amino-ethoxy, pyrrolidinyl-ethoxy, 3-amino-propoxy, or 3-(dimethylamino)-2,2-dimethylpropoxy of R_5 can be unsubstituted or substituted with a group selected from $-NR_{13}C(O)OR_{14}$, $-NR_{13}S(O)_{0-2}R_{14}$, $-NR_{13}C(O)X_1OR_{14}$, -

$NR_{13}C(O)OX_1OR_{14}$, $-NR_{13}C(O)NR_{13}R_{14}$, $-NR_{13}R_{14}$, $-X_1NR_{13}R_{14}$, $-NR_{13}C(O)R_{14}$, $-C(O)R_{14}$, $-C(O)OR_{14}$, $-C(O)NR_{13}R_{14}$, $-C(O)OX_1OR_{14}$, $C(O)NR_{13}X_1OR_{14}$, $-OR_{14}$, $-X_1R_{14}$, $-X_1OR_{14}$, $-NR_{13}X_1R_{14}$, hydroxyl, cyano, branched or unbranched C_{1-6}alkyl, piperidinyl, cyclohexyl, pyridinyl, piperazinyl, phenyl, pyrimidinyl, 4H-1,2,4-triazol-4-yl, 1,3,4-oxadiazol-2-yl, 1H-1,2,4-triazol-3-yl, 5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl, tetrahydro-2H-pyran-4-yl, 2-oxopyrrolidin-1-yl, 2-oxo-1,3-oxazinan-3-yl, 2-oxopiperidin-1-yl, isoxazol-4-yl, 2-oxoimidazolidin-1-yl, 2-oxooxazolidin-3-yl, 1,1-dioxidoisothiazolidin-2-yl, 3-oxomorpholino, 1,1-dioxido-1,2-thiazinan-2-yl, 1,1-dioxido-1,2,6-thiadiazinan-2-yl, 2-oxotetrahydropyrimidin-1(2H)-yl, 2-oxo-1,3-oxazinan-3-yl, 2-oxopiperidin-1-yl, 2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl, 1,1-dioxidothiomorpholino, 2-oxo-1,4-diazepan-1-yl, 7-oxo-1,4-diazepan-1-yl and 2-oxoazepan-1-yl; wherein R_{13} at each occurrence is independently selected from hydrogen, methyl and ethyl; and R_{14} at each occurrence is independently selected from hydrogen, branched or unbranched C_{1-6}alkyl, branched or unbranched hydroxy-substituted-C_{1-6}alkyl, branched or unbranched halo-substituted-C_{1-6}alkyl, phenyl, pyridinyl, pyrazinyl, pyrimidinyl, tetrahydrofuranyl, cyclopentyl, trideuterated-methyl, cyclopropyl, pyrrolidinyl, tetrahydro-2H-pyran-4-yl, azetidin-1-yl and cyclobutyl; wherein each R_{14} can be optionally further substituted with halo, hydroxy, $-X_1OR_{15}$, $-C(O)OR_{15}$ and $-C(O)R_{15}$; wherein R_{15} at each occurrence is independently selected from hydrogen and branched or unbranched C_{1-6}alkyl; wherein said piperidinyl, cyclohexyl, pyridinyl, piperazinyl, phenyl, pyrimidinyl, 4H-1,2,4-triazol-4-yl, 1,3,4-oxadiazol-2-yl, 1H-1,2,4-triazol-3-yl, 5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl, tetrahydro-2H-pyran-4-yl, tetrahydrofuranyl, 2-oxopyrrolidin-1-yl, 2-oxo-1,3-oxazinan-3-yl, 2-oxopiperidin-1-yl, isoxazol-4-yl, 2-oxoimidazolidin-1-yl, 2-oxooxazolidin-3-yl, 1,1-dioxidoisothiazolidin-2-yl, 3-oxomorpholino, 1,1-dioxido-1,2-thiazinan-2-yl, 1,1-dioxido-1,2,6-thiadiazinan-2-yl, 2-oxotetrahydropyrimidin-1(2H)-yl, 2-oxo-1,3-oxazinan-3-yl, 2-oxopiperidin-1-yl, 2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl, 2-oxo-1,4-diazepan-1-yl, 7-oxo-1,4-diazepan-1-yl and 2-oxoazepan-1-yl substituents of R_5 can be optionally further substituted by 1 to 2 groups selected from halo, C_{1-4}alkyl, amino, tetrahydrofuranyl and hydroxy-substituted-C_{1-4}alkyl;

R_7 is selected from hydrogen, C_{1-4}alkyl and C_{1-4}alkoxy;

R_8 is selected from hydrogen, halo, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, $-OX_1OR_{9a}$, $-X_1OR_{9a}$, $-C(O)OR_{9a}$, $-X_1C(O)OR_{9a}$, $-C(O)NR_{9a}R_{9b}$, $-X_1C(O)NR_{9a}R_{9b}$ and $-C(O)NR_{9a}X_1OR_{9b}$; wherein

X_1 is at each occurrence is independently selected from branched or unbranched C_{1-6}alkylene; and

R_{9a} and R_{9b} are independently selected from hydrogen, C_{1-4}alkyl, deutorated-C_{1-4}alkyl, halo-substituted-C_{1-4}alkyl and hydroxy-substituted-C_{1-4}alkyl; or R_{9a} and R_{9b} together with the nitrogen to which they are both attached form a 4-7 member saturated ring containing up to 2 heteroatoms selected from N, O and S; wherein said ring formed by R_{9a} and R_{9b} can be unsubstituted or substituted with a group selected from hydroxyl and C_{1-4}alkyl ; or the pharmaceutically acceptable salts thereof.

3. The compound of claim 2 in which:

Y_1 is selected from N and CR_8;

Y_2 is selected from N and CR_8;

R_6 is selected from hydrogen, methoxy, methyl and fluoro;

R_7 is selected from hydrogen, methyl and methoxy; and

R_8 is selected from hydrogen, chloro, fluoro, cyano, methoxy, hydroxy-methyl, hydroxy-ethoxy, trifluoromethyl, methoxy-ethoxy, methoxy-methyl, 2-hydroxy-2-methylpropyl, carboxy-methyl, hydroxy-carbonyl-methyl, methyl-amino-carbonyl-methyl, dimethylamino-carbonyl-methyl, $-C(O)NR_{9a}R_{9b}$, $-C(O)OR_{9a}$ and $-C(O)NR_{9a}R_{9b}$; wherein R_{9a} is selected from hydrogen, methyl and trideuterated-methyl; and R_{9b} is selected from methyl, trideuterated-methyl, methoxy-ethyl and hydroxy-ethyl; or R_{9a} and R_{9b} together with the nitrogen to which they are both attached form azetidin-1-yl optionally substituted with hydroxyl; or the pharmaceutically acceptable salts thereof.

4. The compound of claim 3 in which: R_5 is selected from methyl, piperidinyl, piperazinyl, 3-oxopiperazin-1-yl, 3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl, 3-oxo-1,2,8-triazaspiro[4.5]decan-8-yl, 2,4-dioxo-1,3,8-triazaspiro[4.5]decan-8-yl, pyrrolidin-1-ylmethyl, piperidin-1-ylmethyl, pyrrolidin-2-ylmethoxy, 3-(piperazin-1-yl)propoxy, 3-(1,1-dioxidothiomorpholino)propoxy, 3-(diethylamino)propoxy, 3-(azepan-1-yl)propoxy, 3-(2-oxopyrrolidin-1-yl)propoxy, pyrrolidin-3-yloxy, 3-(piperazin-1-yl)propoxy, (tetrahydro-2H-pyran-4-yl)methoxy, piperidin-4-ylmethoxy, piperidin-3-ylmethoxy, 2-(tert-butoxy)ethoxy, 2-isobutoxyethoxy, 2-(2,2,2-trifluoroethoxy)ethoxy, phenoxy-ethoxy, piperidin-3-yloxy, piperidin-4-yloxy, cyclohexyloxy, cyclopropyl-methoxy, 2-amino-ethoxy, pyrrolidinyl-ethoxy, 3-amino-propoxy, and 3-(dimethylamino)-2,2-dimethylpropoxy;

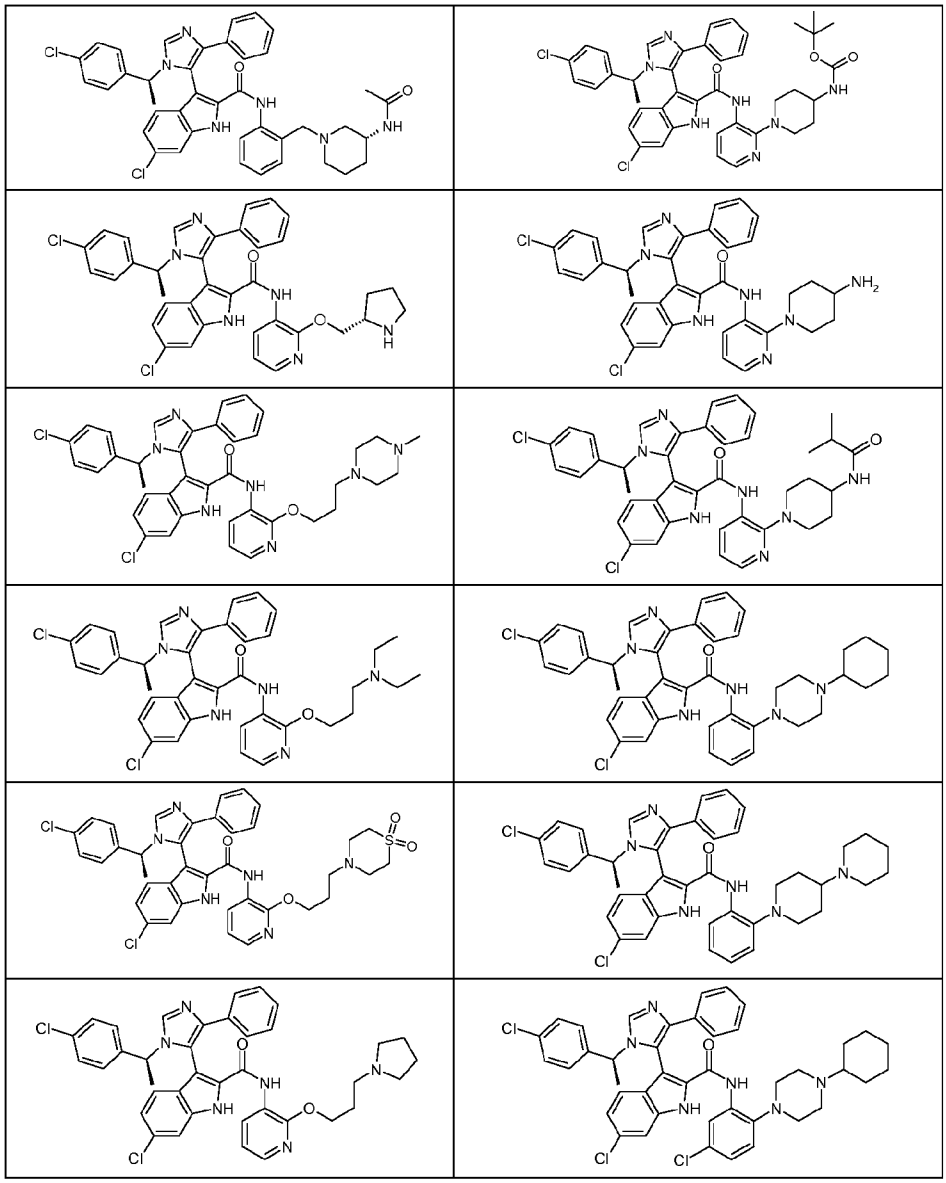
wherein said piperidinyl, piperazinyl, 3-oxopiperazin-1-yl, 3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl, 3-oxo-1,2,8-triazaspiro[4.5]decan-8-yl, 2,4-dioxo-1,3,8-triazaspiro[4.5]decan-8-yl, pyrrolidin-1-ylmethyl, piperidin-1-ylmethyl, pyrrolidin-2-ylmethoxy, 3-(piperazin-1-yl)propoxy, 3-(1,1-dioxidothiomorpholino)propoxy, 3-(diethylamino)propoxy, 3-(azepan-1-yl)propoxy, 3-(2-oxopyrrolidin-1-yl)propoxy, pyrrolidin-3-yloxy, 3-(piperazin-1-yl)propoxy, (tetrahydro-2H-pyran-4-yl)methoxy, piperidin-4-ylmethoxy, piperidin-3-ylmethoxy, 2-(tert-butoxy)ethoxy, 2-isobutoxyethoxy, 2-(2,2,2-trifluoroethoxy)ethoxy, phenoxy-ethoxy, piperidin-3-yloxy, piperidin-4-yloxy, cyclohexyloxy, cyclopropyl-methoxy, 2-amino-ethoxy, pyrrolidinyl-ethoxy, 3-amino-propoxy, or 3-(dimethylamino)-2,2-dimethylpropoxy of R_5 can be unsubstituted or substituted with a group selected from $-NR_{13}C(O)OR_{14}$, $-NR_{13}S(O)_{0-2}R_{14}$, $-NR_{13}C(O)X_1OR_{14}$, $-NR_{13}C(O)OX_1OR_{14}$, $-NR_{13}C(O)NR_{13}R_{14}$, $-NR_{13}R_{14}$, $-X_1NR_{13}R_{14}$, $-NR_{13}C(O)R_{14}$, $-C(O)R_{14}$, $-C(O)OR_{14}$, $-C(O)NR_{13}R_{14}$, $-C(O)OX_1OR_{14}$, $C(O)NR_{13}X_1OR_{14}$, $-OR_{14}$, $-X_1R_{14}$, $-X_1OR_{14}$, $-NR_{13}X_1R_{14}$, hydroxyl, cyano, branched or unbranched C_{1-6}alkyl, piperidinyl, cyclohexyl, pyridinyl, piperazinyl, phenyl, pyrimidinyl, 4H-1,2,4-triazol-4-yl, 1,3,4-oxadiazol-2-yl, 1H-1,2,4-triazol-3-yl, 5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl, tetrahydro-2H-pyran-4-yl, 2-oxopyrrolidin-1-yl, 2-oxo-1,3-oxazinan-3-yl, 2-oxopiperidin-1-yl, isoxazol-4-yl, 2-oxoimidazolidin-1-yl, 2-oxooxazolidin-3-yl, 1,1-dioxidoisothiazolidin-2-yl, 3-oxomorpholino, 1,1-dioxido-1,2-thiazinan-2-yl, 1,1-dioxido-1,2,6-thiadiazinan-2-yl, 2-oxotetrahydropyrimidin-1(2H)-yl, 2-oxo-1,3-oxazinan-3-yl, 2-oxopiperidin-1-yl, 2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl, 1,1-dioxidothiomorpholino, 2-oxo-1,4-diazepan-1-yl, 7-oxo-1,4-diazepan-1-yl and 2-oxoazepan-1-yl; wherein R_{13} at each occurrence is independently selected from hydrogen, methyl and ethyl; and R_{14} at each occurrence is independently selected from hydrogen, t-butyl, isopropyl, methyl, ethyl, pentan-3-yl, trideuterated-methyl, neopentyl, trifluoromethyl, phenyl, pyridinyl, pyrazinyl, pyrimidinyl, tetrahydrofuranyl, cyclopentyl, trideuterated-methyl, cyclopropyl, pyrrolidinyl, tetrahydro-2H-pyran-4-yl, azetidin-1-yl and cyclobutyl; wherein each R_{14} can be optionally further substituted with halo, hydroxy, $-X_1OR_{15}$, $-C(O)OR_{15}$ and $-C(O)R_{15}$; wherein R_{15} at each occurrence is independently selected from hydrogen, methyl, ethyl and t-butyl;

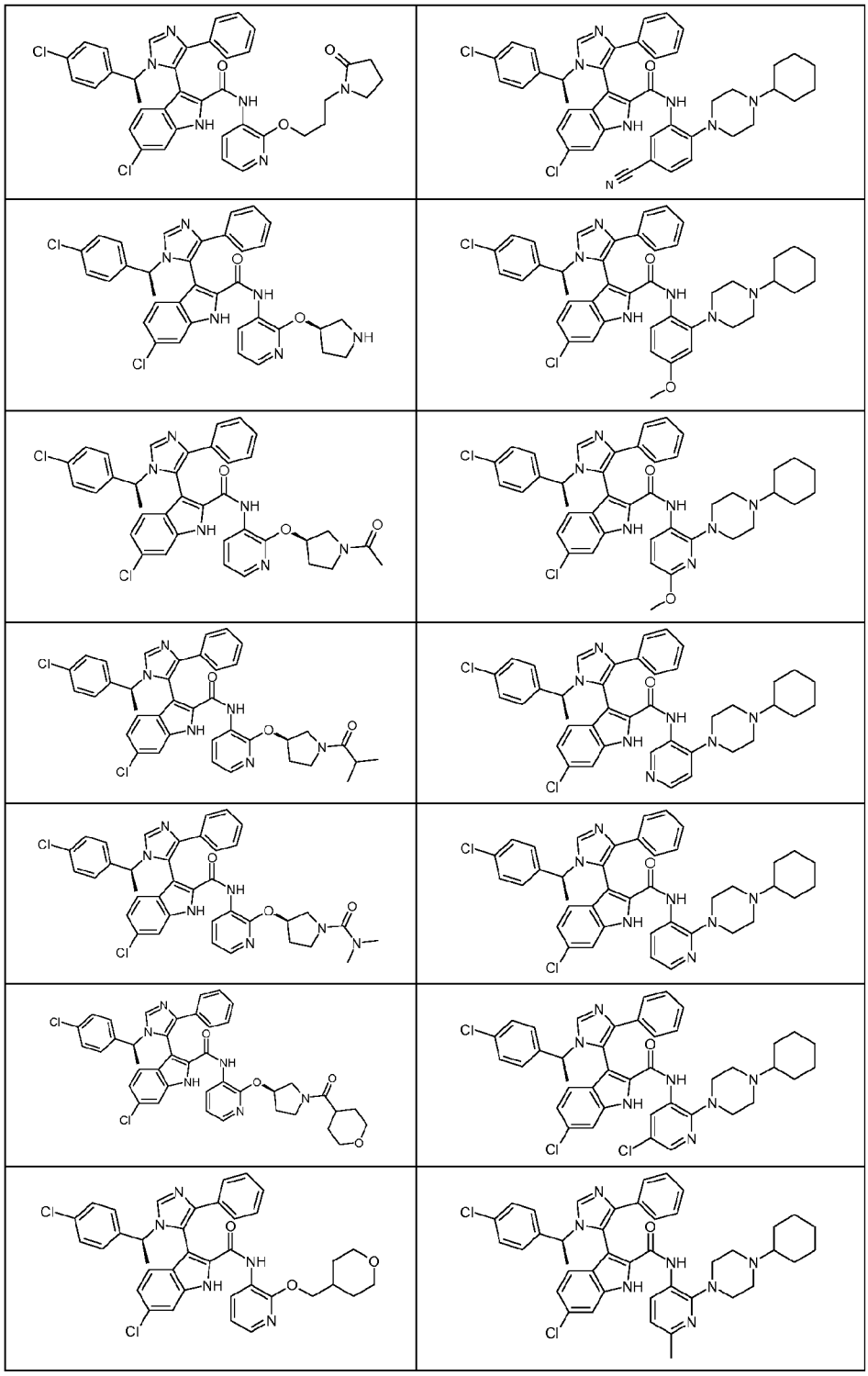
wherein said piperidinyl, cyclohexyl, pyridinyl, piperazinyl, phenyl, pyrimidinyl, 4H-1,2,4-triazol-4-yl, 1,3,4-oxadiazol-2-yl, 1H-1,2,4-triazol-3-yl, 5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl, tetrahydro-2H-pyran-4-yl, tetrahydrofuranyl, 2-oxopyrrolidin-1-yl, 2-oxo-1,3-oxazinan-3-yl, 2-oxopiperidin-1-yl, isoxazol-4-yl, 2-oxoimidazolidin-1-yl, 2-oxooxazolidin-3-yl, 1,1-dioxidoisothiazolidin-2-yl, 3-oxomorpholino, 1,1-dioxido-1,2-thiazinan-2-yl, 1,1-dioxido-1,2,6-

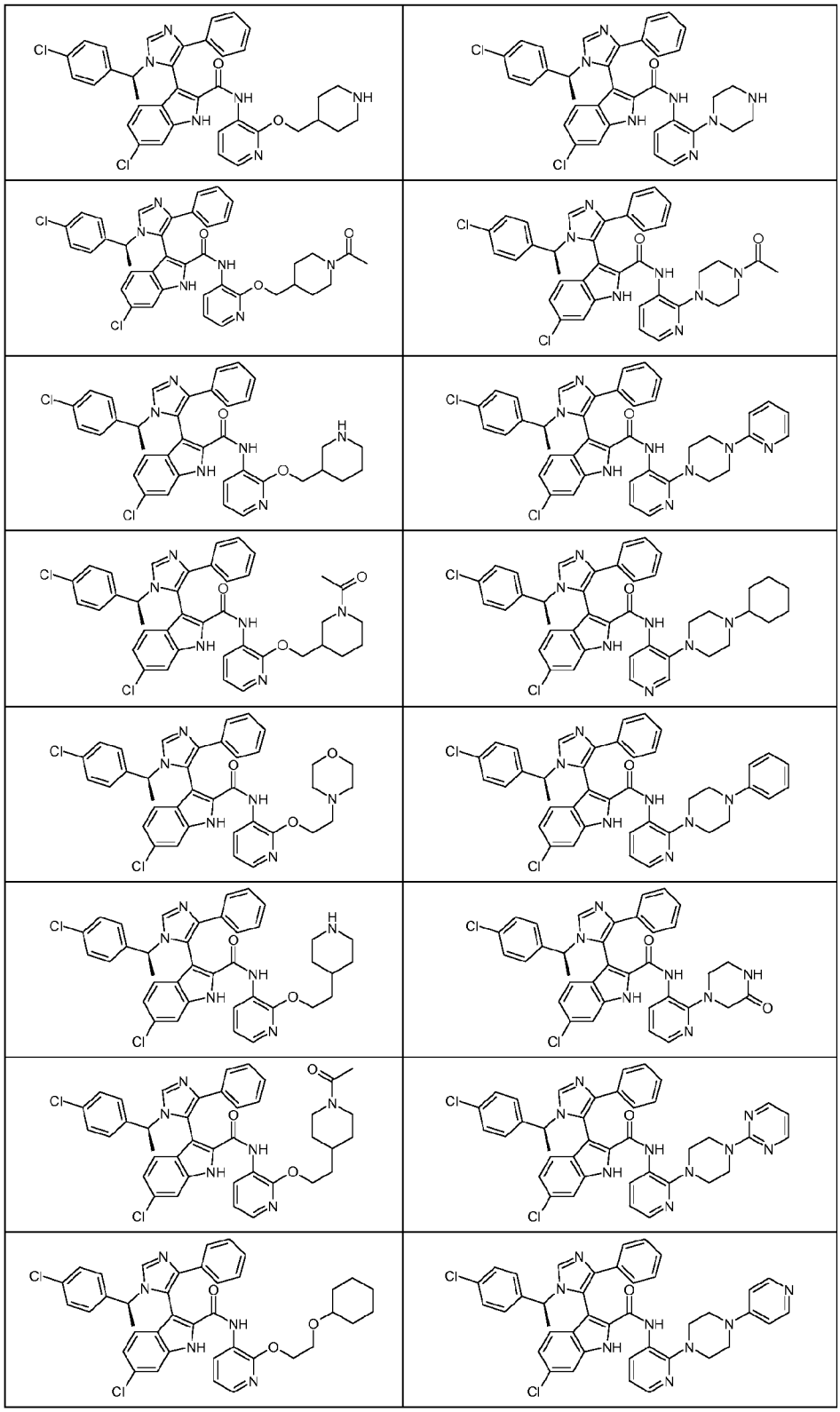
thiadiazinan-2-yl, 2-oxotetrahydropyrimidin-1(2H)-yl, 2-oxo-1,3-oxazinan-3-yl, 2-oxopiperidin-1-yl, 2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl, 2-oxo-1,4-diazepan-1-yl, 7-oxo-1,4-diazepan-1-yl and 2-oxoazepan-1-yl substituents of R_5 can be optionally further substituted by 1 to 2 groups selected from fluoro, methyl, amino, tetrahydrofuranyl and hydroxy-ethyl; and

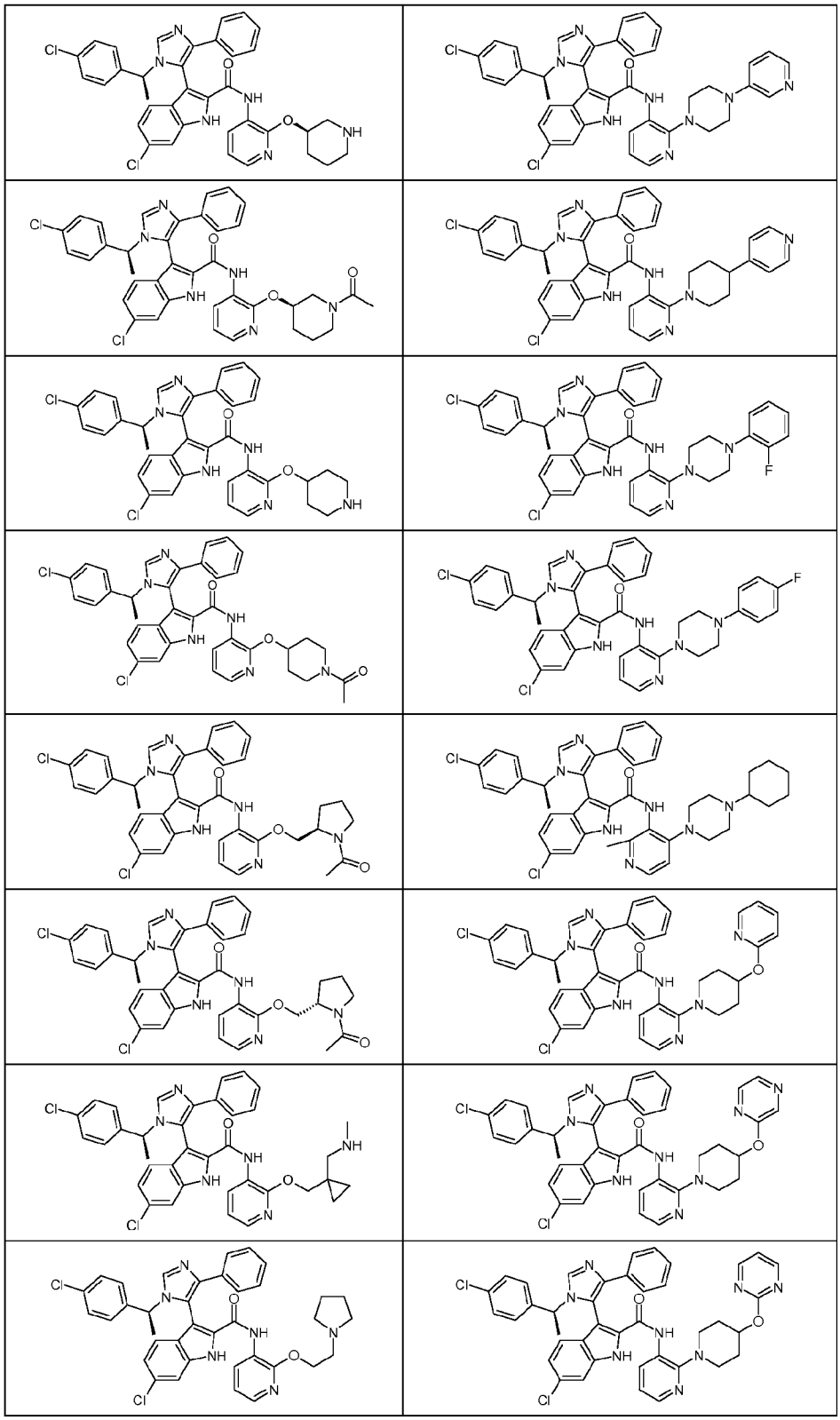
X_1 at each occurrence is independently selected from methylene, ethylene and propylene; or the pharmaceutically acceptable salts thereof

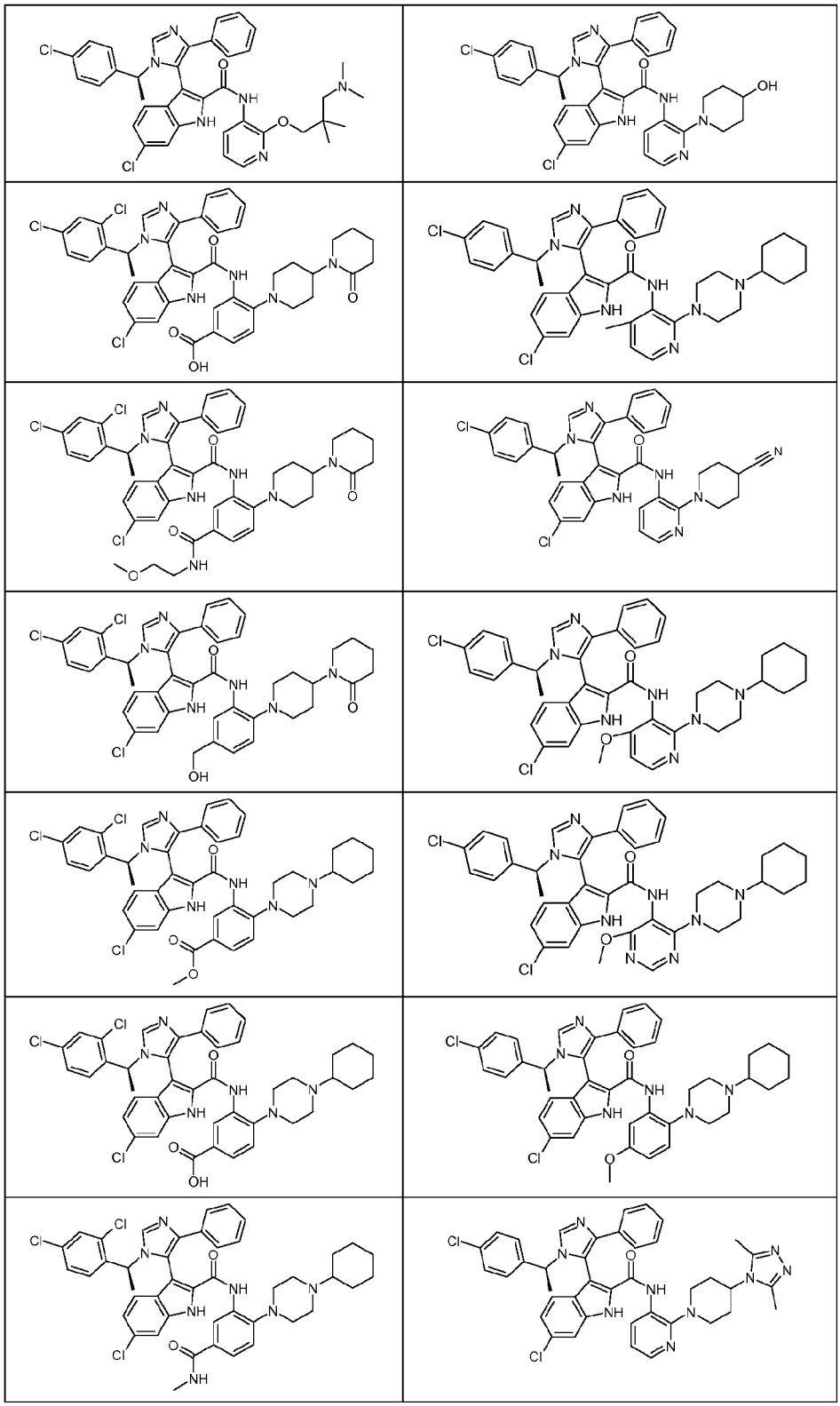
5. The compound of claim 4, or the pharmaceutically acceptable salts thereof, selected from:

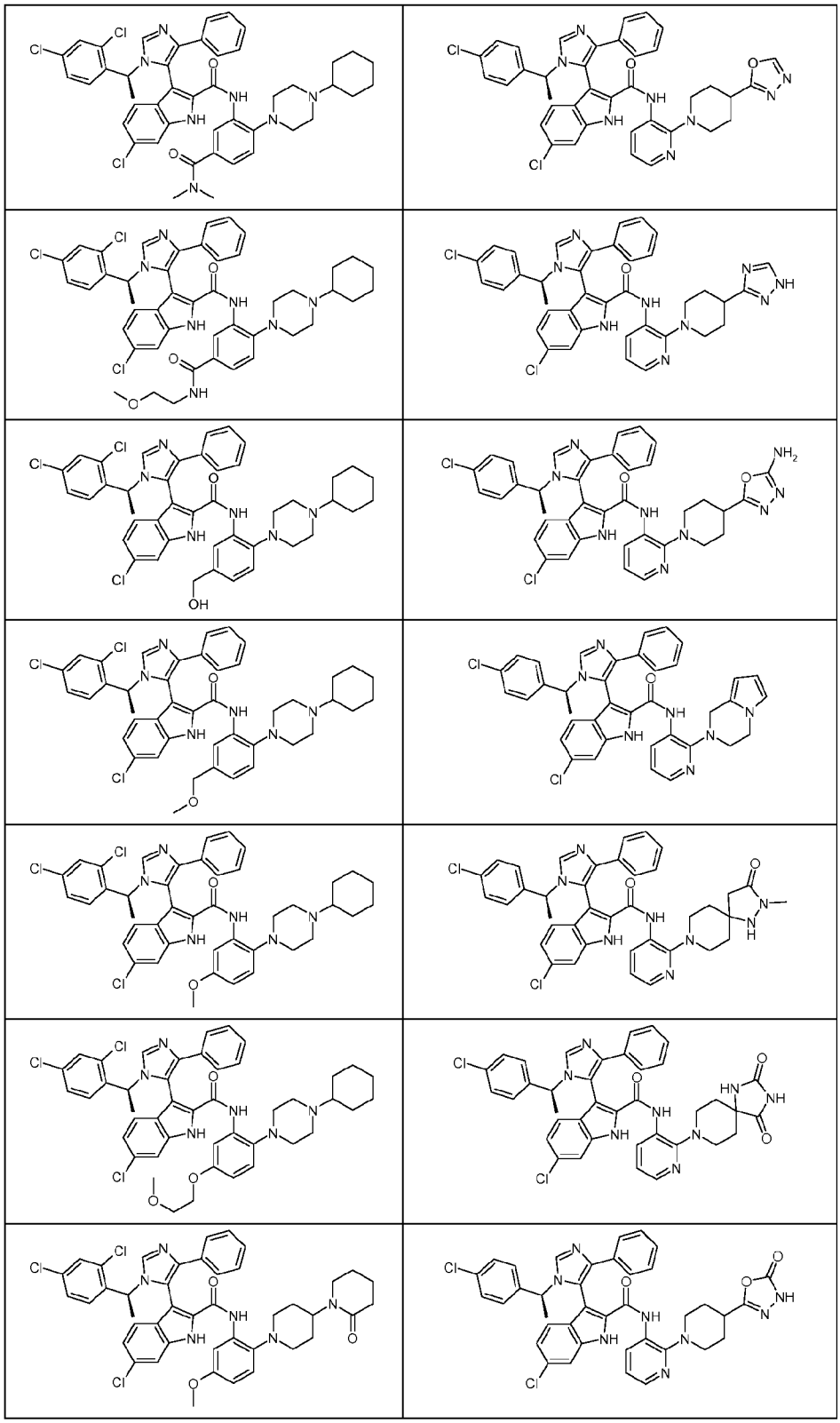


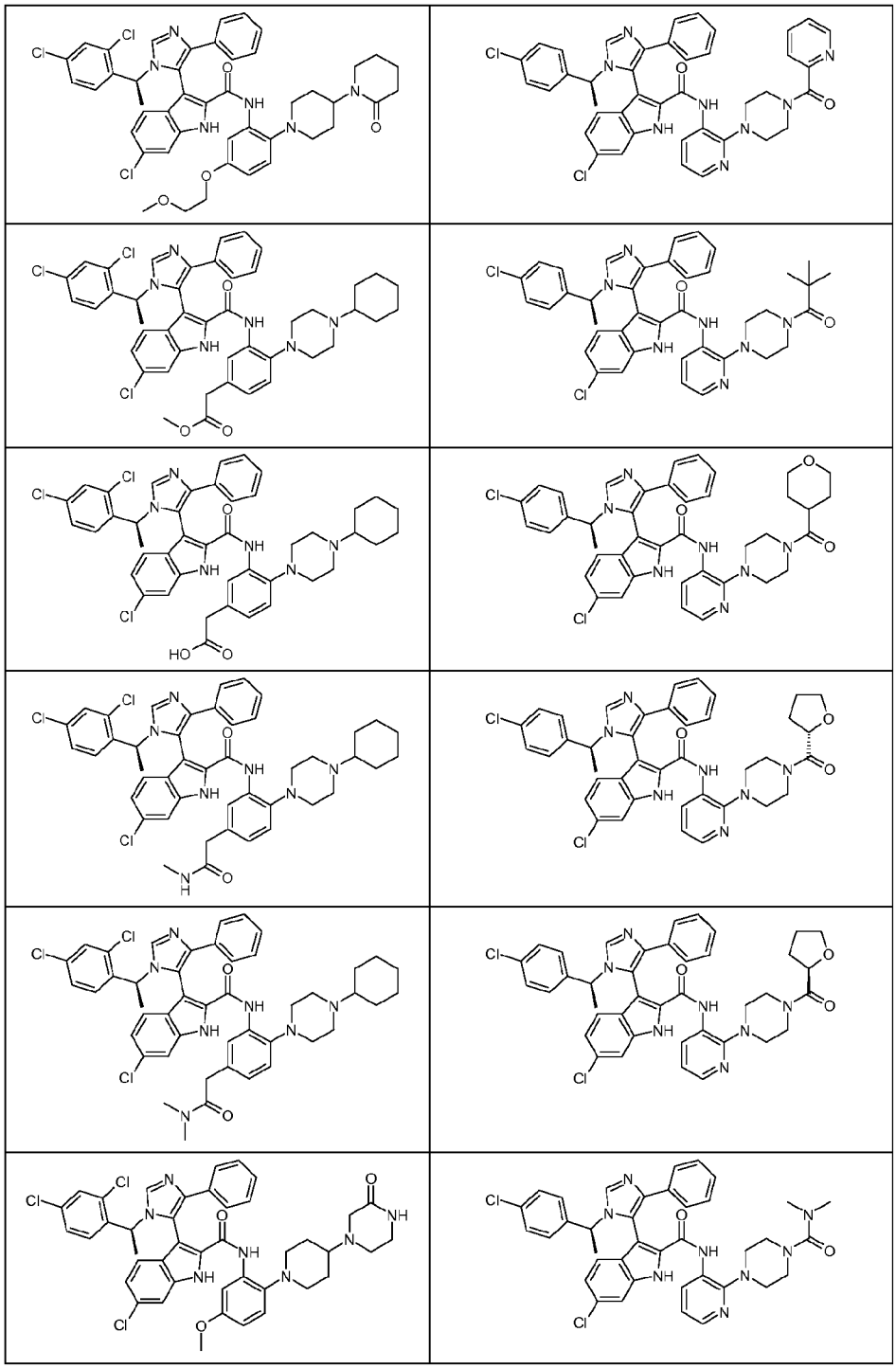


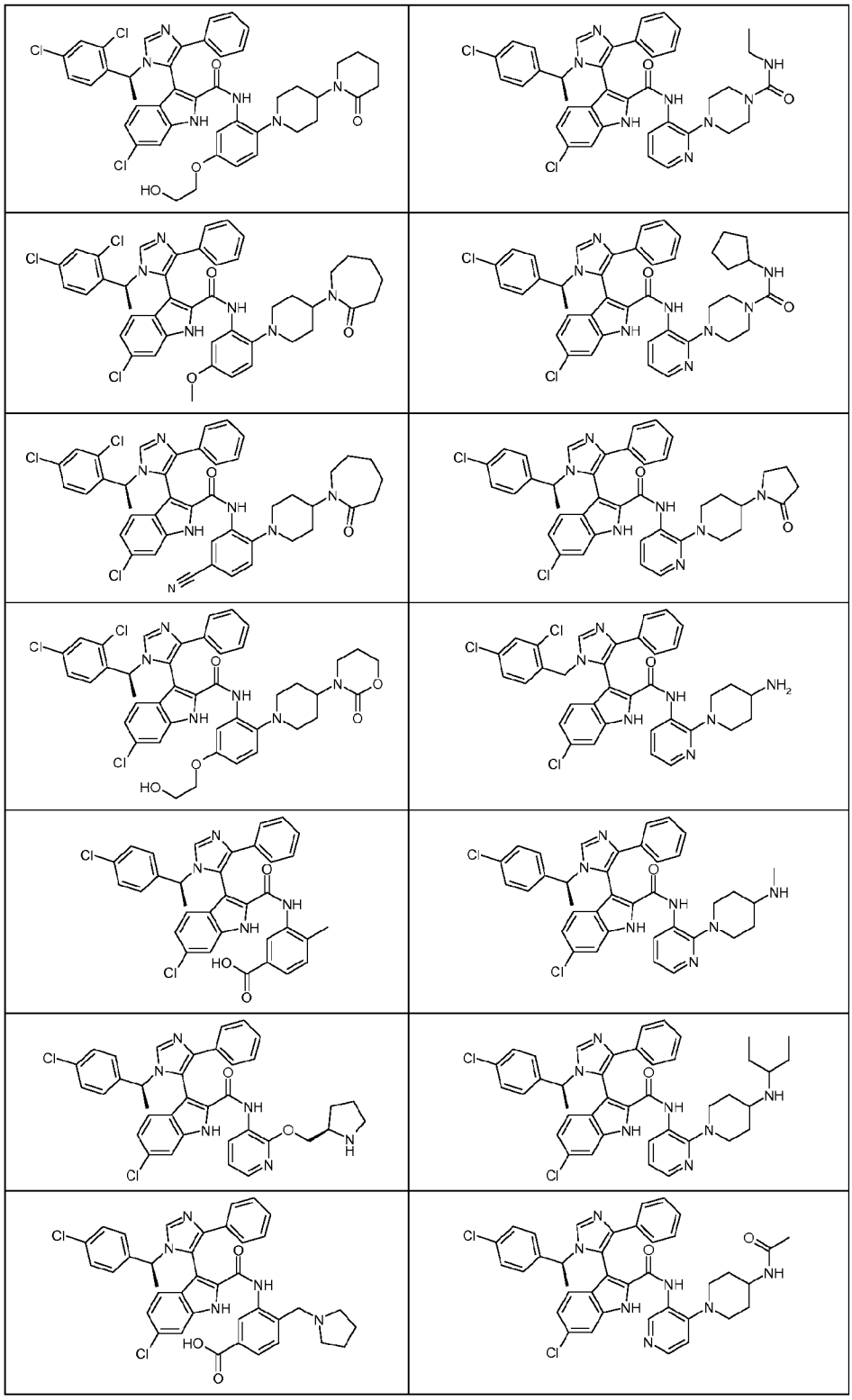


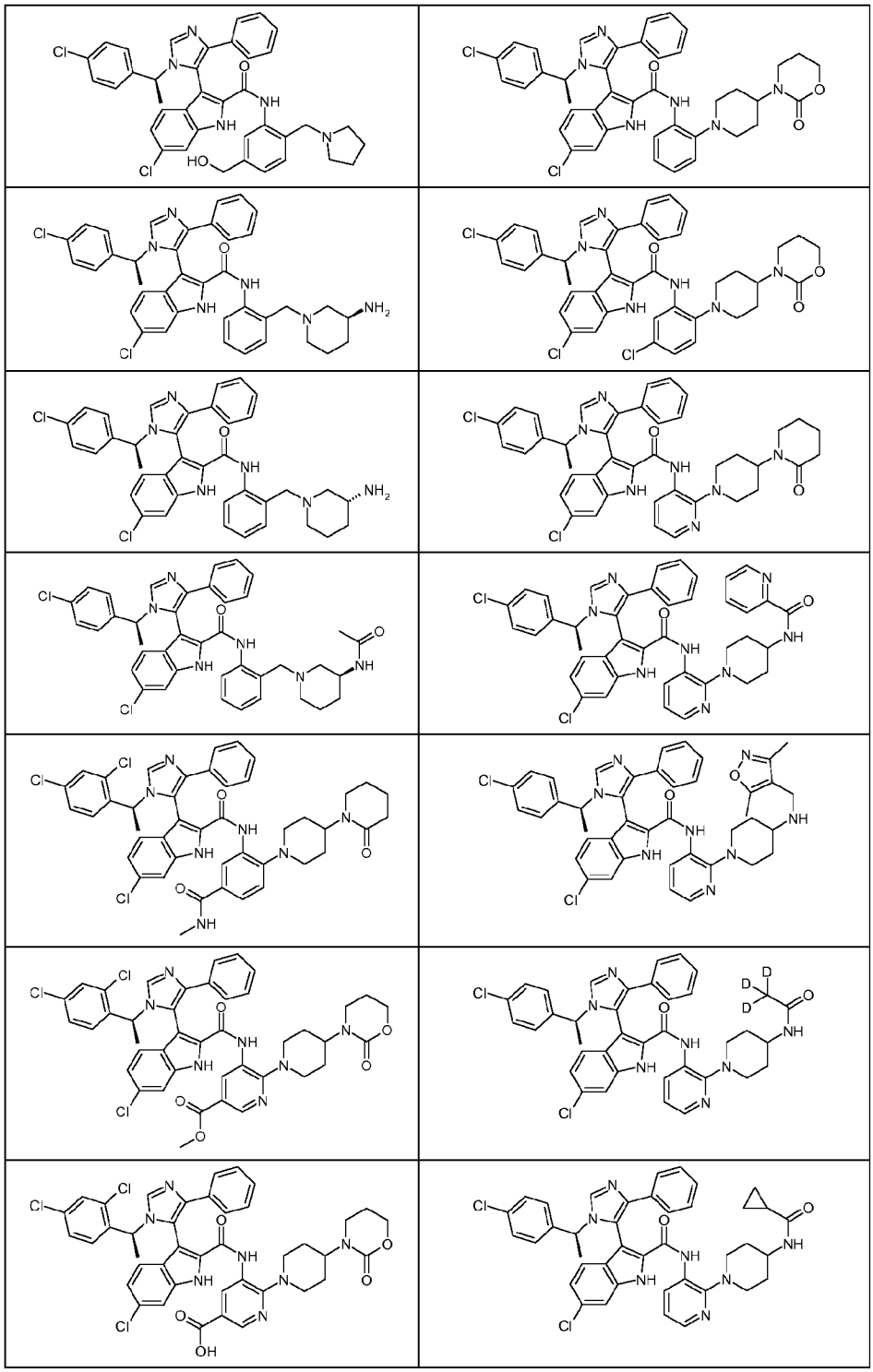


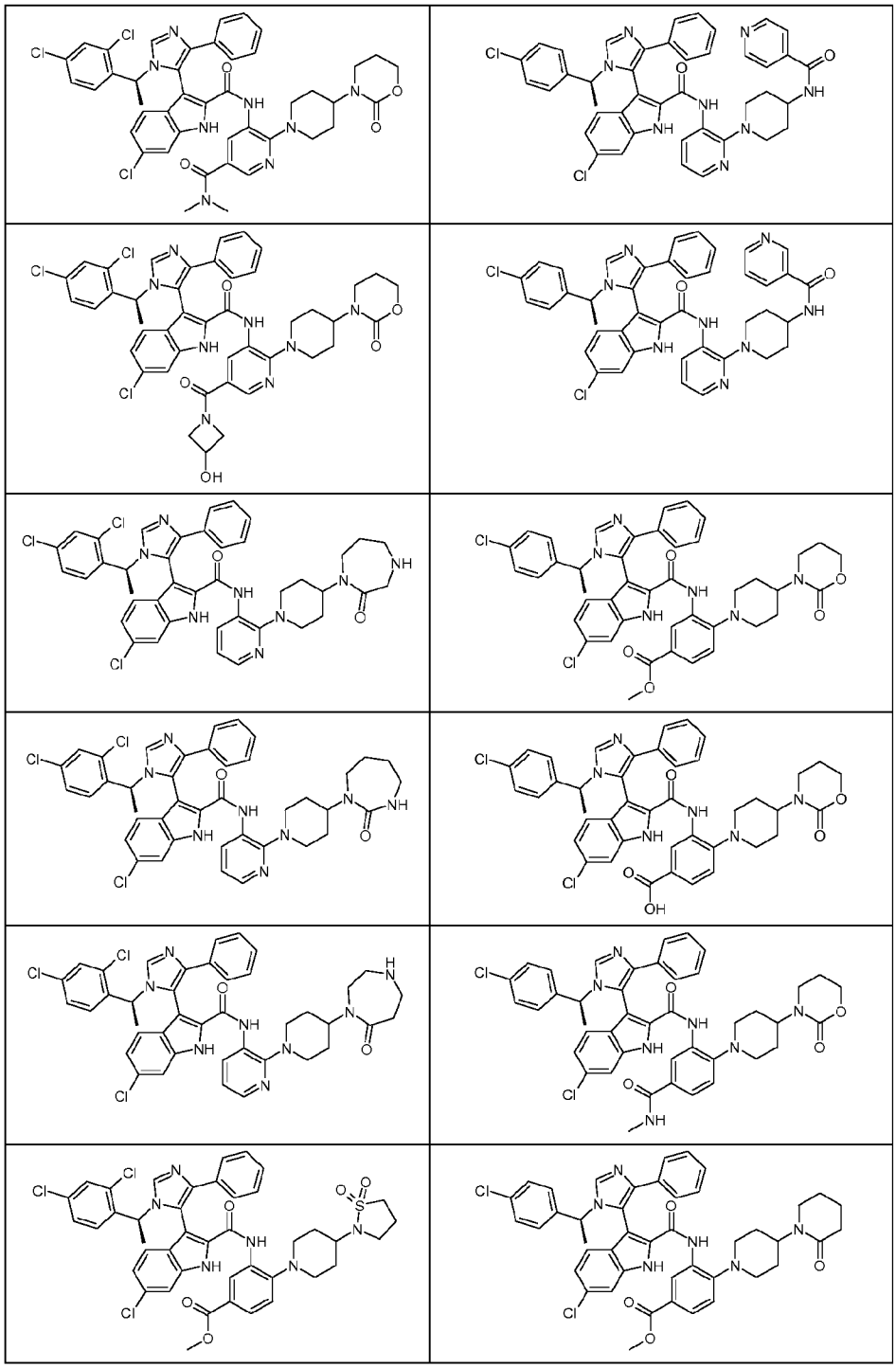


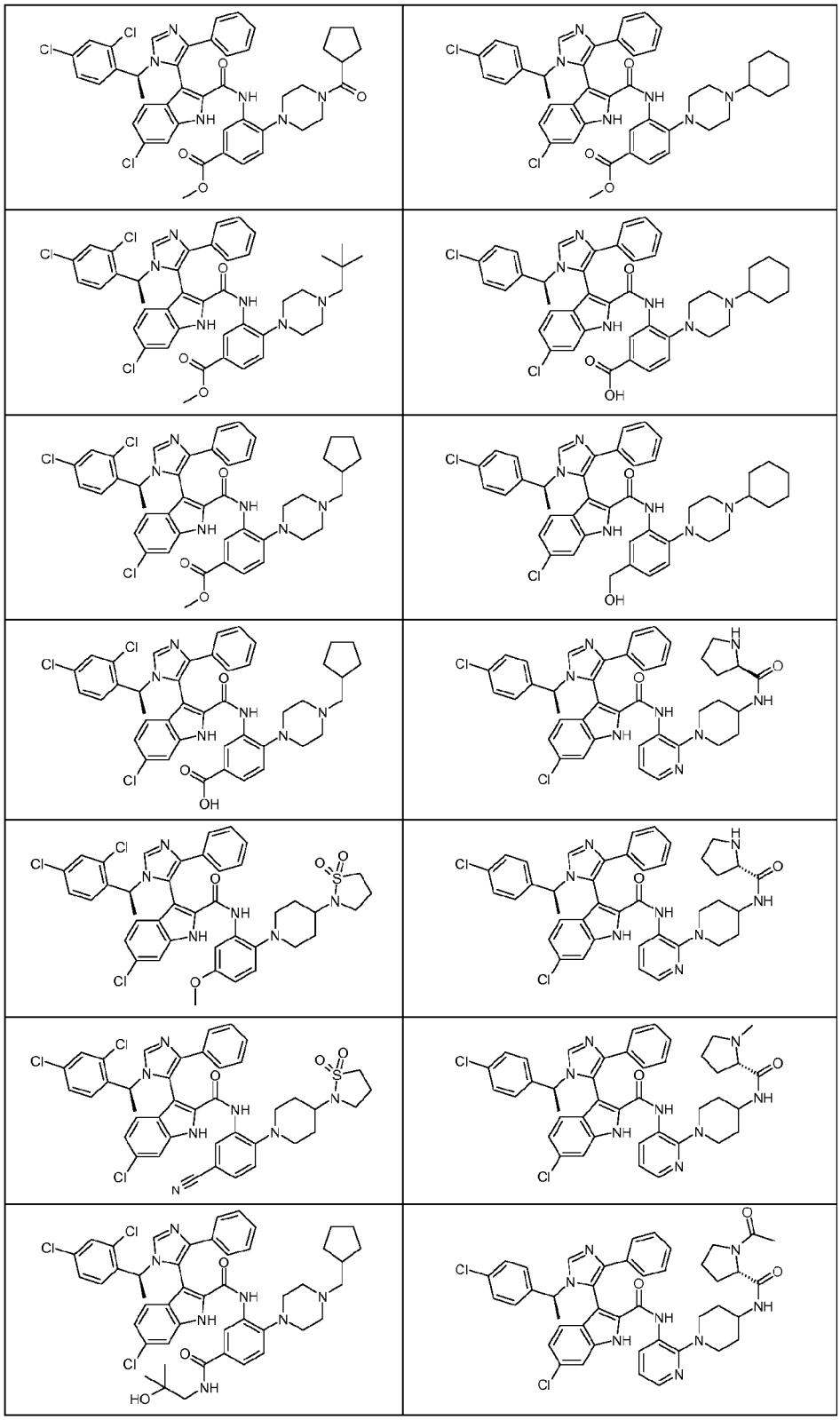


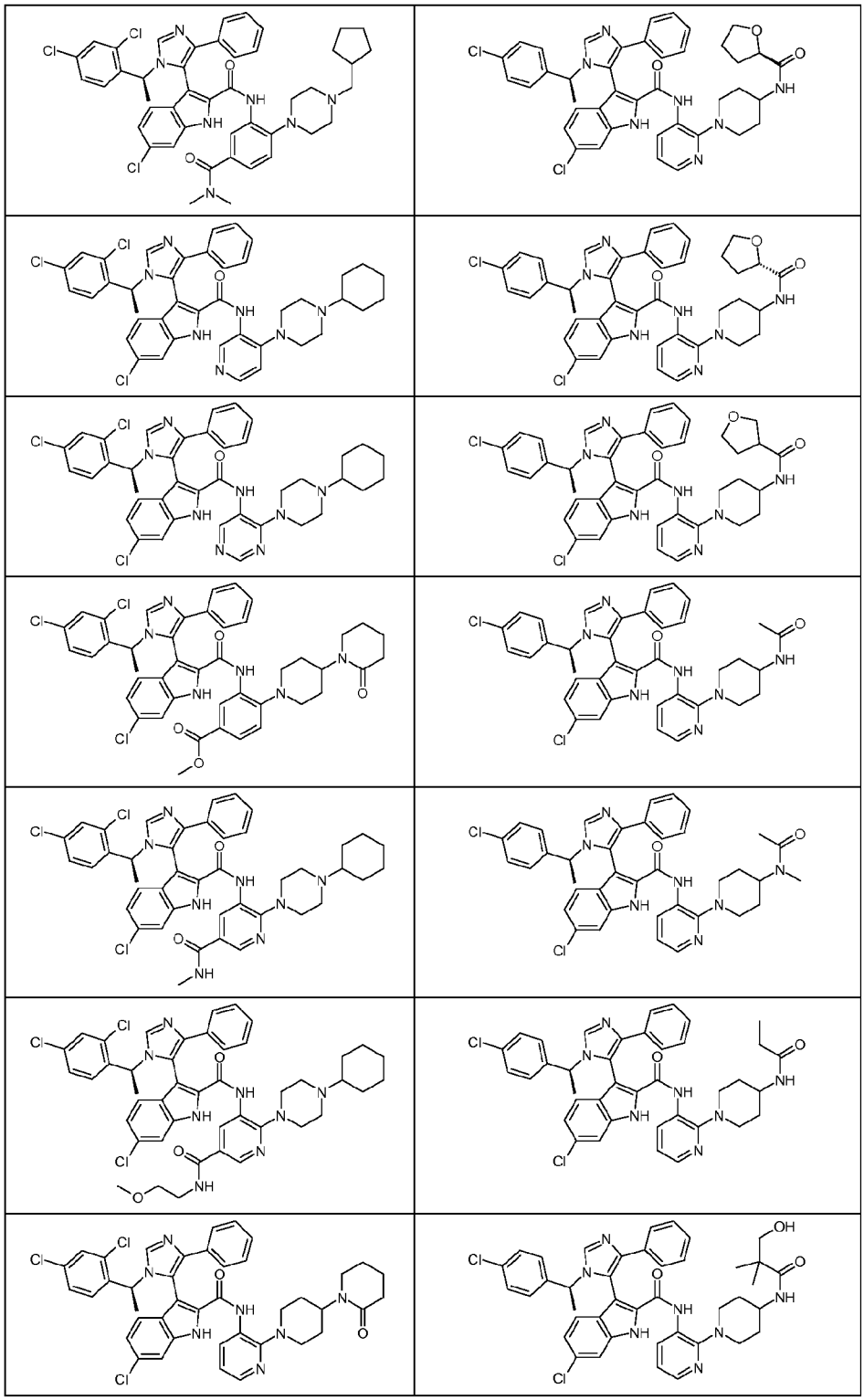


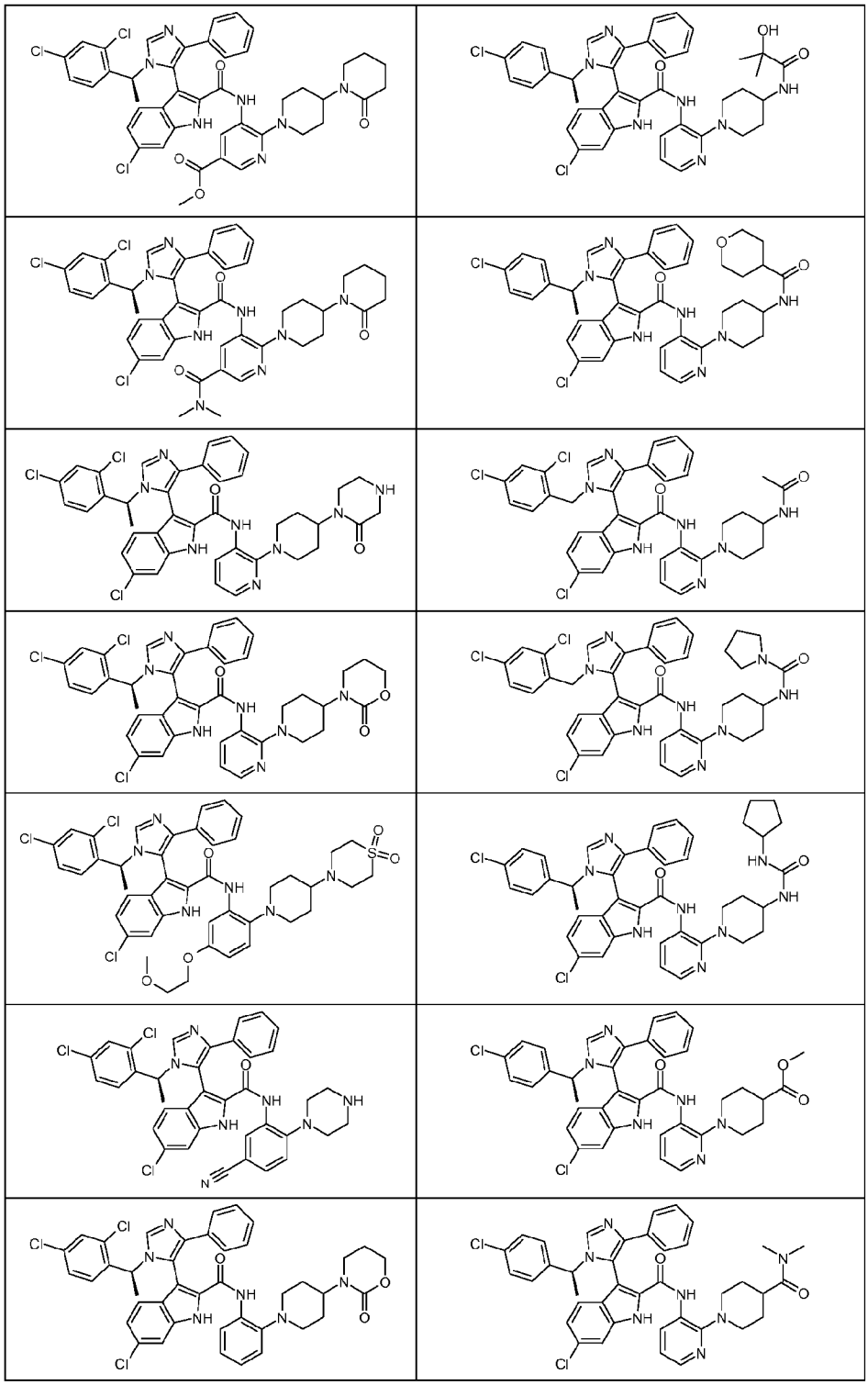


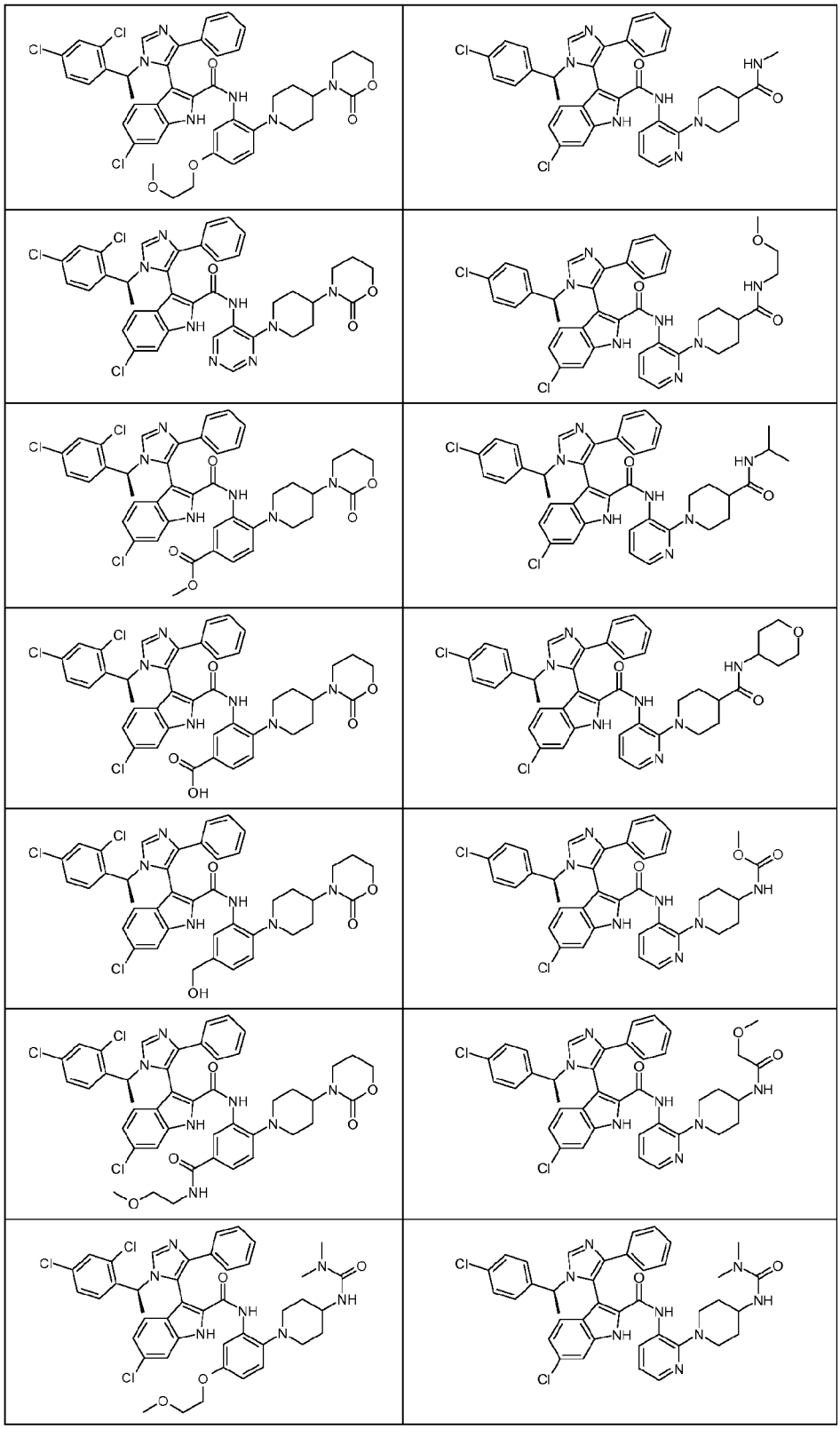


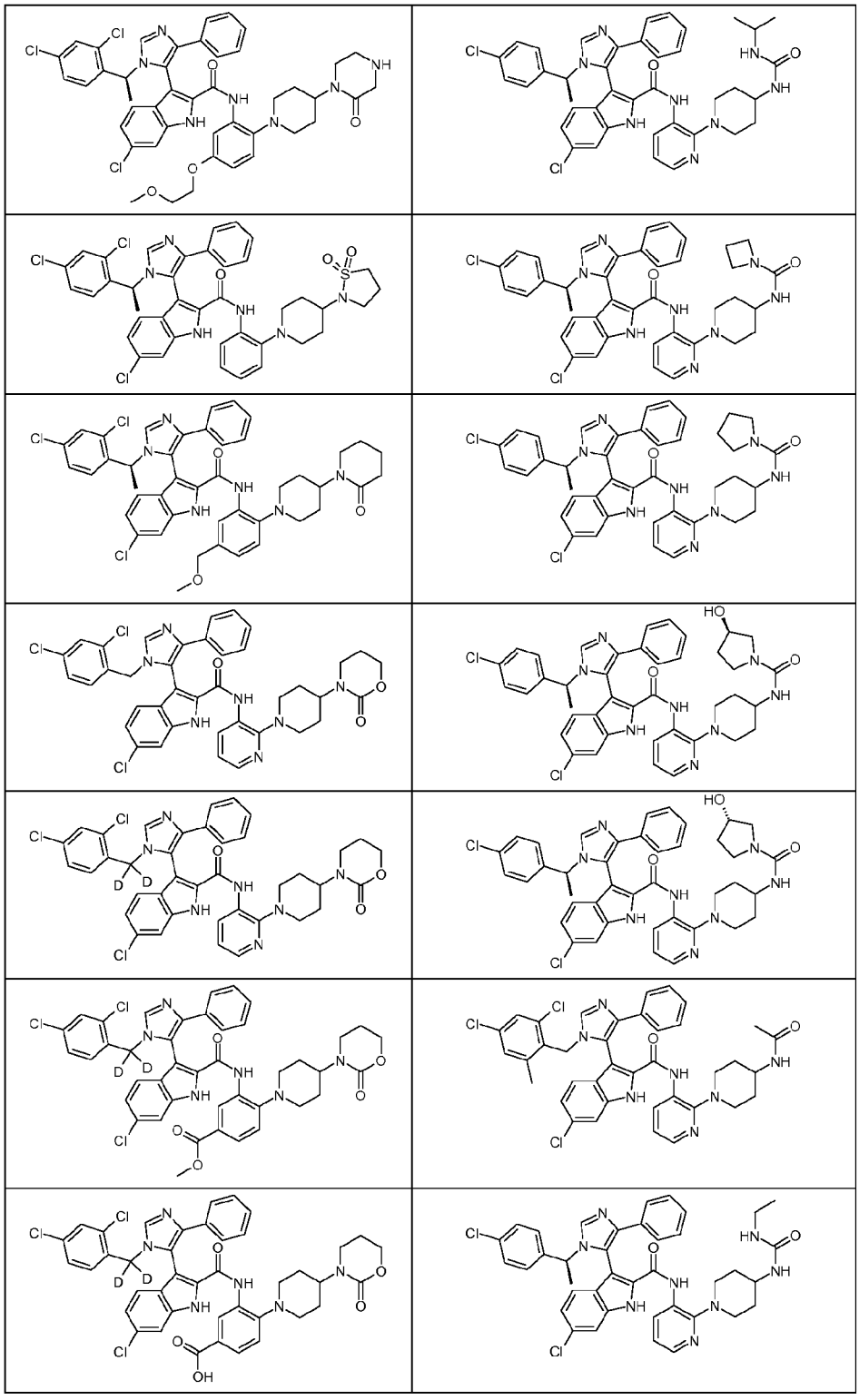


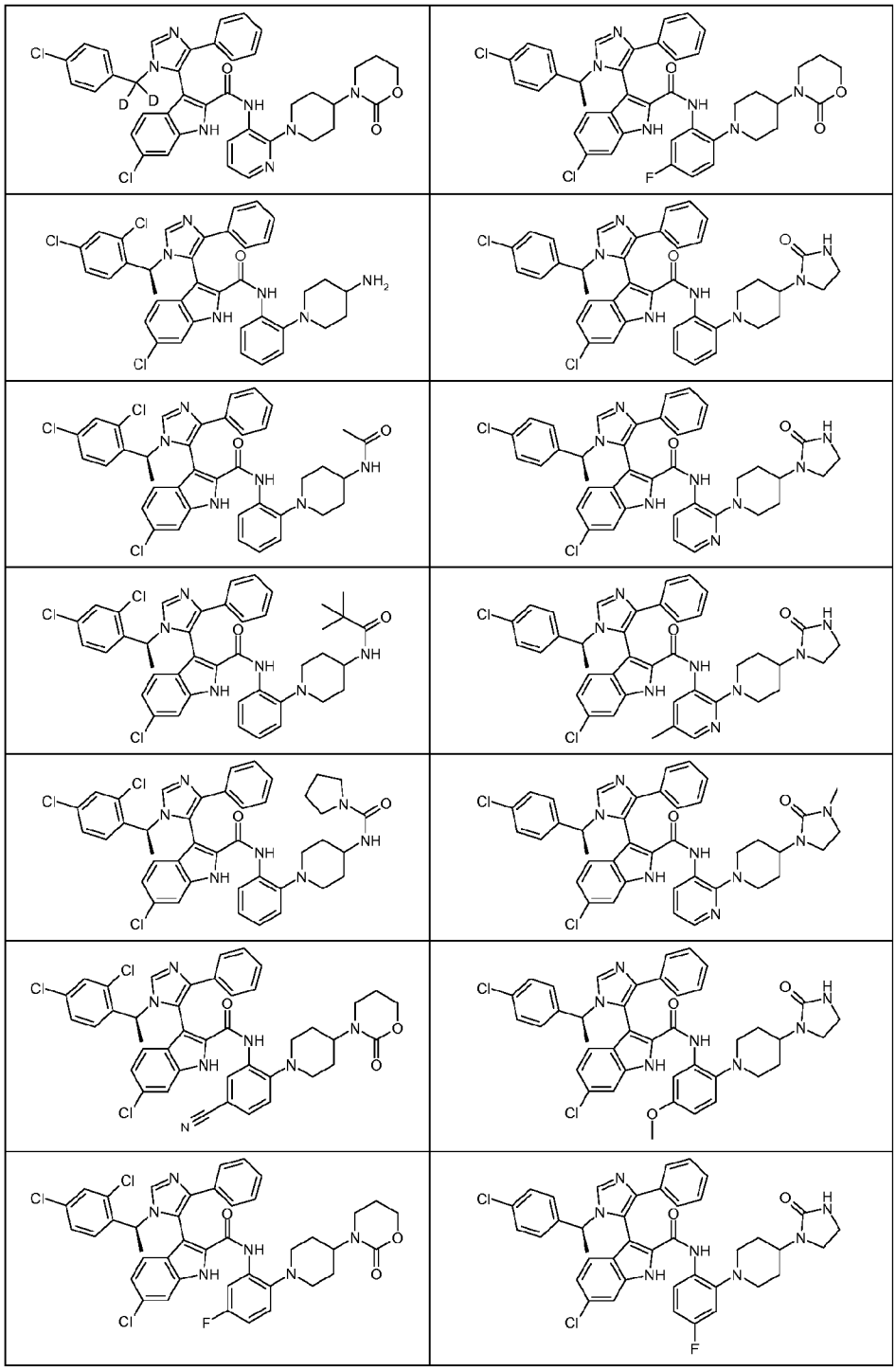


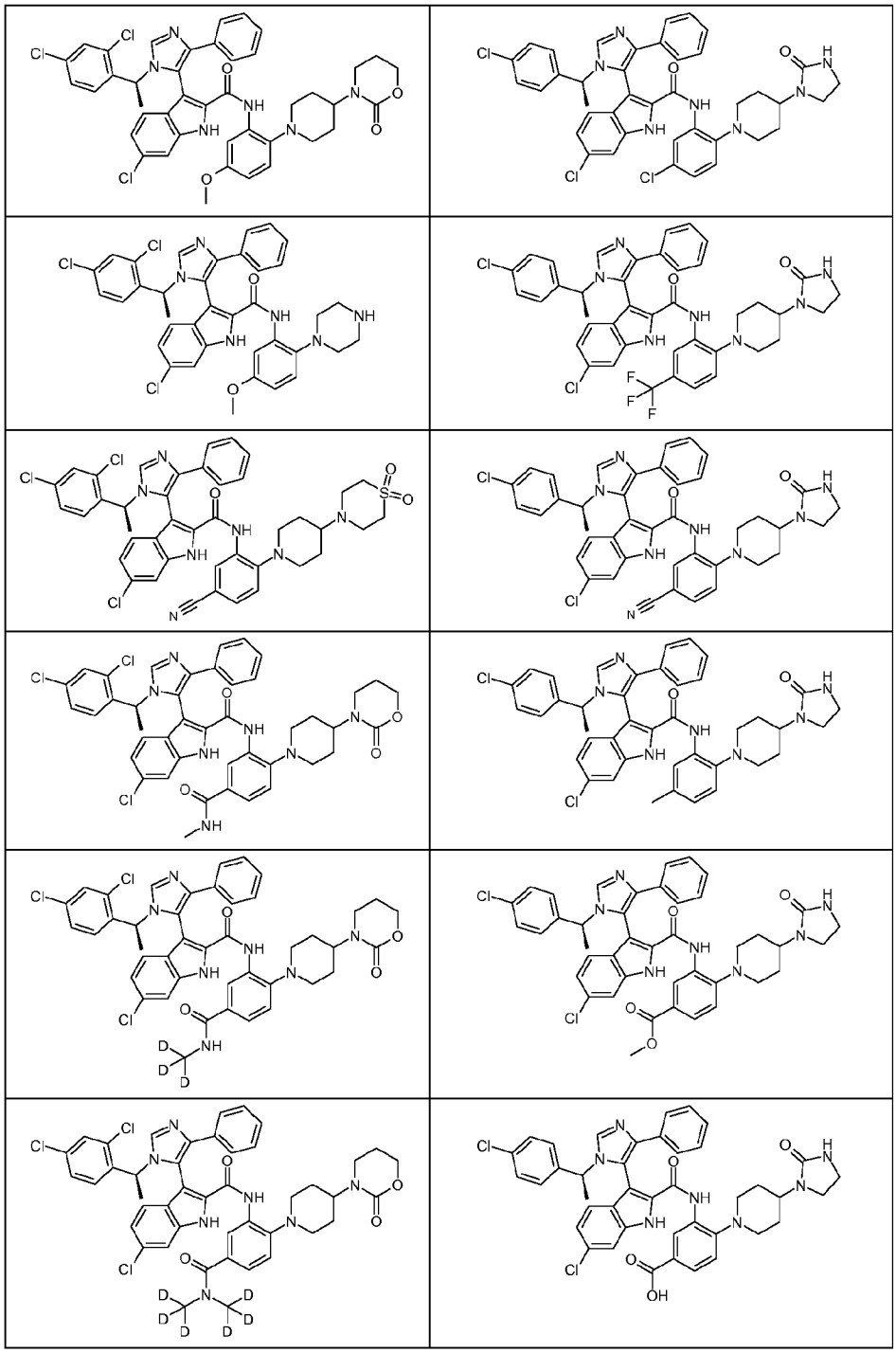


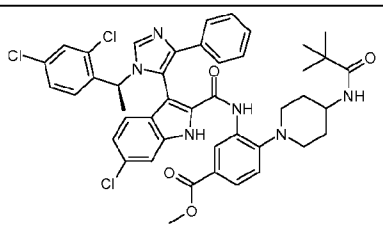
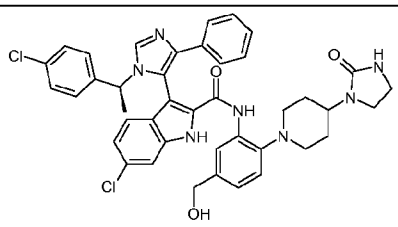
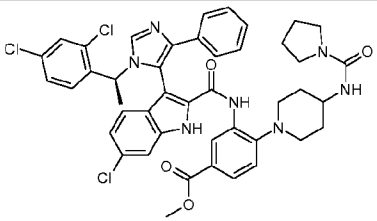
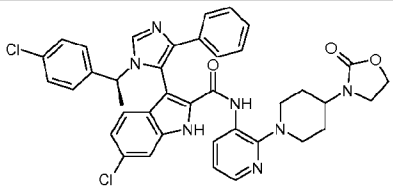
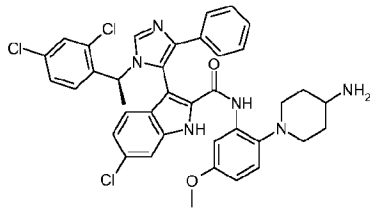
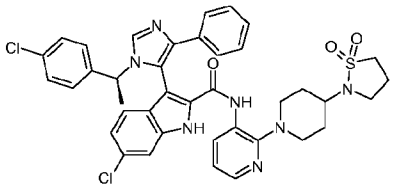
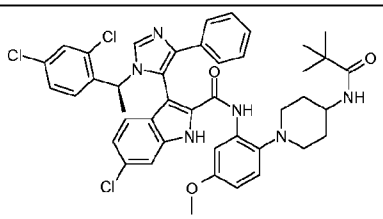
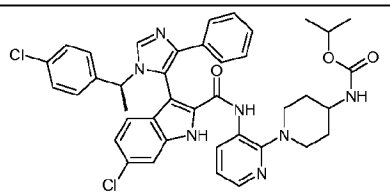
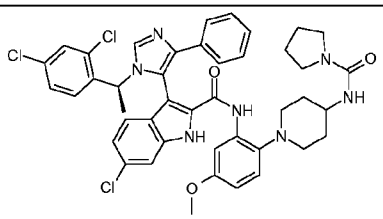
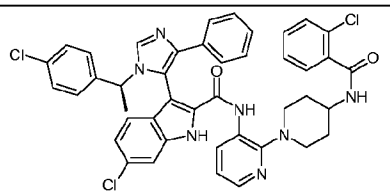
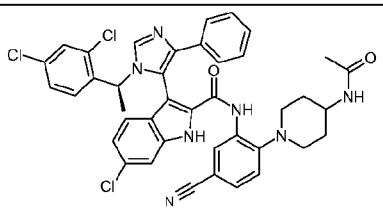
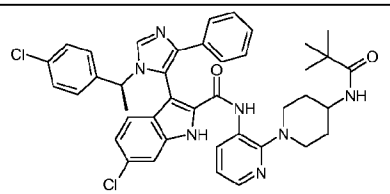
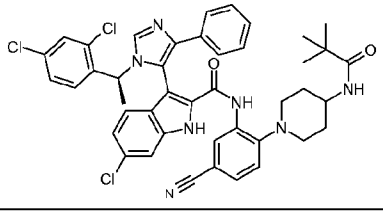
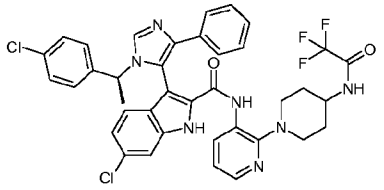


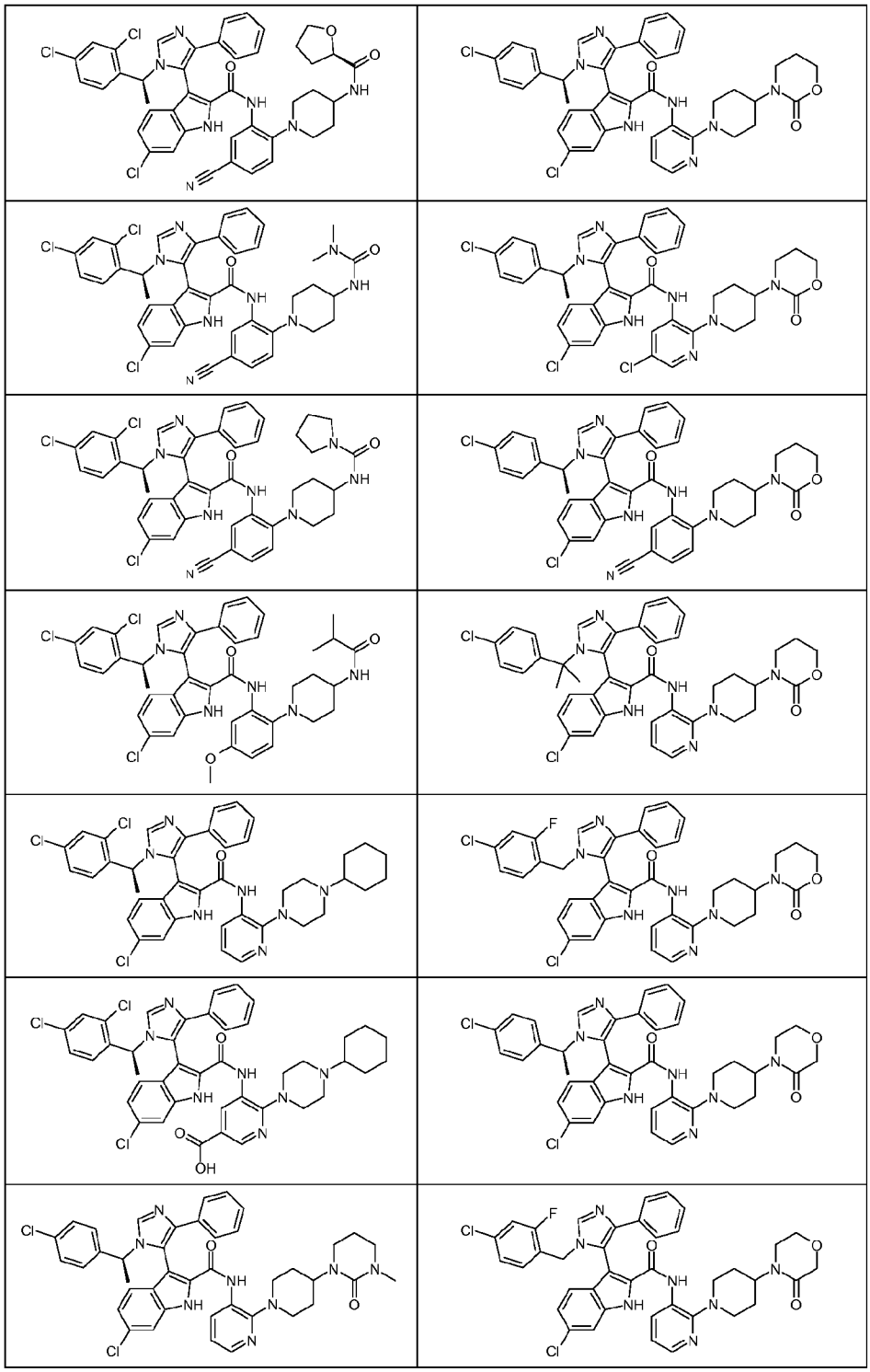


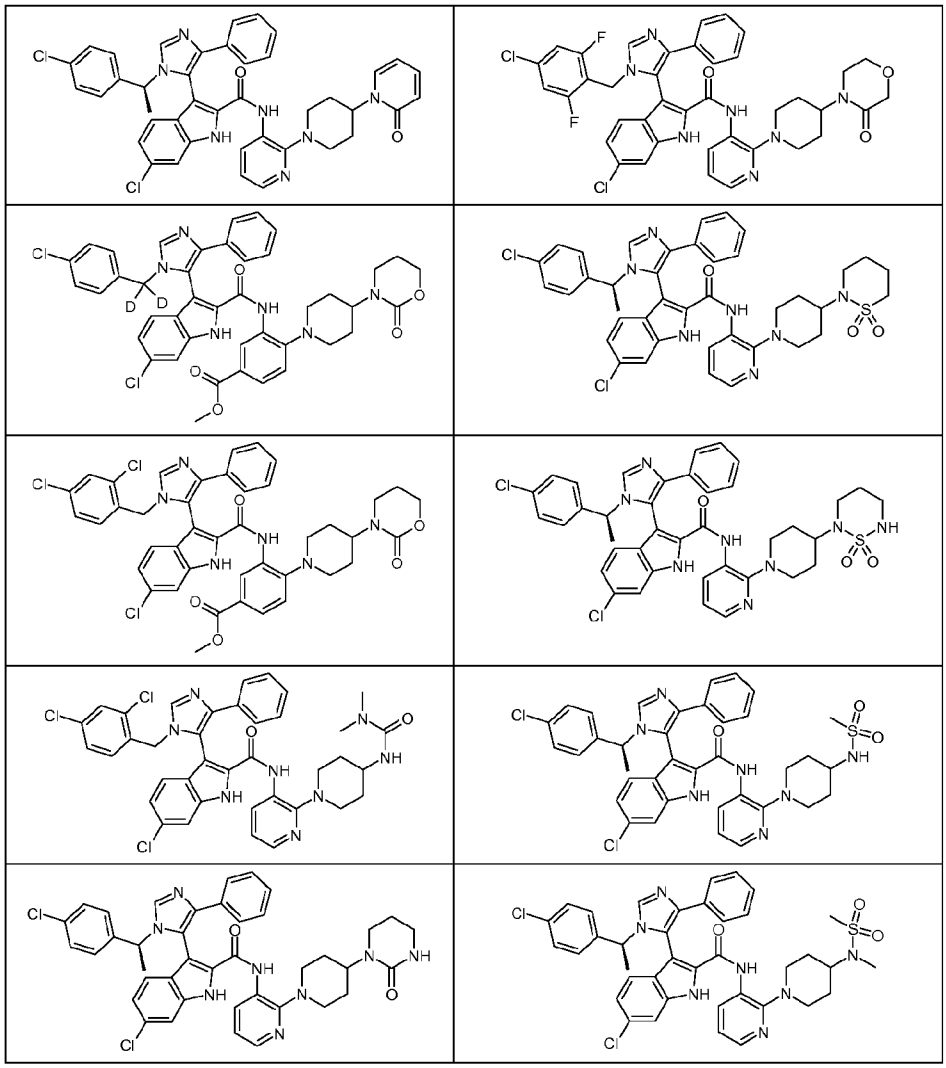




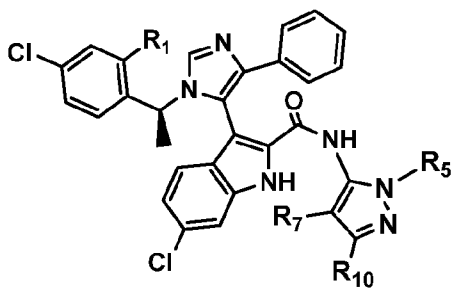






6. The compound of claim 1 of formula Ib:



Ib

in which:

R_1 is selected from hydrogen and chloro;

R_5 is selected from benzyl, pyridinyl-methyl, cyclohexyl-methyl, cyclopentyl, phenyl, piperidinyl, isobutyl and isopentyl; wherein said piperidinyl is substituted with phenyl, cyclohexyl and methyl;

R_7 is selected from hydrogen, C_{1-4}alkyl and C_{1-4}alkoxy; and

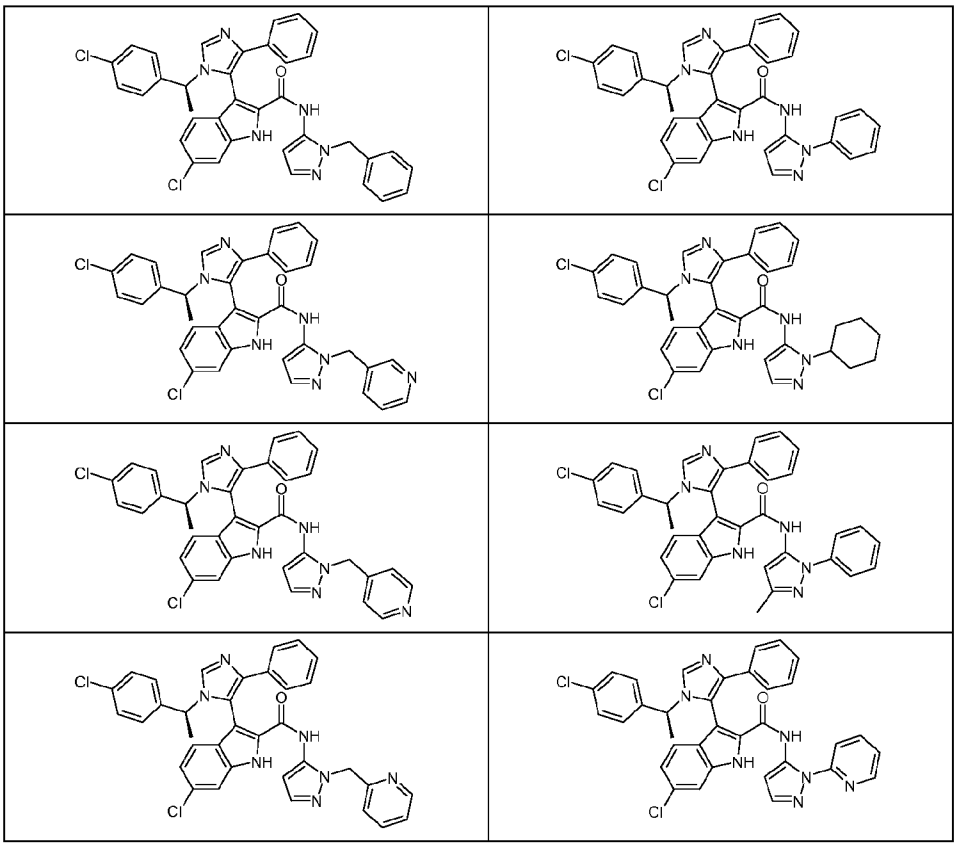
R_{10} is selected from hydrogen and C_{1-4}alkyl.

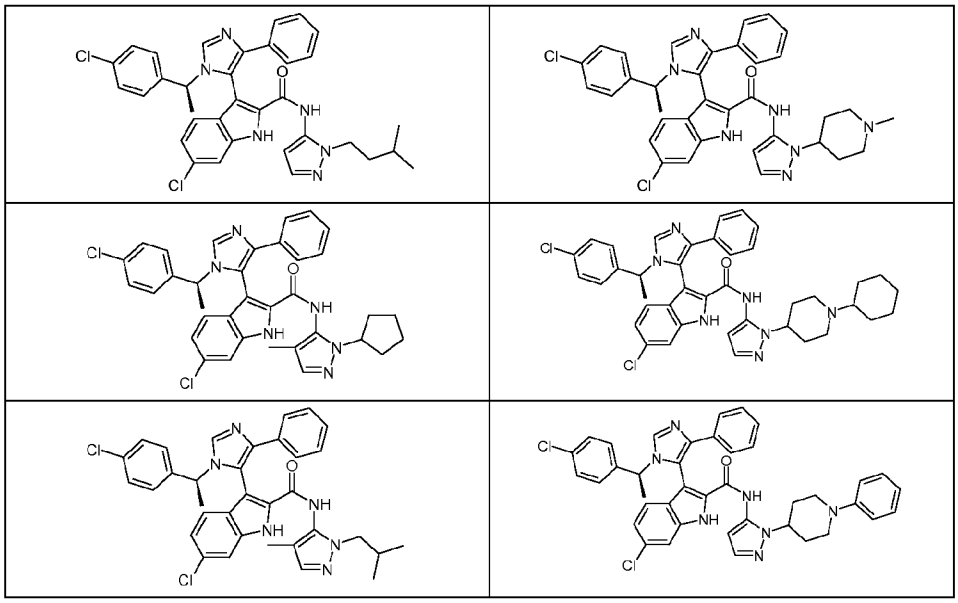
7. The compound of claim 6 in which:

R_7 is selected from hydrogen, methyl and methoxy; and

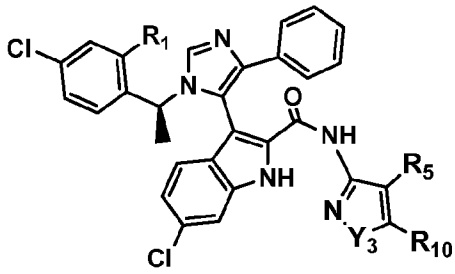
R_{10} is selected from hydrogen and methyl.

8. The compound of claim 7 selected from:





9. The compound of claim 1 of formula Ic:



Ic

in which:

R_1 is selected from hydrogen and chloro;

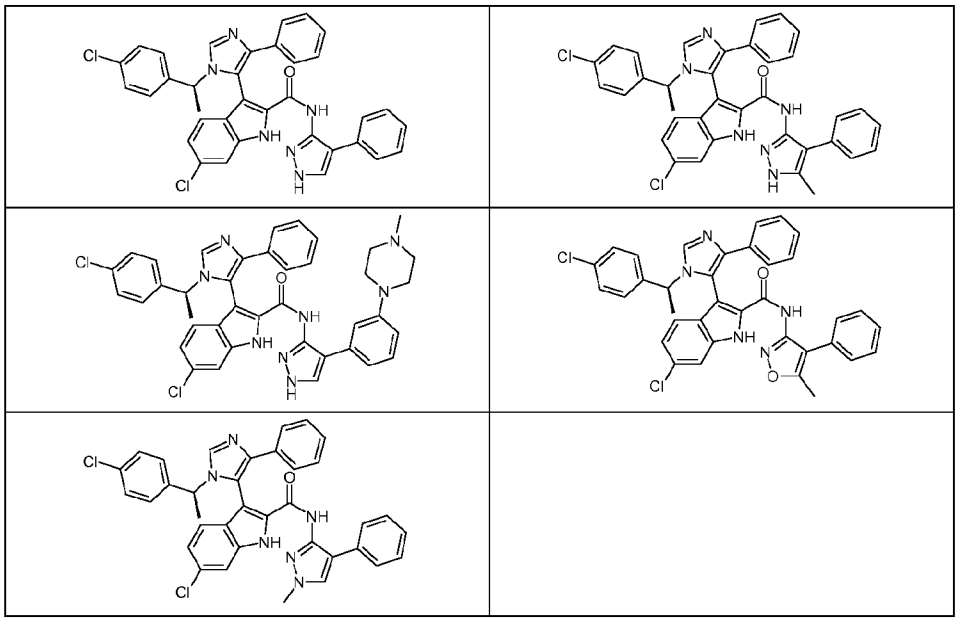
R_5 is selected from phenyl; wherein said phenyl is substituted with piperazinyl; wherein said piperazinyl substituent of R_5 is optionally further substituted with methyl;

R_{10} is selected from hydrogen and methyl;

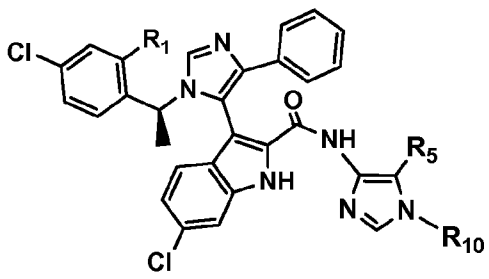
Y_3 is selected from NR_{11} and O; and

R_{11} is selected from hydrogen and methyl; or the pharmaceutically acceptable salts thereof.

10. The compound of claim 9, or the pharmaceutically acceptable salts thereof, selected from:



11. The compound of claim 1 of formula Id:



Id

in which:

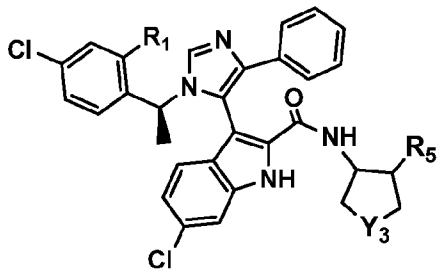
R_1 is selected from hydrogen and chloro;

R_5 is piperidinyl substituted with 2-oxoimidazolidin-1-yl; and

R_{10} is selected from hydrogen and methyl; or the pharmaceutically acceptable salts thereof.

12. The compound of claim 11 that is 6-chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid {1-methyl-5-[4-(2-oxo-imidazolidin-1-yl)-piperidin-1-yl]-1H-imidazol-4-yl}-amide, or the pharmaceutically acceptable salts thereof.

13. The compound of claim 1 of formula Ie:



Ie

in which:

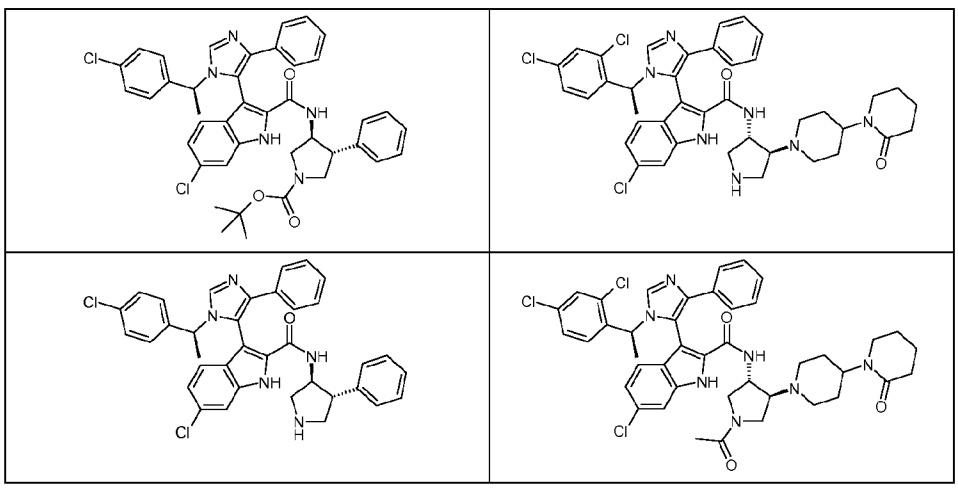
R_1 is selected from hydrogen and chloro;

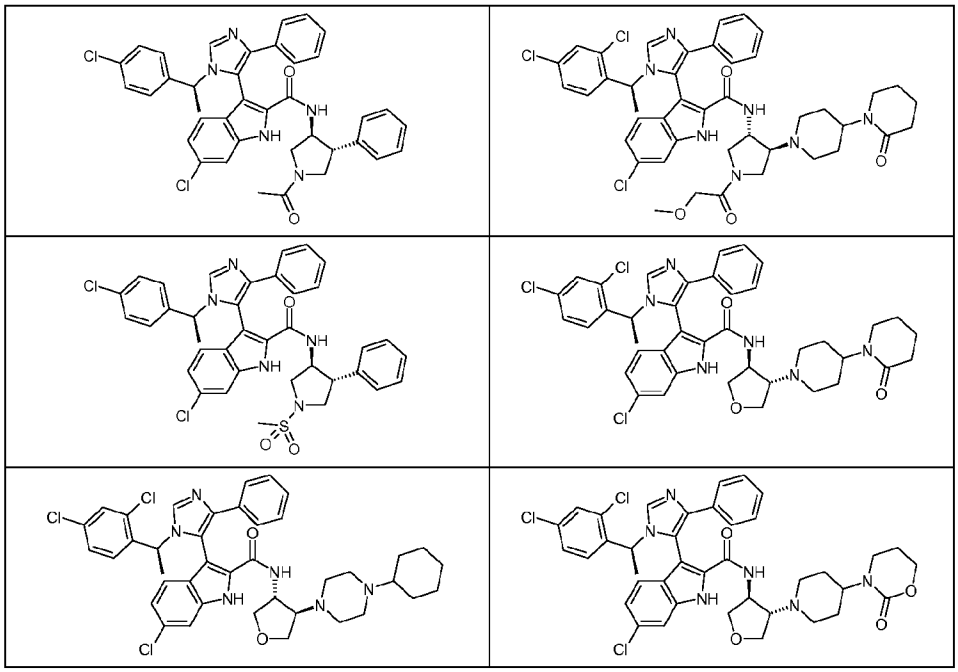
R_5 is phenyl, piperidinyl and piperazinyl; wherein said phenyl, piperidinyl or piperazinyl is optionally substituted with a group selected from cyclohexyl, 2-oxo-1,3-oxazinan-3-yl and 2-oxopiperidin-1-yl;

Y_3 is selected from O and NR_{11};

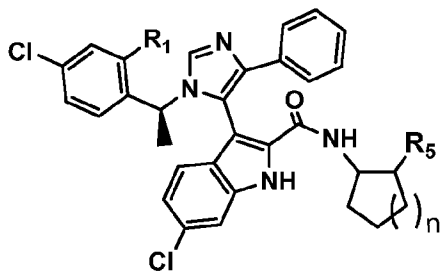
R_{11} is selected from hydrogen, C_{1-4}alkyl, $-S(O)_{0-2}R_{12}$, $-C(O)X_2OR_{12}$ and $-C(O)R_{12}$; wherein R_{12} is selected from isobutyl and methyl; and X_2 is methylene; or the pharmaceutically acceptable salts thereof.

14. The compound of claim 13, or the pharmaceutically acceptable salts thereof, selected from:





15. The compound of claim 2 of formula Ig:



Ig

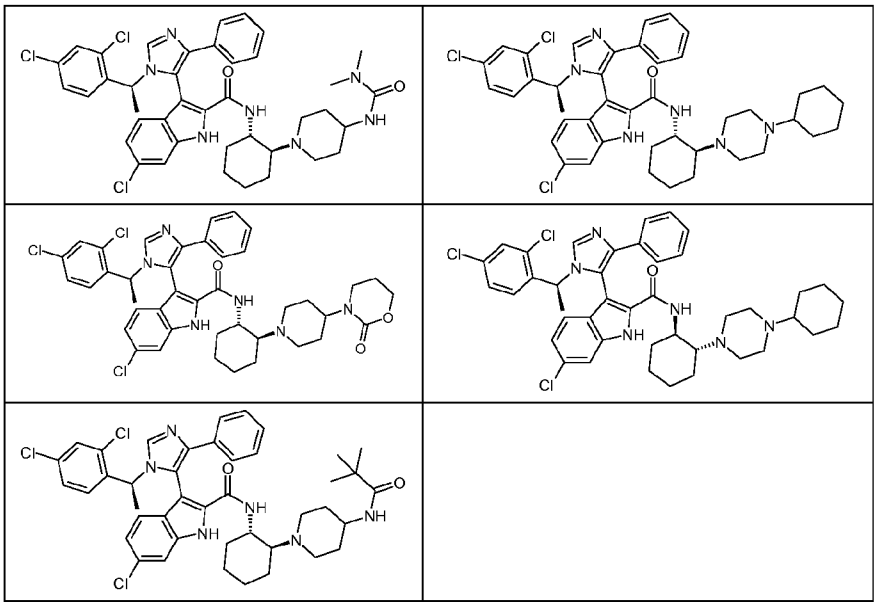
in which:

n is selected from 1 and 2;

R_1 is selected from hydrogen and chloro; and

R_5 is benzoxy, piperidinyl and piperazinyl; wherein said benzoxy, piperidinyl or piperazinyl is optionally substituted with a group selected from methoxy, cyclohexyl, 2-oxo-1,3-oxazinan-3-yl, 2-oxopiperidin-1-yl, -NHC(O)OR_{14}, -NHC(O)R_{14} and -NHC(O)$NR_{13}R_{14}$; wherein R_{13} is methyl and R_{14} at each occurrence is independently selected from methyl and t-butyl; or the pharmaceutically acceptable salts thereof.

16. The compound of claim 15, or the pharmaceutically acceptable salts thereof, selected from:



17. A pharmaceutical composition comprising a compound of claim 1 or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

18. A pharmaceutical composition according to claim 17 for use in the treatment of a disorder or disease which is mediated by the activity of MDM2 and/or MDM4, or variants thereof.

19. A method of treatment comprising administering a compound of claim 1, or a pharmaceutically acceptable salt thereof, to a person in need of such treatment in an effective amount for the prophylactic and/or therapeutic treatment of a disease or disorder which is mediated by the activity of MDM2 and/or MDM4, or variants thereof.

20. The method of claim 19, wherein the disease or disorder is selected from soft tissue sarcomas, bone cancer, breast tumors, bladder cancer, Li-Fraumeni syndrome, brain tumor, rhabdomyosarcoma and adrenocortical carcinoma.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/053095

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 C07D403/04 C07D403/14 C07D405/14 C07D413/14
C07D417/14 C07D471/04 C07D471/10 A61K31/4178 A61P35/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/119741 A2 (NOVARTIS AG [CH]; BOETTCHER ANDREAS [CH]; BUSCHMANN NICOLE [CH]; FURET) 9 October 2008 (2008-10-09) claims; examples 47, 49, 50; table 5 -----	1-20

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 September 2012	12/09/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Gavriliu, Daniela

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2012/053095

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		CR 11019 A	20-10-2009
		DO P2009000229 A	31-10-2009
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		EC SP099660 A	30-10-2009
		EP 2142535 A2	13-01-2010
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		SM AP200900085 A	19-01-2010
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		UY 30987 A1	31-10-2008
		WO 2008119741 A2	09-10-2008
		ZA 200906210 A	26-05-2010