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(71) Applicant: **JANSSEN R&D IRELAND** [IE/IE]; Eastgate Village, Eastgate, Little Island, Co Cork (IE).

(72) Inventors: **TAHRI, Abdellah**; Rue Maurice Albert Raskin 30, B-1070 Anderlecht (BE). **VENDEVILLE, Sandrine Marie Helene**; Rue du Bémel 142, B-1150 Woluwe-Saint-Pierre (BE). **JONCKERS, Tim Hugo Maria**; Bollostraat 2a, B-2220 Heist-op-den-Berg (BE). **RABOISSON, Pierre Jean-Marie Bernard**; Rue Jolie 3, B-1331 Rosieres (BE). **HU, Lili**; Augustijnenstraat 11 bus 101, B-2800 Mechelen (BE). **DEMIN, Samuël Dominique**; Professor Claraplein 14 Bus 308, B-2018 Antwerpen (BE). **COOYMANS, Ludwig Paul**; Grote Beekstraat 24, B-2340 Beerse (BE).

(74) Agent: **VERBERCKMOES, Filip**; Turnhoutseweg 30, B-2340 Beerse (BE).

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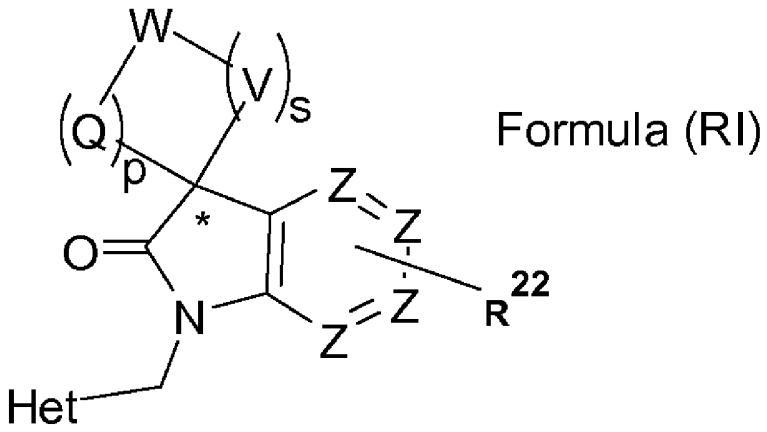
(54) Title: RSV ANTIVIRAL COMPOUNDS



Formula (RI)

(57) Abstract: Inhibitors of RSV replication of formula RI including stereochemically isomeric forms, and salts or solvates thereof, wherein R^{22}, W, Q, V, Z p,s,and Het have the meaning as defined herein. The present invention also relates to processes for preparing said compounds, pharmaceutical compositions containing them and their use, alone or in combination with other RSV inhibitors, in RSV therapy.

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RSV ANTIVIRAL COMPOUNDS

Field of the Invention

The invention concerns novel spiro compounds having antiviral activity, in particular, having an inhibitory activity on the replication of the respiratory syncytial virus (RSV). The invention further concerns the preparation of such novel compounds, compositions comprising these compounds, and the compounds for use in the treatment of respiratory syncytial virus infection.

Background

Human RSV or Respiratory Syncytial Virus is a large RNA virus, member of the family of Paramyxoviridae, subfamily pneumoviridae together with Bovine Respiratory Syncytial Virus. Human RSV is responsible for a spectrum of respiratory tract diseases in people of all ages throughout the world. It is the major cause of lower respiratory tract illness during infancy and childhood. Over half of all infants encounter RSV in their first year of life, and almost all within their first two years. The infection in young children can cause lung damage that persists for years and may contribute to chronic lung disease in later life (chronic wheezing, asthma). Older children and adults often suffer from a (bad) common cold upon RSV infection. In old age, susceptibility again increases, and RSV has been implicated in a number of outbreaks of pneumonia in the aged resulting in significant mortality.

Infection with a virus from a given subgroup does not protect against a subsequent infection with an RSV isolate from the same subgroup in the following winter season. Re-infection with RSV is thus common, despite the existence of only two subtypes, A and B.

Today only three drugs have been approved for use against RSV infection. A first one is ribavirin, a nucleoside analogue that provides an aerosol treatment for serious RSV infection in hospitalized children. The aerosol route of administration, the toxicity (risk of teratogenicity), the cost and the highly variable efficacy limit its use. The other two drugs, RespiGam® (RSV-IG) and Synagis® (palivizumab), polyclonal and monoclonal antibody immunostimulants, are intended to be used in a preventive way. Both are very expensive, and require parenteral administration.

Other attempts to develop a safe and effective RSV vaccine have all met with failure thus far. Inactivated vaccines failed to protect against disease, and in fact in some cases enhanced disease during subsequent infection. Life attenuated vaccines have been tried with limited success. Clearly there is a need for an efficacious non-toxic and easy to

administer drug against RSV replication. It would be particularly preferred to provide drugs against RSV replication that could be administered perorally.

A reference on structure-activity relations, in respect of RSV inhibition, of 5-substituted benzimidazole compounds is X.A. Wang et al., Bioorganic and Medicinal Chemistry Letters 17 (2007) 4592-4598.

Compounds that exhibit anti-RSV activity are disclosed in WO2012/080446, WO2012/080447, WO2012/080449, WO2012/080450 and WO2012/080451.

WO-2004/069256 discloses 2-cyanopyrrolopyrimidines and WO-2004/076455 discloses spiro-substituted 2-cyanopyrrolopyrimidines as capthepsin K or S inhibitors useful in the treatment of various pain disorders. Teno N. et al. in *Bioorganic & Medicinal* Chemistry *Letters*, vol. 17, 6096 - 6100 (2007) and Teno N. et al. in *J. Med. Chem.*, vol. 51, 5459 - 5462 (2008) disclose 2-cyanopyrrolopyrimidines as cathepsin K inhibitors.

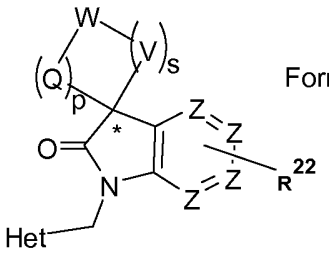
Potential problems which RSV antivirals may encounter are toxicity, mutagenicity, lack of selectivity, poor efficacy, poor bioavailability, and difficulty of synthesis.

It is desired to provide new compounds that have antiviral activity. Particularly, it would be desired to provide new drugs that have RSV replication inhibitory activity. Further, it would be desired to retrieve compound structures that allow obtaining antiviral biological activities of the order of magnitude in the stronger regions of the prior art, and preferably at a level of about the most active, more preferably of even stronger activity, than compounds disclosed in the art. A further desire is to find compounds having oral antiviral activity.

There is a need for additional RSV inhibitors that may overcome at least one of these disadvantages or having one of the desired effects.

Summary of the Invention

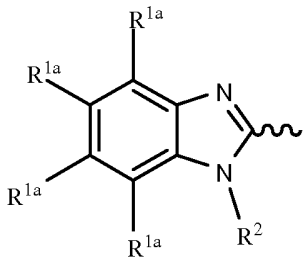
In order to better address one or more of the foregoing desires, the invention, in one aspect, presents antiviral compounds represented by Formula (RI),



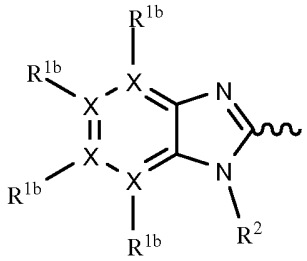
Formula (RI)

or any stereoisomeric form thereof, wherein:

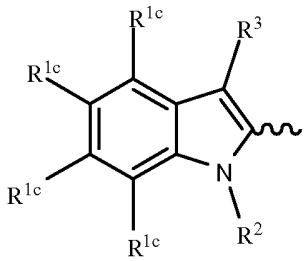
Het is a heterocycle of either of the following formula (a), (b), (c), (d):



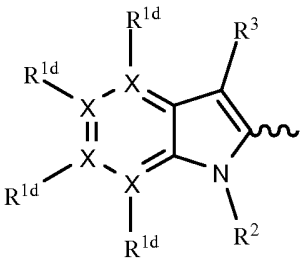
(a)



(b)



(c)



(d)

each X independently is C or N; provided that at least two X is C;

each of R^{1a}, R^{1b}, R^{1c} or R^{1d} is independently selected from the group consisting of H, halogen, C_1-C_6alkyl, C_3-C_7cycloalkyl, C_1-C_6alkyloxy, $N(R^6)_2$, $CO(R^7)$, CH_2NH_2, CH_2OH, CN, $C(=NOH)NH_2$, $C(=NOCH_3)NH_2$, $C(=NH)NH_2$, CF_3 and OCF_3;

R^{1b} or R^{1d} is absent when the X to which it is bound is N;

each R^2 is $-(CR^8R^9)_m-R^{10}$;

m is an integer from 0 to 6;

each R^3 is independently selected from the group consisting of H, halogen, aryl, heteroaryl, C_1-C_6alkyl, C_3-C_7cycloalkyl, C_1-C_6alkyloxy and $CO(R^7)$;

each R^6 is independently selected from the group consisting of H, C_1-C_6alkyl, $COOCH_3$ and $CONHSO_2CH_3$;

each R^7 is independently selected from the group consisting of H, C_1-C_6alkyl, OH, C_1-C_6alkyloxy, NH_2, $NHSO_2N(C_1\text{-}C_6\text{alkyl})_2$, $NHSO_2NHCH_3$, $NHSO_2(C_1\text{-}C_6\text{alkyl})$, $NHSO_2(C_3\text{-}C_7\text{cycloalkyl})$ and $N(C_1\text{-}C_6\text{-alkyl})_2$ NR^8R^9 and NR^9R^{10};

each R^8 and R^9 are independently selected from the group consisting of H, C_1-C_{10}alkyl and C_3-C_7cycloalkyl; or R^8 and R^9 taken together form a 4 to 6 membered saturated ring that optionally contains one or more heteroatoms selected from the group consisting of N, S and O;

each R^{10} is independently selected from the group consisting of H, halogen, OH, CN, CF_2H, CF_3, C_1-C_6 alkyl, C_3-C_7cycloalkyl, C(=O)C_1-C_6alkyl, C(=O)C_3-C_7cycloalkyl, C(=O)NR^8R^9, C(=O)OR^8, SO_2R^8, C(=O)N(R^8)SO_2R^9, C(=O)N(R^8)SO_2N(R^8R^9), NR^8R^9, NR^8C(=O)OR^9, OC(=O)R^8, O-benzyl, $NR^8SO_2R^9$, $SO_2NR^8R^9$, SO_2R^8, OC(=O)NR^8R^9, OC(=O)NR^8R^{12}, N(R^8)C(=O)N(R^8R^9), R^{11}, N(R^8)C(=O)OR^{12}, OR^{11}, C(=O)R^{11} and a 4 to 6 membered saturated ring containing one oxygen atom;

$R^{11}$is phenyl, pyridinyl or pyrazolyl; each of which can be optionally substituted with one or more substituents each independently selected from the group consisting of CF_3, CH_3, OCH_3, OCF_3 and halogen;

R^{12} is C_1-C_6 alkyl or C_3-C_7cycloalkyl; each substituted with one or more substituents each independently selected from the group consisting of CF_3, CH_3, OCH_3, OCF_3 and halogen;

each Z independently is C or N, provided that at least two Z is C;

Q and V each independently represent C=O, SO_2 or $CR^{20}R^{21}$;

p and s independently represent an integer from 0 to 3, wherein the sum of p and s minimally should be 2, and when p = 0 or s = 0 then the carbon atom marked with * is directly bound to W;

R^{20} and R^{21} are independently selected from the group consisting of hydrogen, hydroxyl, C_1-C_3alkyl, C_3-C_7cycloalkyl, CF_3, OCH_3, OCF_3 and halogen;

R^{22} is selected from the group consisting of hydrogen, hydroxyl, C_1-C_6alkyl, C_3-C_7cycloalkyl, CF_3, OCH_3, OCF_3 and halogen;

W is selected from the group consisting of SO, SO_2, S, C, O and N, wherein such C or N is optionally substituted with one or more R^{23};

R^{23} is selected from the group consisting of hydrogen, hydroxyl, C_1-C_6alkyl, C_3-C_7cycloalkyl , C_1-C_6alkyl-R^{24}, SO_2R^{24} , $SO_2N(R^{24})_2$, aryl, heteroaryl, C(=O)OR^{24}, OR^{24} , C(=O)R^{24}, C(=O)N(R^{24})$_2$, OC(=O)N(R^{24})$_2$, P(=O)-(O-C_1-C_6-alkyl)$_2$, N(R^{24})$_2$, NR^{25}C(=O)OR^{24}, NR^{25}C(=O)N(R^{24})$_2$, $NR^{25}SO_2R^{24}$ and a 4 to 6 membered saturated

ring containing one oxygen atom, wherein any of such C_1-C_6alkyl, C_3-C_7cycloalkyl, aryl or heteroaryl is optionally substituted with one or more of the substituents selected from the group consisting of halogen, OH, CN, OCH_3;

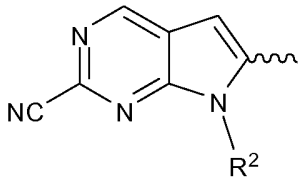
R^{24} is selected from the group of hydrogen, OH, halogen, C_1-C_6alkyl, C_3-C_7cycloalkyl, C(=O) C_1-C_6alkyl, C(=O) C_3-C_7cycloalkyl, aryl, heteroaryl, benzyl, and a 4 to 6 membered saturated ring containing one oxygen atom wherein any of such C_1-C_6alkyl, C_3-C_7cycloalkyl, C(=O) C_1-C_6alkyl, C(=O) C_3-C_7cycloalkyl, aryl, heteroaryl, benzyl is optionally substituted with one or more substituents selected from the group consisting of halogen, CF_3, OH, CN, OCH_3,OC(=O)CH_3) and C_1-C_3alkyl substituted with at least one CN;

R^{25} is selected from the group consisting of hydrogen and C_1-C_3 alkyl;

aryl represents phenyl or naphthalenyl;

heteroaryl represents a monocyclic 5 to 6 membered aromatic heterocycle containing one or more heteroatoms each independently selected from the group consisting of O, S and N; or a bicyclic 8 to 12 membered aromatic heterocycle containing one or more heteroatoms each independently selected from the group consisting of O, S and N;

provided that Het does not satisfy a formula d(x)



d(x)

or a pharmaceutically acceptable addition salt or a solvate thereof.

Preferably, R^{23} is selected from the group consisting of hydrogen, hydroxyl, C_1-C_6alkyl, C_3-C_7cycloalkyl, C_1-C_6alkyl-R^{24}, SO_2R^{24}, $SO_2N(R^{24})_2$, aryl, heteroaryl, C(=O)OR^{24}, OR^{24}, C(=O)R^{24}, C(=O)N(R^{24})$_2$, OC(=O)N(R^{24})$_2$ and a 4 to 6 membered saturated ring containing one oxygen atom, wherein any of such C_1-C_6alkyl, C_3-C_7cycloalkyl, aryl or heteroaryl is optionally substituted with one or more of the substituents selected from the group consisting of halogen, OH, CN, OCH_3;

R^{24} is selected from the group of hydrogen, OH, halogen, C_1-C_6alkyl, C_3-C_7cycloalkyl, C(=O) C_1-C_6alkyl, C(=O) C_3-C_7cycloalkyl, aryl, heteroaryl, benzyl, and a 4 to 6 membered saturated ring containing one oxygen atom wherein any of such C_1-C_6alkyl, C_3-C_7cycloalkyl, C(=O) C_1-C_6alkyl, C(=O) C_3-C_7cycloalkyl, aryl, heteroaryl, benzyl is

optionally substituted with one or more substituents selected from the group consisting of halogen, CF_3, OH, CN, OCH_3,and $OC(=O)CH_3$).

In another aspect, the invention relates to the foregoing compounds for use in the treatment of RSV infections in warm-blooded animals, preferably humans. In yet another aspect, the invention presents a method of treatment of viral RSV infections in a subject in need thereof, comprising administering to said subject an effective amount of a compound as defined above. In still another aspect, the invention resides in the use of a compound as defined above, for the manufacture of a medicament in the treatment of RSV infections.

In a further aspect, the invention relates to a pharmaceutical composition comprising a compound as defined above, and a pharmaceutically acceptable excipient.

In a still further aspect, the invention provides methods for preparing the compounds defined above.

Detailed description of the invention

The invention, in a broad sense, is based on the judicious recognition that the compounds of Formula (RI) generally possess an interesting RSV inhibitory activity.

The present invention will further be described with respect to particular embodiments and with reference to certain examples but the invention is not limited thereto but only by the claims. Where the term "comprising" is used in the present description and claims, it does not exclude other elements or steps. Where an indefinite or definite article is used when referring to a singular noun e.g. "a" or "an", "the", this includes a plural of that noun unless something else is specifically stated.

Whenever the term “substituted” is used in the present invention, it is meant, unless otherwise is indicated or is clear from the context, to indicate that one or more hydrogens, in particular from 1 to 4 hydrogens, preferably from 1 to 3 hydrogens, more preferably 1 hydrogen, on the atom or radical indicated in the expression using “substituted” are replaced with a selection from the indicated group, provided that the normal valency is not exceeded, and that the substitution results in a chemically stable compound, i.e. a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into a therapeutic agent.

As used herein “C_1-C_6alkyl” as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 6 (1, 2, 3, 4, 5 or 6) carbon

atoms such as methyl, ethyl, propyl, 1-methylethyl, butyl, pentyl, hexyl, 2-methylbutyl and the like.

"C_1-C_{10}alkyl" as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 10 carbon atoms such as the groups defined for C_1-C_6alkyl and heptyl, octyl, nonyl, 2-methylhexyl, 2-methylheptyl, decyl, 2-methylnonyl, and the like.

"C_1-C_4alkyloxy" or "C_1-C_4alkoxy", as a group or part of a group defines an O-C_1-C_4alkyl radical, wherein C_1-C_4alkyl has, independently, the meaning given above.

"C_1-C_6alkyloxy" or "C_1-C_6alkoxy", as a group or part of a group defines an O-C_1-C_6alkyl radical, wherein C_1-C_6alkyl has, independently, the meaning given above.

The term "C_3-C_7cycloalkyl" alone or in combination, refers to a cyclic saturated hydrocarbon radical having from 3 to 7 carbon atoms. Non-limiting examples of suitable C_3-C_7cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term "-$(CR^8R^9)_m$-" used herein defines m repetitions of the CR^8R^9 subgroup, wherein each of these subgroups is independently defined.

The term "halo" or "halogen" as a group or part of a group is generic for fluoro, chloro, bromo, iodo unless otherwise is indicated or is clear from the context.

A term of the form NRCOOR is identical to N(R)COOR.

Preferred examples of a 4 to 6 membered aliphatic ring optionally containing one or more heteroatoms selected from the group consisting of N, S and O are; cyclobutyl, cyclopentyl, cyclohexyl, piperidinyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, azetidinyl, thiolanyl, piperazinyl and pyrrolidinyl.

Heteroaryl represents a monocyclic 5 to 6 membered aromatic heterocycle containing one or more heteroatoms each independently selected from the group consisting of O, S and N; or a bicyclic 8 to 12 membered aromatic heterocycle containing one or more heteroatoms each independently selected from the group consisting of O, S and N. Examples of such heteroaryl are furanyl, thiophenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinoxalinyl, and benzimidazolyl.

It should be noted that the radical positions on any molecular moiety used in the definitions may be anywhere on such moiety as long as it is chemically stable.

Radicals used in the definitions of the variables include all possible isomers unless otherwise indicated. For instance pentyl includes 1-pentyl, 2-pentyl and 3-pentyl.

When any variable occurs more than one time in any constituent, each definition is independent.

Hereinbefore and hereinafter, the term "compound of Formula (RI)" or "compounds of Formula (RI)" is meant to include the tautomers and stereoisomeric forms thereof, and the pharmaceutically acceptable addition salts, and the solvates thereof.

The terms "stereoisomers", "stereoisomeric forms" or "stereochemically isomeric forms" hereinbefore or hereinafter are used interchangeably.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible compounds made up of the same atoms bonded by the same sequence of bonds but having different three-dimensional structures which are not interchangeable, which the compounds of Formula (RI) may possess.

It will be appreciated that some of the compounds of Formula (RI) may contain one or more centers of chirality and exist as stereochemically isomeric forms.

The invention includes all stereoisomers of the compound of Formula (RI) and tautomers thereof, either as a pure stereoisomer or as a mixture of two or more stereoisomers.

Enantiomers are stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a racemate or racemic mixture. Diastereomers (or diastereoisomers) are stereoisomers that are not enantiomers, i.e. they are not related as mirror images. If a compound contains a double bond, the substituents may be in the E or the Z configuration. Substituents on bivalent cyclic (partially) saturated radicals may have either the cis- or trans-configuration; for example if a compound contains a disubstituted cycloalkyl group, the substituents may be in the cis or trans configuration. Therefore, the invention includes enantiomers, diastereomers, racemates, E isomers, Z isomers, cis isomers, trans isomers and mixtures thereof, whenever chemically possible.

The absolute configuration is specified according to the Cahn-Ingold-Prelog system. The configuration at an asymmetric atom is specified by either R or S. Resolved compounds whose absolute configuration is not known can be designated by (+) or (-) depending on the direction in which they rotate plane polarized light.

When a specific stereoisomer is identified, this means that said stereoisomer is substantially free, i.e. associated with less than 50 %, preferably less than 20 %, more preferably less than 10 %, even more preferably less than 5%, in particular less than 2 % and most preferably less than 1 %, of the other isomers. Thus, when a compound of Formula (RI) is for instance specified as (R), this means that the compound is substantially free of the (S) isomer; when a compound of Formula (RI) is for instance specified as E, this means that the compound is substantially free of the Z isomer; when a compound of Formula (RI) is for instance specified as cis, this means that the compound is substantially free of the trans isomer.

Some of the compounds according to Formula (RI) may also exist in their tautomeric form. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

Unless otherwise mentioned or indicated, the chemical designation of a compound encompasses the mixture of all possible stereochemically isomeric forms which said compound may possess. Said mixture may contain all diastereomers and/or enantiomers of the basic molecular structure of said compound. All stereochemically isomeric forms of the compounds of the present invention both in pure form or in admixture with each other are intended to be embraced within the scope of the present invention.

Pure stereoisomeric forms of the compounds and intermediates of this invention may be obtained by the application of art-known procedures. The diastereomeric racemates of Formula (RI) can be obtained separately by conventional methods.

For some of the compounds of Formula (RI), tautomers and stereoisomeric forms thereof, and the pharmaceutically acceptable addition salts, and the solvates thereof; and the intermediates used in the preparation thereof, the absolute stereochemical configuration was not experimentally determined. A person skilled in the art is able to determine the absolute configuration of such compounds using art-known methods such as, for example, X-ray diffraction.

The present invention is also intended to include all isotopes of atoms occurring on the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

A compound according to the invention therefore inherently comprises a compound with one or more isotopes of one or more element, and mixtures thereof, including a radioactive compound, also called radiolabelled compound, wherein one or more non-

radioactive atoms has been replaced by one of its radioactive isotopes. By the term "radiolabelled compound" is meant any compound according to Formula (RI) which contains at least one radioactive atom. For example, a compound can be labelled with positron or with gamma emitting radioactive isotopes. For radioligand-binding techniques, the ^{3}H-atom or the ^{125}I-atom is the atom of choice to be replaced. For imaging, the most commonly used positron emitting (PET) radioactive isotopes are ^{11}C, ^{18}F, ^{15}O and ^{13}N, all of which are accelerator produced and have half-lives of 20, 100, 2 and 10 minutes (min) respectively. Since the half-lives of these radioactive isotopes are so short, it is only feasible to use them at institutions which have an accelerator on site for their production, thus limiting their use. The most widely used of these are ^{18}F, ^{99m}Tc, ^{201}Tl and 123I. The handling of these radioactive isotopes, their production, isolation and incorporation in a molecule are known to the skilled person.

In particular, the radioactive atom is selected from the group of hydrogen, carbon, nitrogen, sulfur, oxygen and halogen. In particular, the radioactive isotope is selected from the group of ^{3}H, ^{11}C, ^{18}F, ^{122}I, ^{123}I, ^{125}I, ^{131}I, ^{75}Br, ^{76}Br, ^{77}Br and ^{82}Br.

For therapeutic use, salts of the compounds of Formula (RI) are those wherein the counterion is pharmaceutically acceptable. However, salts of acids and bases which are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether pharmaceutically acceptable or not are included within the ambit of the present invention.

The pharmaceutically acceptable acid and base addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid and base addition salt forms which the compounds of Formula (RI) are able to form. The pharmaceutically acceptable acid addition salts can conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic (i.e. hydroxybutanedioic acid), tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

Conversely said salt forms can be converted by treatment with an appropriate base into the free base form.

The compounds of Formula (RI) containing an acidic proton may also be converted into their non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

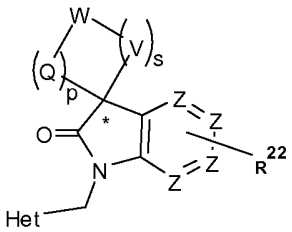
The term solvate comprises the hydrates and solvent addition forms which the compounds of Formula (RI) are able to form, as well as the salts thereof. Examples of such forms are e.g. hydrates, alcoholates and the like.

Without detracting from the overall scope of the invention, certain embodiments are discussed in more detail below.

The terms described above and others used in the specification are well understood to those in the art.

Preferred features of the compounds of this invention are now set forth.

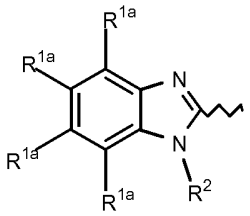
The present invention concerns novel compounds of Formula (RI),



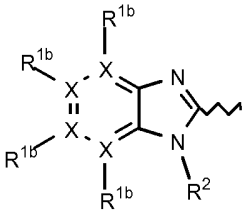
Formula (RI)

or any stereoisomeric form thereof, wherein:

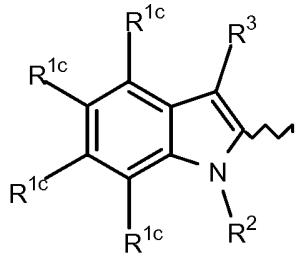
Het is a heterocycle of either of the following formula (a), (b), (c), (d):



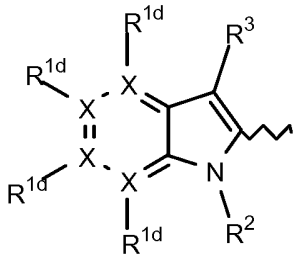
(a)



(b)



(c)



(d)

each X independently is C or N; provided that at least two X is C;

each of R^{1a}, R^{1b}, R^{1c} or R^{1d} is independently selected from the group consisting of H, halogen, C_1-C_6alkyl, C_3-C_7cycloalkyl, C_1-C_6alkyloxy, $N(R^6)_2$, $CO(R^7)$, CH_2NH_2, CH_2OH, CN, $C(=NOH)NH_2$, $C(=NOCH_3)NH_2$, $C(=NH)NH_2$, CF_3 and OCF_3;

R^{1b} or R^{1d} is absent when the X to which it is bound is N;

each R^2 is $-(CR^8R^9)_m-R^{10}$;

m is an integer from 0 to 6;

each R^3 is independently selected from the group consisting of H, halogen, aryl, heteroaryl, C_1-C_6alkyl, C_3-C_7cycloalkyl, C_1-C_6alkyloxy and $CO(R^7)$;

each R^6 is independently selected from the group consisting of H, C_1-C_6alkyl, $COOCH_3$ and $CONHSO_2CH_3$;

each R^7 is independently selected from the group consisting of H, C_1-C_6alkyl, OH, C_1-C_6alkyloxy, NH_2, $NHSO_2N(C_1$-$C_6alkyl)_2$, $NHSO_2NHCH_3$, $NHSO_2(C_1$-$C_6alkyl)$, $NHSO_2(C_3$-$C_7cycloalkyl)$ and $N(C_1$-C_6-$alkyl)_2$ NR^8R^9 and NR^9R^{10};

each R^8 and R^9 are independently selected from the group consisting of H, C_1-C_{10}alkyl and C_3-C_7cycloalkyl; or R^8 and R^9 taken together form a 4 to 6 membered saturated ring that optionally contains one or more heteroatoms selected from the group consisting of N, S and O;

each R^{10} is independently selected from the group consisting of H, halogen, OH, CN, CF_2H, CF_3, C_1-C_6 alkyl, C_3-C_7cycloalkyl, $C(=O)C_1$-C_6alkyl, $C(=O)C_3$-C_7cycloalkyl, $C(=O)NR^8R^9$, $C(=O)OR^8$, SO_2R^8, $C(=O)N(R^8)SO_2R^9$, $C(=O)N(R^8)SO_2N(R^8R^9)$, NR^8R^9, $NR^8C(=O)OR^9$, $OC(=O)R^8$, O-benzyl, $NR^8SO_2R^9$, $SO_2NR^8R^9$, SO_2R^8, $OC(=O)NR^8R^9$, $OC(=O)NR^8R^{12}$, $N(R^8)C(=O)N(R^8R^9)$, R^{11}, $N(R^8)C(=O)OR^{12}$, OR^{11}, $C(=O)R^{11}$ and a 4 to 6 membered saturated ring containing one oxygen atom;

R^{11} is phenyl, pyridinyl or pyrazolyl; each of which can be optionally substituted with one or more substituents each independently selected from the group consisting of CF_3, CH_3, OCH_3, OCF_3 and halogen;

R^{12} is C_1-C_6 alkyl or C_3-C_7cycloalkyl; each substituted with one or more substituents each independently selected from the group consisting of CF_3, CH_3, OCH_3, OCF_3 and halogen;

each Z independently is C or N, provided that at least two Z is C;

Q and V each independently represent C=O, SO_2 or $CR^{20}R^{21}$;

p and s independently represent an integer from 0 to 3, wherein the sum of p and s minimally should be 2, and when p = 0 or s = 0 then the carbon atom marked with * is directly bound to W;

R^{20} and R^{21} are independently selected from the group consisting of hydrogen, hydroxyl, C_1-C_3alkyl, C_3-C_7cycloalkyl, CF_3, OCH_3, OCF_3 and halogen;

R^{22} is selected from the group consisting of hydrogen, hydroxyl, C_1-C_6alkyl, C_3-C_7cycloalkyl, CF_3, OCH_3, OCF_3 and halogen; R^{22} is attached to one Z that is not N;

W is selected from the group consisting of SO, SO_2, S, C, O and N, wherein such C or N is optionally substituted with one or more R^{23};

R^{23} is selected from the group consisting of hydrogen, hydroxyl, C_1-C_6alkyl, C_3-C_7cycloalkyl, C_1-C_6alkyl-R^{24}, SO_2R^{24}, $SO_2N(R^{24})_2$, aryl, heteroaryl, $C(=O)OR^{24}$, OR^{24}, $C(=O)R^{24}$, $C(=O)N(R^{24})_2$, $OC(=O)N(R^{24})_2$, $P(=O)$-$(O$-C_1-C_6-alkyl$)_2$, $N(R^{24})_2$, $NR^{25}C(=O)OR^{24}$, $NR^{25}C(=O)N(R^{24})_2$ $NR^{25}SO_2R^{24}$ and a 4 to 6 membered saturated ring containing one oxygen atom, wherein any of such C_1-C_6alkyl, C_3-C_7cycloalkyl, aryl or heteroaryl is optionally substituted with one or more of the substituents selected from the group consisting of halogen, OH, CN, OCH_3;

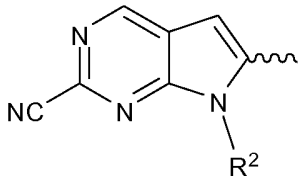
R^{24} is selected from the group of hydrogen, OH, halogen, C_1-C_6alkyl, C_3-C_7cycloalkyl, C(=O) C_1-C_6alkyl, C(=O) C_3-C_7cycloalkyl, aryl, heteroaryl, benzyl, and a 4 to 6 membered saturated ring containing one oxygen atom wherein any of such C_1-C_6alkyl, C_3-C_7cycloalkyl, C(=O) C_1-C_6alkyl, C(=O) C_3-C_7cycloalkyl, aryl, heteroaryl, benzyl is optionally substituted with one or more substituents selected from the group consisting of halogen, CF_3, OH, CN, OCH_3,$OC(=O)CH_3$) and C_1-C_3alkyl substituted with at least one CN;

R^{25} is selected from the group consisting of hydrogen and C_1-C_3 alkyl;

aryl represents phenyl or naphthalenyl;

heteroaryl represents a monocyclic 5 to 6 membered aromatic heterocycle containing one or more heteroatoms each independently selected from the group consisting of O, S and N; or a bicyclic 8 to 12 membered aromatic heterocycle containing one or more heteroatoms each independently selected from the group consisting of O, S and N;

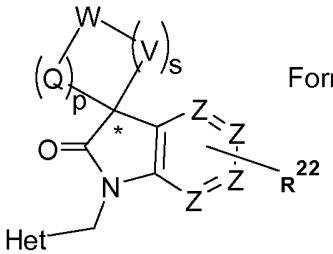
provided that Het does not satisfy a formula d(x)



d(x)

or a pharmaceutically acceptable addition salt or a solvate thereof.

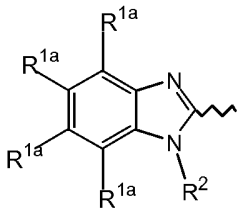
In an embodiment the present invention relates to compounds of formula (RI)



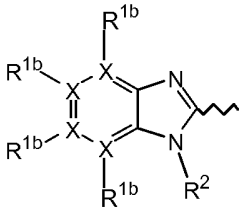
Formula (RI)

or any stereoisomeric form thereof, wherein

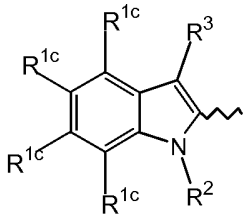
Het is a heterocycle of either of the following formula (a), (b), (c), (d):



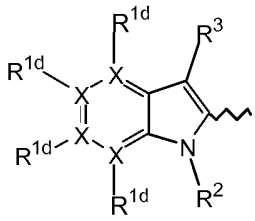
(a)



(b)



(c)



(d)

each X independently is C or N; provided that at least two X is C;

each of R^{1a}, R^{1b}, R^{1c} or R^{1d} is independently selected from the group consisting of H, halogen, C_1-C_6alkyl, C_1-C_6alkyloxy, CF_3 and OCF_3;

R^{1b} or R^{1d} is absent when the X to which it is bound is N;

each R^2 is $-(CR^8R^9)_m-R^{10}$;

m is an integer from 2 to 6;

each R^3 is H, halogen or C_1-C_6alkyl;

each R^8 and R^9 are independently selected from the group consisting of H and C_1-C_{10}alkyl;

each R^{10} is independently selected from the group consisting of H, halogen, OH, CN, CF_2H, CF_3, C_1-C_6 alkyl, C_3-C_7cycloalkyl, $C(=O)NR^8R^9$, $C(=O)OR^8$, and SO_2R^8;

each Z independently is C or N, provided that at least two Z is C;

Q and V each independently represent $CR^{20}R^{21}$;

p and s independently represent an integer from 0 to 3, wherein the sum of p and s minimally should be 2, and when p = 0 or s = 0 then the carbon atom marked with * is directly bound to W;

R^{20} and R^{21} are hydrogen;

R^{22} is selected from the group consisting of hydrogen, hydroxyl, C_1-C_6alkyl, CF_3, OCH_3, OCF_3 and halogen;

W is selected from the group consisting of SO_2, C, O and N, wherein such C or N is optionally substituted with one or more R^{23};

R^{23} is selected from the group consisting of hydrogen, hydroxyl, C_1-C_6alkyl, C_3-C_7cycloalkyl, C_1-C_6alkyl-R^{24}, SO_2R^{24}, $SO_2N(R^{24})_2$, aryl, heteroaryl, $C(=O)OR^{24}$, OR^{24},

$C(=O)R^{24}$, $C(=O)N(R^{24})_2$, $OC(=O)N(R^{24})_2$, $P(=O)-(O-C_1-C_6\text{-alkyl})_2$, $N(R^{24})_2$, $NR^{25}C(=O)OR^{24}$, $NR^{25}C(=O)N(R^{24})_2$ $NR^{25}SO_2R^{24}$ and a 4 to 6 membered saturated ring containing one oxygen atom, wherein any of such C_1-C_6alkyl, C_3-C_7cycloalkyl, aryl or heteroaryl is optionally substituted with one or more of the substituents selected from the group consisting of halogen, OH, CN, OCH_3;

R^{24} is selected from the group of hydrogen, OH, halogen, C_1-C_6alkyl, C_3-C_7cycloalkyl, C(=O) C_1-C_6alkyl, C(=O) C_3-C_7cycloalkyl, aryl, heteroaryl, benzyl, and a 4 to 6 membered saturated ring containing one oxygen atom wherein any of such C_1-C_6alkyl, C_3-C_7cycloalkyl, C(=O) C_1-C_6alkyl, C(=O) C_3-C_7cycloalkyl, aryl, heteroaryl, benzyl is optionally substituted with one or more substituents selected from the group consisting of halogen, CF_3, OH, CN, OCH_3,$OC(=O)CH_3$) and C_1-C_3alkyl substituted with at least one CN;

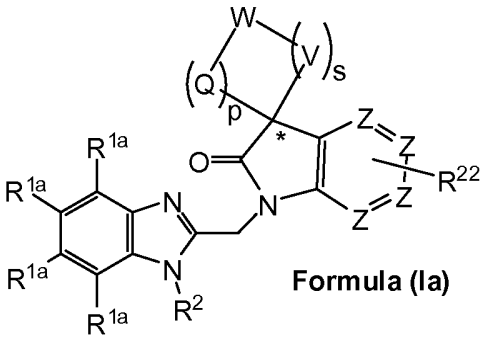
R^{25} is selected from the group consisting of hydrogen and C_1-C_3 alkyl;

aryl represents phenyl or naphthalenyl;

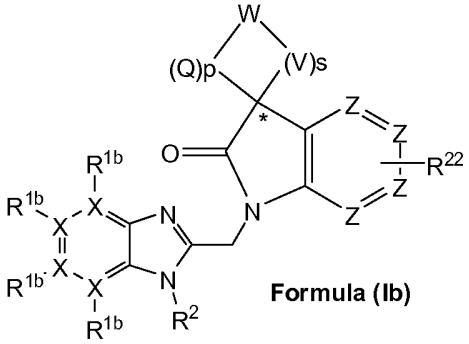
heteroaryl is furanyl, thiophenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinoxalinyl, or benzimidazolyl;

or a pharmaceutically acceptable addition salt or a solvate thereof.

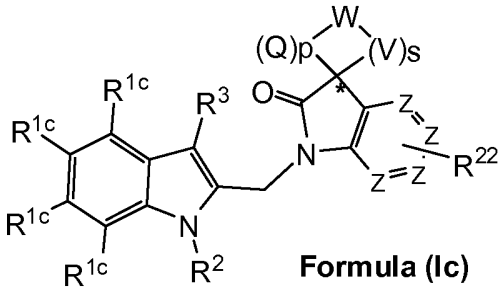
Embodiments of compounds RI according to the present invention are represented by formula Ia, Ib, Ic and Id respectively.



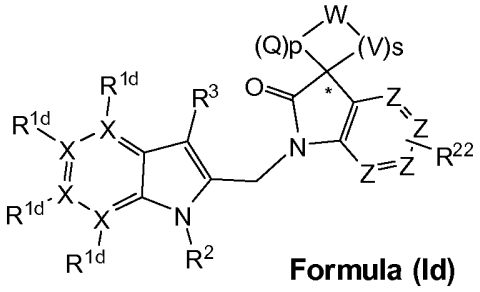
Formula (Ia)



Formula (Ib)



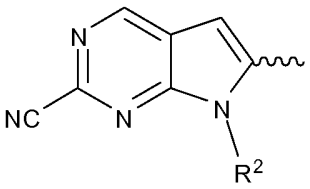
Formula (Ic)



Formula (Id)

In one embodiment, R^{1d} is independently selected from the group consisting of H, halogen, C_1-C_6alkyl, C_3-C_7cycloalkyl, C_1-C_6alkyloxy, $N(R^6)_2$, $CO(R^7)$, CH_2NH_2, CH_2OH, $C(=NOH)NH_2$, $C(=NOCH_3)NH_2$, $C(=NH)NH_2$, CF_3 and OCF_3

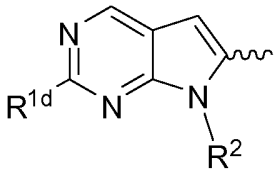
Preferably, in any of the embodiments defined herein, Het does not satisfy a formula d(x)



d(x)

wherein R^2 is as defined herein in any of the embodiments.

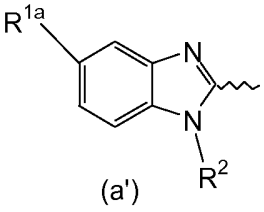
In an even more preferred embodiment, Het does not satisfy a formula d(y)



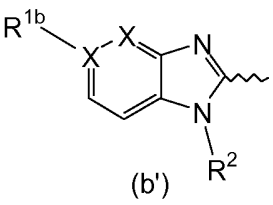
d(y)

wherein R^{1d} and R^2 are as defined herein in any of the embodiments.

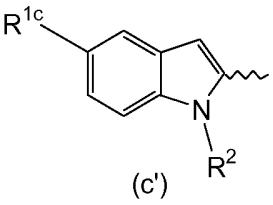
In another embodiment, Het is represented by formula (a'), (b'), (c') or (d'):



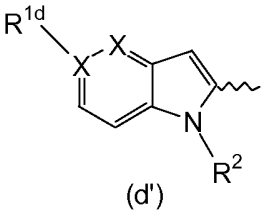
(a')



(b')



(c')



(d')

wherein at least one X is N. More preferably, for Formula (b') and (d') only one X is N.

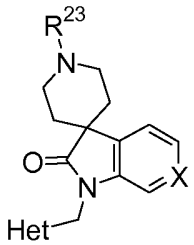
R^{1a}, R^{1b} R^{1c} or R^{1d} are independently selected from the group consisting of H and halogen, more preferably from chloro, bromo and fluoro. Most preferred is chloro.

Compounds according to the present invention have a radical R^2 that is $-(CR^8R^9)_m-R^{10}$ and wherein m is an integer from 0 to 6, 1 to 4 or 3 or 4.
Preferably each R^8 and R^9 are independently chosen from H or C_1-C_6alkyl. In a particular embodiment, R^2 is C_1-C_6 alkyl-R^{10}. In an sub-embodiment, R^2 is C_3-C_4 alkyl-R^{10}

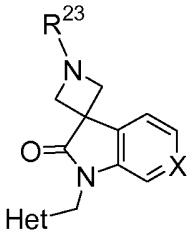
Each R^{10} is independently selected from the group consisting of H, halogen, OH, CN, CF_2H, CF_3, C_1-C_6 alkyl, C_3-C_7cycloalkyl, $C(=O)C_1$-C_6alkyl, $C(=O)C_3$-C_7cycloalkyl, $C(=O)NR^8R^9$, $C(=O)OR^8$, SO_2R^8, $C(=O)N(R^8)SO_2R^9$, $C(=O)N(R^8)SO_2N(R^8R^9)$, NR^8R^9, $NR^8C(=O)OR^9$, $OC(=O)R^8$, O-benzyl, $NR^8SO_2R^9$, $SO_2NR^8R^9$, SO_2R^8, $OC(=O)NR^8R^9$, $OC(=O)NR^8R^{12}$, $N(R^8)C(=O)N(R^8R^9)$, R^{11}, $N(R^8)C(=O)OR^{12}$, OR^{11}, $C(=O)R^{11}$ and a 4 to 6 membered saturated ring containing one oxygen atom.

In a specific embodiment, R^{10} is selected from the group consisting of C_1-C_3 alkyl, H, OH, CN, F, CF_2H, CF_3, SO_2-C_1-C_3alkyl, SO_2C_3-C_6cycloalkyl.

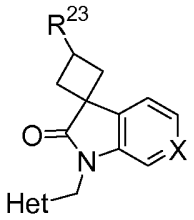
A particular embodiment of the invention relates to compounds having Formula RII, RIII, RIV, RV, RVI or RVII;



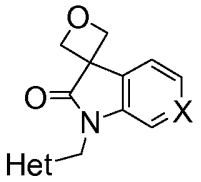
Formula RII



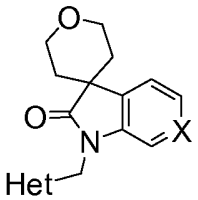
Formula RIII



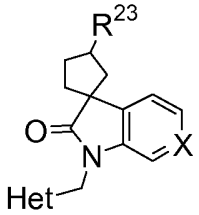
Formula RIV



Formula RV



Formula RVI



Formula RVII

or any stereoisomeric form thereof, wherein Het, X and R^{23} are defined as in any of the described embodiments.

In another embodiment of compounds of Formula RI, RII, RIII, RIV, RV or RVI, R^{23} is selected from the group consisting of hydrogen, hydroxyl, C_1-C_6alkyl, C_1-C_3alkyl-R^{24}, $SO_2R^{24,}$ O-R^{24}, phenyl, pyridinyl pyrimidyl, pyrazolyl, C(=O)$OR^{24,}$ C(=O)R^{24}, wherein any of such C_1-C_6alkyl, phenyl, pyridinyl, pyrimidyl, pyrazolyl is optionally substituted with one or more of the following substituents; OCH_3, halogen, OH and CN.

General Synthetic Schemes

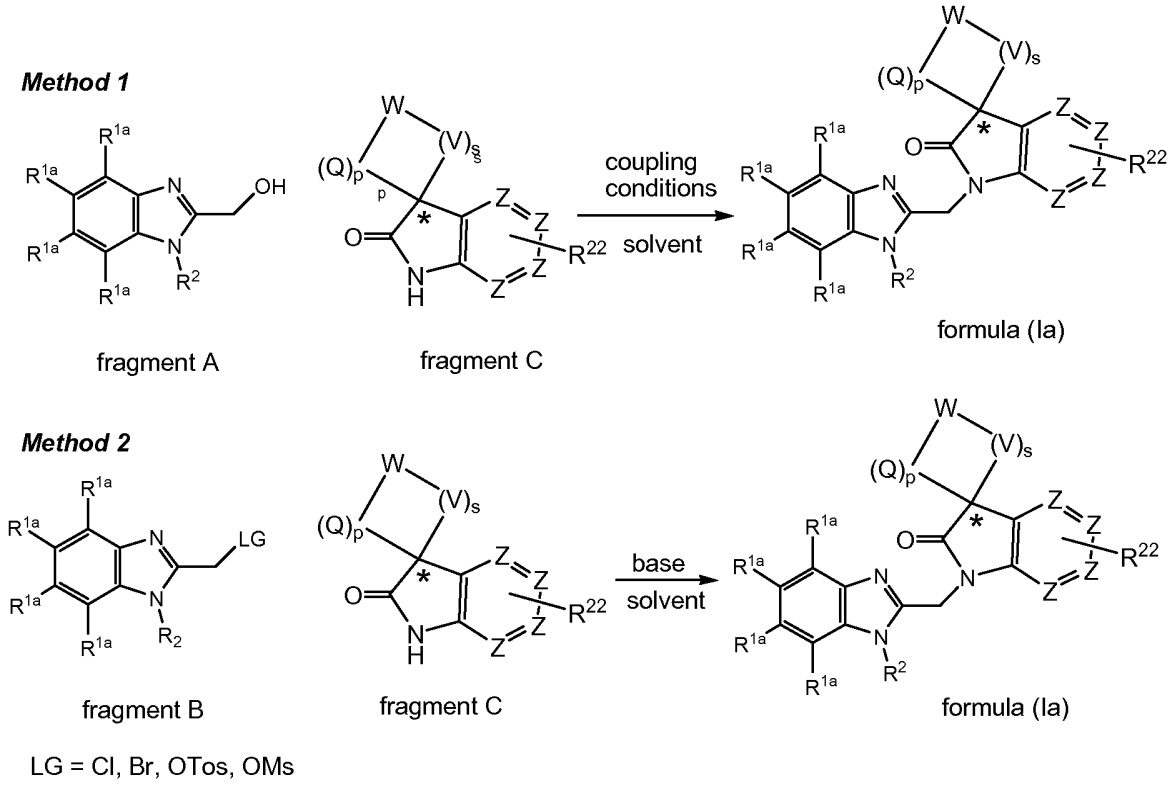
Compounds of formula R**I**, or their pharmaceutically acceptable salts, can be prepared according to the reaction schemes discussed herein below using synthetic methods known in the art of organic chemistry, or modifications and derivatisations that are familiar to those skilled in the art. The starting materials used herein are commercially available or may be prepared by routine methods known in the art such as those methods disclosed in standard reference books. Preferred methods include, but are not limited to, those described below.

During any of the following synthetic sequences it may be necessary and /or desirable to protect sensitive or reactive groups on any of the molecules concerned. This can be achieved by means of conventional protecting groups, such as those described in T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Chemistry, John Wiley & Sons, 1999, which are hereby incorporated by reference.

Unless otherwise indicated, the substituent in the schemes are defined as above. Isolation and purification of the products is accomplished by standard procedures, which are known to a chemist of ordinary skill.

The following schemes are exemplary of the processes for making compounds of formula R**I**. In the schemes below, the numerals used, including numerals from **I** to **XXVIII**, are used for convenience to designate the formulae in the schemes.

The compounds of formula (**Ia**) can be synthesized for instance using one of the methods shown in Scheme 1. In general, a fragment A or B is coupled with a fragment C resulting in derivatives of formula (**Ia**).

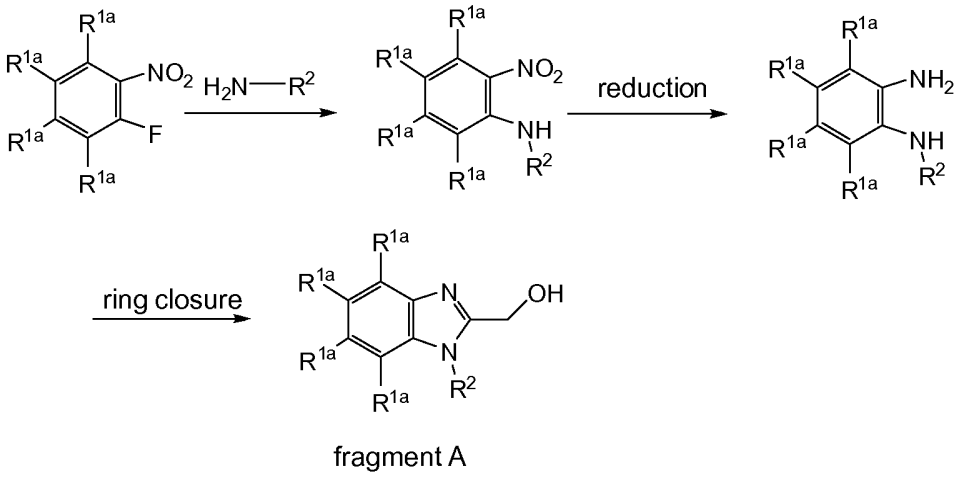


Scheme 1. General synthesis of compounds of formula (**Ia**)

For method 1, an example of suitable "coupling conditions" to react a fragment A with a fragment C to form formula (**Ia**) type compounds is a Mitsunobu reaction. A suitable solvent for this type of reaction is THF (tetrahydrofuran).

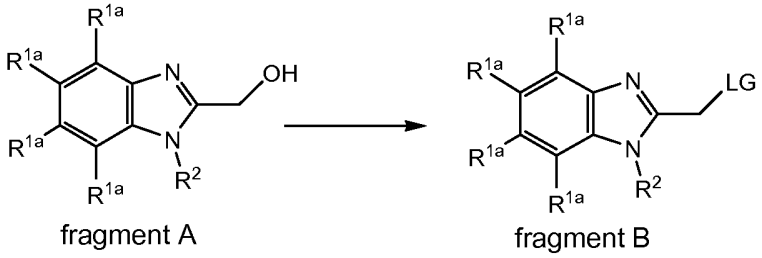
Alternatively (but not limited to), a fragment B type compound wherein the LG is a leaving group, such as halide, preferably chlorine, or sulfonate, can be reacted with a fragment C type compound through a base mediated coupling reaction. (Method 2) Possible bases to effect this reaction (but not limited to) are K_2CO_3, Cs_2CO_3, triethylamine, sodium hydride. A suitable solvent (but not limited to) for this type of base mediated coupling is DMF (dimethylformamide) or THF (tetrahydrofurane).

Fragment A type compounds can be generally prepared as depicted in scheme 2.



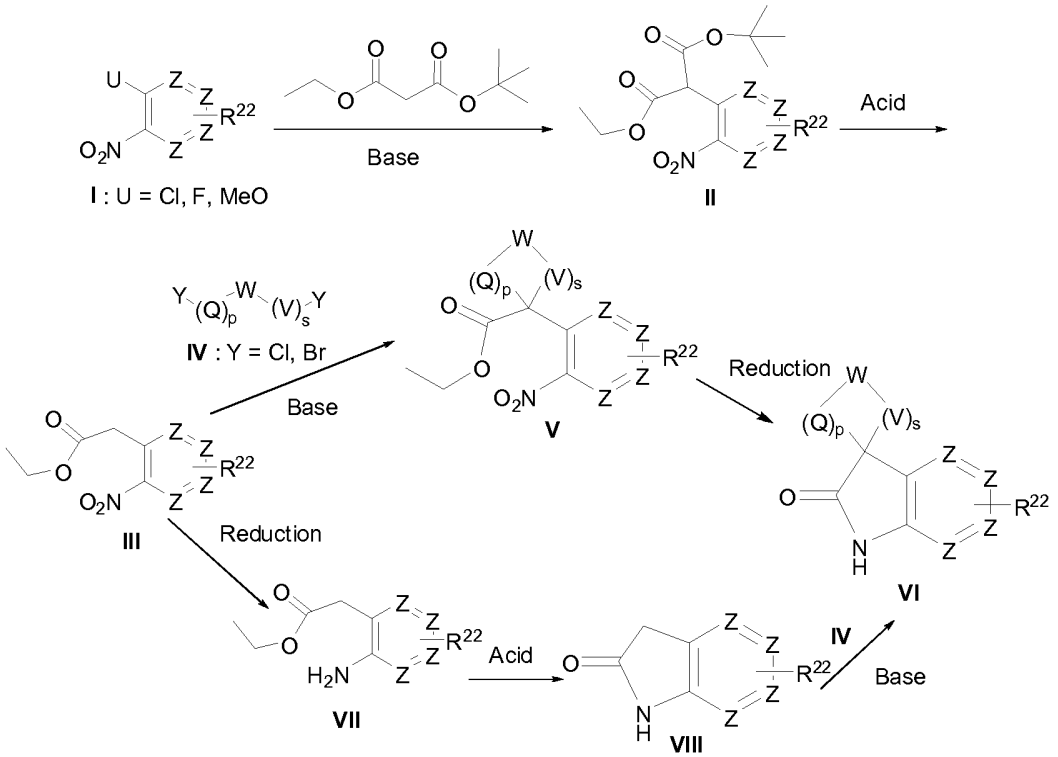
Scheme 2. General synthesis of fragment A type compounds

In general, fragment B type compounds can be prepared from fragment A type compounds through reaction with reagents like (but not limited to) $SOCl_2$, PBr_3, *p*-TsCl, MsCl.



Scheme 3. General synthesis of fragment B type compounds

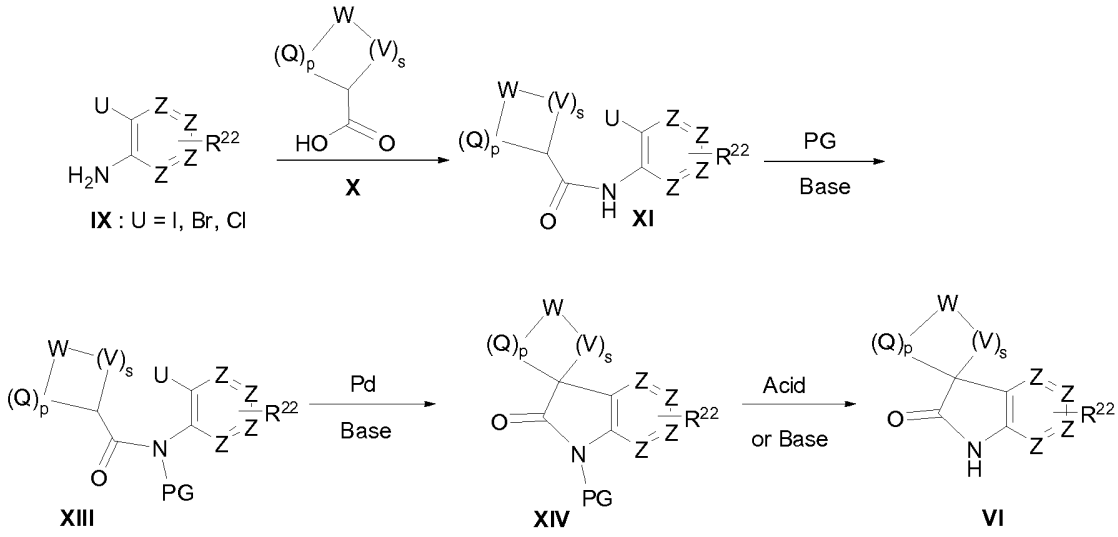
Fragment C type intermediates of formula (**VI**) can be prepared as depicted in Scheme 4.



Scheme 4. General synthesis of fragment C (**VI**) type compounds

The Synthesis of spiro-2-oxo-indole derivatives and spiro-2-oxo-azaindole derivatives is shown in scheme 4. Intermediates of formula **VI** can be synthesized using the procedure depicted in scheme 4. Displacement of (U), which is a halide, preferably fluorine, or an alkyloxy group, preferably methoxy, of the nitro pyridine or of nitro aryl of formula **I** with *tert*-butyl ethyl malonate, in a suitable solvent such as THF or DMF, in the presence of a base such as sodium hydride or potassium carbonate, gives an intermediate of formula (**II**). The treatment of intermediate **II** with an acid such as trifluoroacetic acid or dry hydrochloric acid gives intermediate **III**. The latter can be transformed to intermediate **V** by a condensation with a bis halo compound **IV** preferably bromo in the presence of a suitable base such as potassium carbonate, sodium carbonate, sodium hydride and the like in a suitable solvent such as DMF, THF or a like. Reduction of the nitro group of the intermediate **V** when it's done in a stoichiometric way using iron in the presence of ammonium chloride or tin chloride in the presence of concentrated hydrochloric acid gives directly compound **VI**. Alternatively, the intermediate of formula **III** can be reduced first in a catalytic way using hydrogen in the presence of a catalyst such as palladium or platinum, in a suitable solvent such as methanol, to give intermediate **VII**. The latter can be transformed to intermediate **VIII** in acidic conditions using hydrochloric acid or a like in a suitable solvents such as alcohols for example isopropanol. The condensation of intermediate

VIII with a bis halo compound **IV**, preferably chloro or bromo, is performed in the presence of a suitable inorganic base such as potassium carbonate, sodium carbonate, sodium hydride or a like in a suitable solvent such as DMF, THF or a like or using an organic base such as sodium hexamethyldisilazide (NaHMDS) or alkyl lithium bases e.g. nBuLi in a suitable solvents such THF or ether to give intermediate **VI**.



Scheme 5. General synthesis of fragment C (**VI**) type compounds

Alternatively compounds of formula **VI** can be prepared, but not limited to, by general procedures illustrated by scheme 5.

The starting material **IX** can be commercially available or prepared using known in the art procedures. The acid **X** can be activated as the Weinreb amide using standard peptide coupling procedures e.g. EDCI/HOBT, HATU, DCC, etc. Once the acid is activated as the ester or Weinreb amide, the aniline **IX** can be added to convert it to intermediate **XI**.

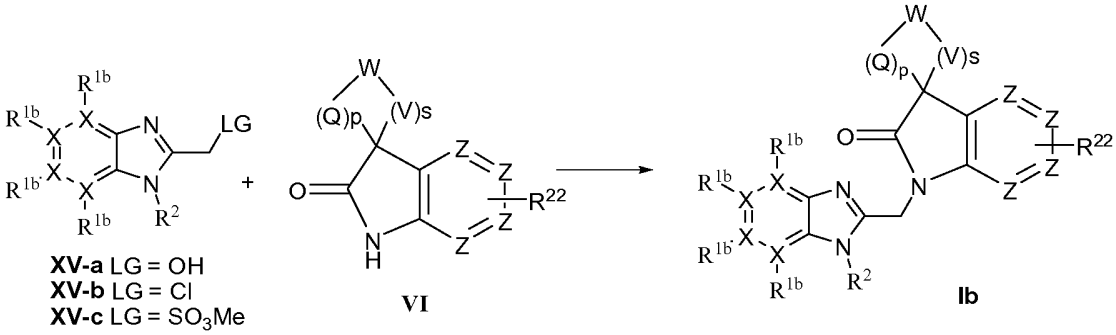
The reaction of the intermediate **XI** with PG where PG, is a protecting group such as para-methoxybenzyl, benzyl, *tert*-butoxycarbonyl, mesyl or tosyl, in the presence of a suitable base such as potassium carbonate, cesium carbonate or sodium hydride in a suitable solvent such as DMF or THF gives intermediate **XIII**. Intermediate **XIV** was prepared according to the procedure reported in Lee, S. and J. F. Hartwig (2001). J. Org. Chem. 66(10): 3402-3415. The displacement of (U) which is an halo, preferably bromine, using Palladium (II) acetate as catalyst in presence of a base such as potassium tert-butoxide and a ligant such as tricyclohexylphosphene in a solvent such as 1,4-dioxane gives intermediate **XIV**. The removal of protecting group in

intermediate **XIV**, can be performed using the conditions described in Green and Wurts, Protecting groups in Organic Synthesis 3rd Edition, to give intermediate **VI**.

Scheme 6 illustrates a method for the preparation of compounds of formula **Ib**, where R^{1b}, R^2, R^{22}, Q, V, W, X and Z are defined as above.

Referring to scheme 6, a compound of formula **Ib** can be synthesized by coupling 2-hydroxymethylene imidazopyridines **XV-a** with spiro oxo-indole or spiro oxo-azaindole **VI** in a known in the art method such as a Mitsunobu reaction which uses for example azadiisopropyldicarboxylate and triphenyl phosphine in a suitable solvent such as DMF or THF. Alternatively, compound of formula **Ib** may be prepared by displacement of (LG) where (LG) is a leaving group, which is a halide, preferably chlorine **XV-b**, or a sulfonate such as mesylate **XV-c** in the presence of a base such as sodium hydride, potassium carbonate or cesium carbonate in a suitable solvent such as DMF or THF.

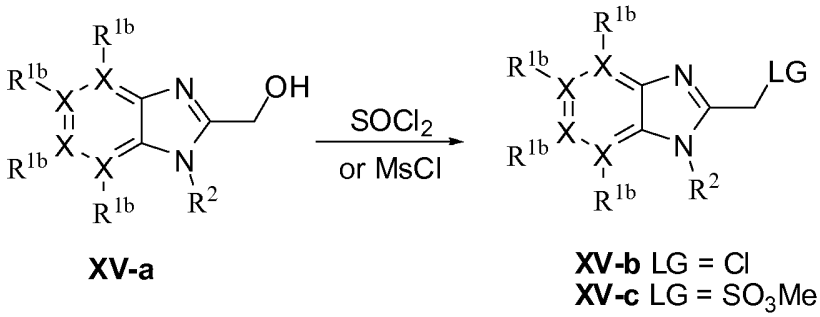
Scheme 6



Preparation of compound **XV-b** and **XV-c**

Treatment of the alcohol **XV-a** with thionyl chloride provides 2-chloromethyl imidazo-pyridines **XV-b**. Alternatively, alcohol **XV-a** may be transformed to the intermediate **XV-c** by a reaction with methane sulfonyl chloride in the presence of an organic base such as triethyl amine or diisopropyl ethyl amine in a suitable solvent such as dichloromethane (scheme 7).

Scheme 7



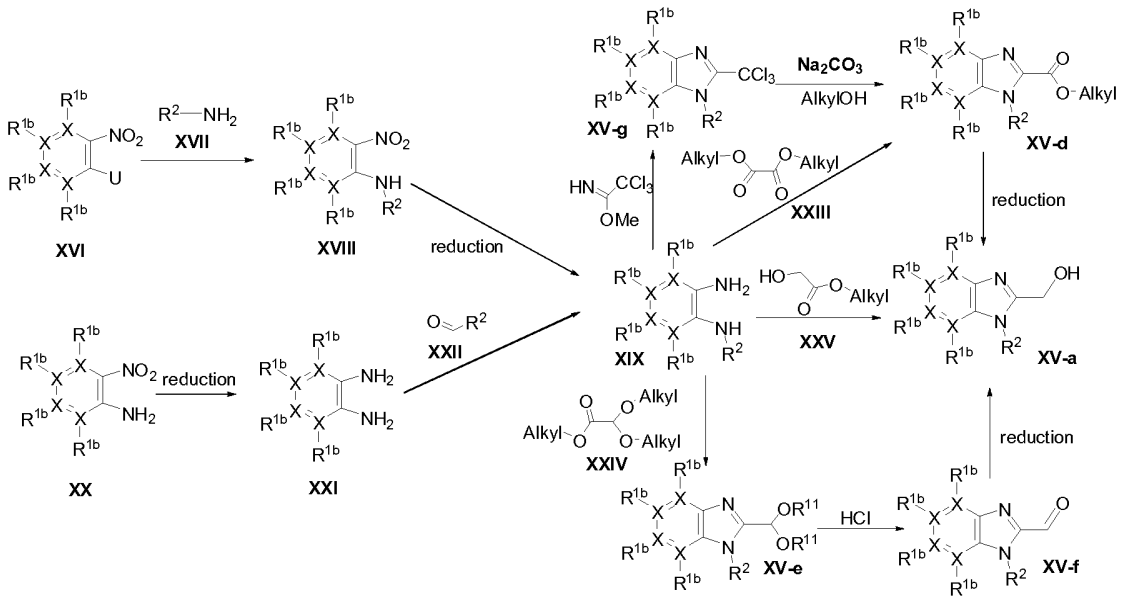
Preparation of compound **XV-a**

Compounds of formula **XV-a** are either commercially available or can be prepared, but not limited to, by general procedures illustrated by scheme 8, wherein R^{1b}, R^2, X are defined as above. Referring to scheme 8 below, haloheteroaryls **XVI**, where (U) is an halide preferably fluorine, can be treated with primary amines of formula **XVII** in the presence of a suitable base such as potassium carbonate and the like, in a suitable solvent such as ethanol or dichloromethane at a reaction temperature ranging from room temperature to 100°C to give compounds of formula **XVIII**. Hydrogenation of the nitro group using well-precedented conditions such as Pd/C, or other catalyst, under hydrogen or Fe/EtOH/$CaCl_2$ can yield diamine of formula **XIX**. Alternatively, the hydrogenation of the nitro group of compound **XX** using well-precedented conditions such as Pd/C, or another catalyst, under hydrogen atmosphere or Fe/EtOH/$CaCl_2$ yield diamine of formula **XXI.**This can be treated with the aldehydes of formula **XXII** in the presence of suitable reducing agents such as $NaBH(OAc)_3$, or $Na(CN)BH_3$ in solvents such as methylene chloride, DMF or THF, at about room temperature to give compounds of formula **XIX**. The imidazol ring can be formed by treating diamines **XIX** with glycolic acid or an ester like **XXV** under strong acidic conditions, such as aqueous hydrochloric acid, at elevated temperature such as reflux to yield the alcohols of formula **XV-a**.

Alternatively, diamines **XIX** can be condensed with dialkoxyacetate of formula **XXIV**, in the presence of acetic acid, in a suitable solvent such as methanol gives the acetal **XV-e**. The acetal of compounds **XV-e** can be removed with acids such as hydrochloric acid to give the aldehydes of formula **XV-f**. The resulting aldehydes of formula **XV-f** can be reduced to alcohols using a suitable reducing agent such as $NaBH_4$ or $LiAlH_4$ in a suitable solvent such as ethanol or THF to yield the desired alcohols of formula **XV-a**. In addition, diamines **XIX** can be cyclized with dialkyl oxalate of formula **XXIII** in a suitable solvent such as ethanol at elevated temperature with or without microwave heating to produce imidazoles of formula **XV-d**. Alternatively, compounds of formula

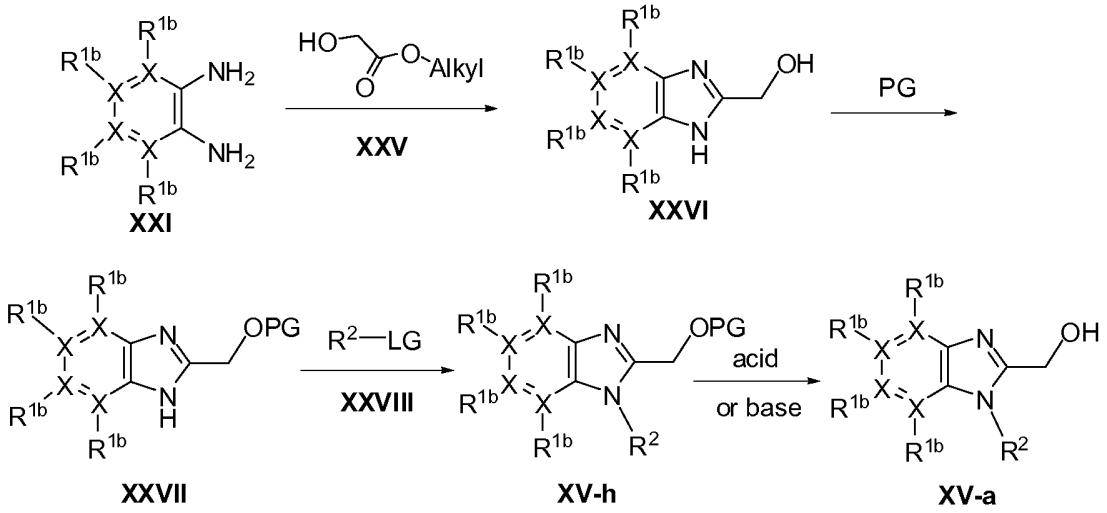
XV-d may be prepared in a two steps synthesis starting from diamines **XIX**. Firstly diamine **XIX** may be reacted with an alkyl trihaloacetimidate, preferably methyl 2,2,2-trichloroacetimidate, in an acidic media, preferably acetic acid, at a temperature ranging between 25 and 50°C to yield compound of formula **XV-g**. Secondly a reaction of compounds of formula **XV-g** with metalcarbonate, preferably sodium carbonate in a suitable solvent such as methanol, lead to compounds of formula **XV-d**. Compounds **XV-d** can be subsequently reduced to the desired alcohols of formula **XV-a** using a suitable reducing agent such as $NaBH_4$ or $LiAlH_4$ in a suitable solvent such as ethanol or THF.

Scheme 8



An alternative route for the preparation of compounds of type **XV-a** is depicted in scheme 9. Diamine **XXI** may be first coupled to an alkyl glycolic acid or an ester like **XXV** under strong acidic conditions, such as aqueous hydrochloric acid, at elevated temperature such as reflux to yield the alcohols of formula **XXVI**. This alcohol may be protected by a PG, where PG is a protecting group such as, but not limiting to, a trityl which consequently results in compounds **XXVII**. A suitable solvent for this type of reactions can be, but not limiting to, dichloromethane. The treatment of compound **XXVII** with compound **XXVIII**, wherein the LG is a leaving group, such as halide, preferably bromine, or sulfonate, in the presence of a base such as sodium hydride, potassium carbonate or cesium carbonate in a suitable solvent such as DMF or THF, gives compound **XV-h**. The removal of the PG in compound **XV-h** may be done in the presence of an acid such as hydrochloric acid in the presence of a solvent, not limited to, such as dioxane to yield compound **XV-a**.

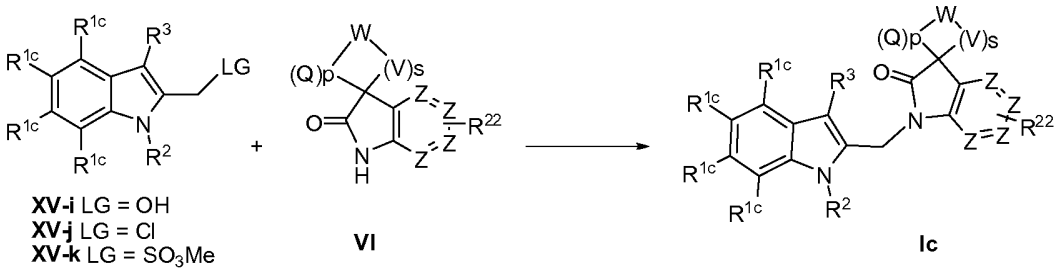
Scheme 9



Compounds of formula **Ic**, or their pharmaceutically acceptable salts, can be prepared according to the reaction schemes discussed herein below. Unless otherwise indicated, the substituents in the schemes are defined as above. Isolation and purification of the products is accomplished by standard procedures, which are known to a chemist of ordinary skill.

Referring to scheme 10, a compound of formula **Ic**, where R^{1c}, R^2, R^3, R^{22}, Q, V, W and Z are defined as above, can be synthesized by coupling 2-hydroxymethylene indole (**XV-i**) with (**VI**) with a method known in the art method such as a Mitsunobu reaction which uses azadiisopropyldicarboxylate and triphenyl phosphine in a suitable solvent such as DMF or THF. Alternatively, compound of formula **Ic** may be prepared by displacement of LG (leaving group), which is a halide, preferably chlorine (**XV-j**), or a sulfonate such as mesylate (**XV-k**) in the presence of a base such as sodium hydride, potassium carbonate or cesium carbonate in a suitable solvent such as DMF or THF.

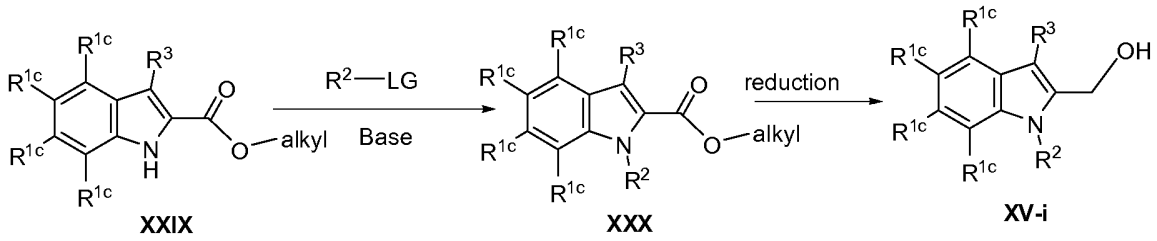
Scheme 10



Preparation of compound **XV-i**

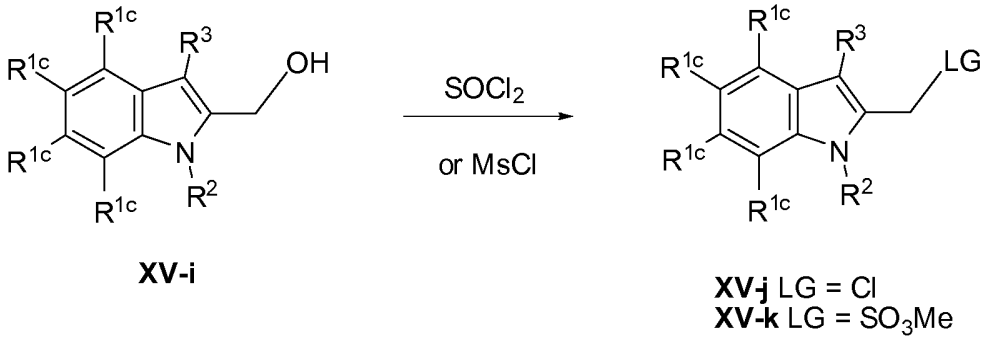
Starting materials **XXIX** used in this invention are commercially available, or can be synthesized, but not limited to, by methods known in the art such as Reissert synthesis or Fischer synthesis, reaction of such indoles with R^2-LG, where LG is a leaving group such as halide, preferably bromine, or sulfonate, in the presence of a base such as sodium hydride, potassium carbonate or cesium carbonate in a suitable solvent such as DMF or THF, gives compound **XXX** (scheme 11). The conversion of the alkyl ester of compound **XXX** to the alcohol **XV-i** can be carried out with metal hydride such as lithium aluminum hydride or sodium borohydride in a suitable solvent such as THF, methanol or ethanol.

Scheme 11

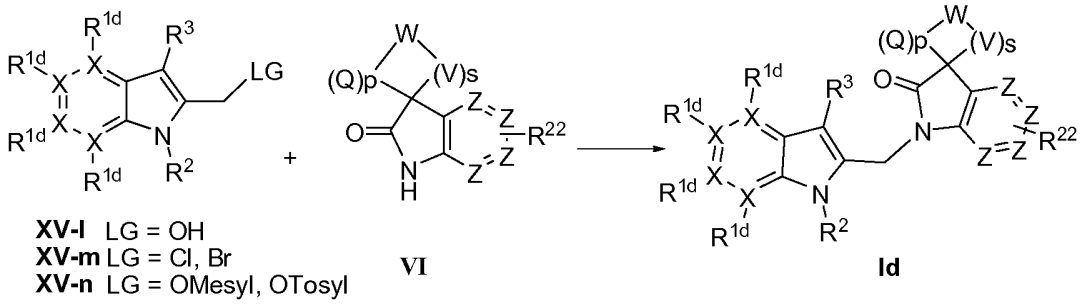


Treatment of the alcohol **XV-i** with thionyl chloride provides 2-chloromethyl indole **XV-j**. Alternatively, alcohol **XV-i** may be transformed to the intermediate **XV-k** by a reaction with methane sulfonyl chloride in the presence of an organic base such as triethyl amine or diisopropyl ethyl amine in a suitable solvent such dichloromethane (scheme 12).

Scheme 12



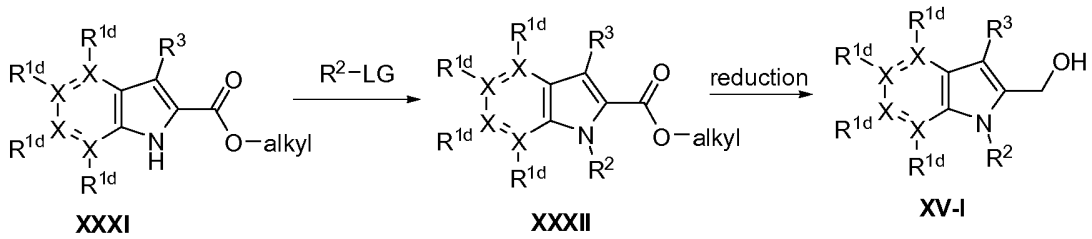
Scheme 13 illustrates a method for the preparation of compounds of formula (**Id**), where R^{1d}, R^2, R^3, R^{22}, Q, V, W, X and Z are defined as above.



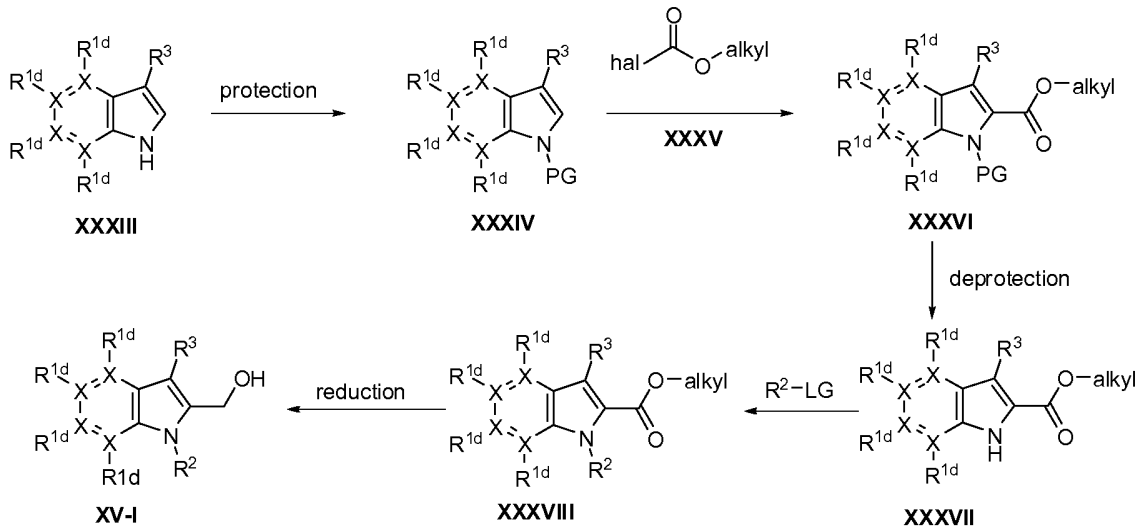
Scheme 13: General synthesis of compounds of formula (**Id**)

A compound of formula **Id** can be synthesized by coupling 2-hydroxymethylene azaindole **XV-l** with a spiro oxo-indole or spiro oxo-azaindole **VI** in a known in the art method such as Mitsunobu reaction which uses azadiisopropyldicarboxylate (DIAD) and triphenylphosphine in a suitable solvent such as DMF or THF. Alternatively, compounds of formula **Id** may be prepared by displacement of LG, where LG is a leaving group, which is a halide, preferably chlorine **XV-m** or sulfonate such as mesylate **XV-n** in the presence of a base such as, but not limited to, sodium hydride, potassium carbonate or cesium carbonate in a suitable solvent such as DMF or THF.

Method 1



Method 2

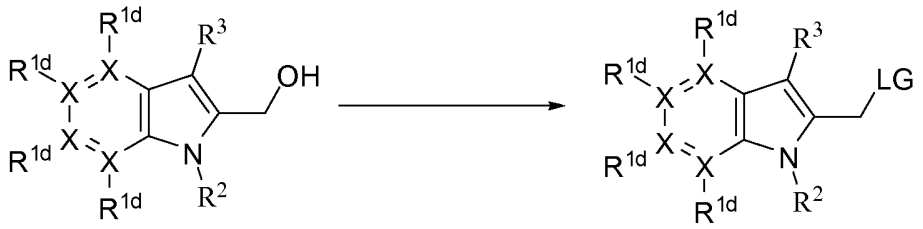


Scheme 14: General synthesis of **XV-l** type compounds

Compound **XV-l** is prepared according to the methods as depicted in scheme 14.

Starting materials **XXXI** used in this invention, according to method 1, are commercially available, or can be synthesized, but not limited to, by methods known in the art such as Reissert synthesis or Fischer synthesis. Reaction of such a compound with R^2-LG, where LG is a leaving group such as halide, preferably bromine, or sulfonate, in the presence of a base such as sodium hydride, potassium carbonate or cesium carbonate in a suitable solvent such as DMF or THF, gives compound **XXXII**. The conversion of the alkyl ester of compound **XXXII** to the alcohol **XV-l** can be done with a metal hydride such as lithium aluminum hydride or sodium borohydride in a suitable solvent such as THF or methanol.

Alternatively a **XV-l** type compound can also be synthesized as shown in scheme 14, method 2. The commercially available starting material **XXXIII** is protected by a PG, where PG is a protecting group such as, but not limited to, a tosyl, which consequently results in compound **XXXIV**. A suitable solvent for this kind of reactions can be, but not limiting to, toluene. The metallation of compound **XXXIV** followed by treatment with compound **XXXV**, wherein the halide is preferably chlorine, in a suitable solvent such as, but not limited to, THF, yields compound **XXXVI**. The removal of the PG in compound **XXXVI** may be done in the presence of a base such as potassium carbonate or cesium carbonate in a suitable solvent such as THF and methanol to obtain indole **XXXVII**. Reaction of indoles **XXXVII** with R^2-LG, where LG is a leaving group such as a halide, preferably bromine, or sulfonate, in the presence of a base such as sodium hydride, potassium carbonate or cesium carbonate in a suitable solvent such as DMF or THF, gives compound **XXXVIII**. The conversion of the alkyl ester of compound **XXXVIII** to the alcohol **XV-l** can be carried out with a metal hydride such as lithium aluminum hydride or sodium borohydride in a suitable solvent such as THF or ethanol.



XV-l

XV-m LG = Cl, Br
XV-n LG = OMesyl, OTosyl

Scheme 15: General synthesis of **XV-m** and **XV-n** type compounds

Treatment of the alcohol **XV-l** with reagents like, but not limited to, $SOCl_2$, PBr_3, *p*-TsCl, MsCl provides 2-chloromethyl indole **XV-m** or compounds like **XV-n**.

The compounds of Formula (RI) may be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of Formula (RI) with appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. t.butyl hydro-peroxide. Suitable solvents are, for example, water, lower alcohols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

All starting materials can be obtained commercially or can be prepared by those skilled in the art.

Pure stereochemically isomeric forms of the compounds of Formula (RI) may be obtained by the application of art-known procedures. Diastereomers may be separated by physical methods such as selective crystallization and chromatographic techniques, e.g., counter-current distribution, liquid chromatography and the like. Appropriate physical separation methods that may advantageously be employed are, for example, selective crystallization and chromatography, e.g. column chromatography.

The compounds of Formula (RI) as prepared in the hereinabove described processes are generally racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of Formula (RI) which are sufficiently basic or acidic may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid, respectively chiral base. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali or acid. An alternative manner of separating the enantiomeric forms of the compounds of Formula (RI) involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will

be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

In a further aspect, the present invention concerns a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (RI) as specified herein, or a compound of any of the embodiments of compounds of Formula (RI) as specified herein, and a pharmaceutically acceptable carrier. A therapeutically effective amount in this context is an amount sufficient to prophylaxictically act against, to stabilize or to reduce viral infection, and in particular RSV viral infection, in infected subjects or subjects being at risk of being infected. In still a further aspect, this invention relates to a process of preparing a pharmaceutical composition as specified herein, which comprises intimately mixing a pharmaceutically acceptable carrier with a therapeutically effective amount of a compound of Formula (RI), as specified herein, or of a compound of any of the embodiments of compounds of Formula (RI) as specified herein.

Therefore, the compounds of the present invention or any embodiment thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs.

To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, particularly, for administration orally, rectally, percutaneously, or by parenteral injection. Preferred is oral administration. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules, and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable

suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin.

The compounds of the present invention may also be administered via oral inhalation or insufflation by means of methods and formulations employed in the art for administration via this way. Thus, in general the compounds of the present invention may be administered to the lungs in the form of a solution, a suspension or a dry powder, a solution being preferred. Any system developed for the delivery of solutions, suspensions or dry powders via oral inhalation or insufflation are suitable for the administration of the present compounds.

Thus, the present invention also provides a pharmaceutical composition adapted for administration by inhalation or insufflation through the mouth comprising a compound of Formula (RI) and a pharmaceutically acceptable carrier. Preferably, the compounds of the present invention are administered via inhalation of a solution in nebulized or aerosolized doses.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, suppositories, powder packets, wafers, injectable solutions or suspensions and the like, and segregated multiples thereof.

The compounds of Formula (RI) show antiviral properties. Viral infections treatable using the compounds and methods of the present invention include those infections brought on by ortho- and paramyxoviruses and in particular by human and bovine respiratory syncytial virus (RSV). A number of the compounds of this invention moreover are active against mutated strains of RSV. Additionally, many of the compounds of this invention show a favorable pharmacokinetic profile and have attractive properties in terms of bioavailabilty, including an acceptable half-life, AUC

and peak values and lacking unfavourable phenomena such as insufficient quick onset and tissue retention.

The *in vitro* antiviral activity against RSV of the present compounds was tested in a test as described in the experimental part of the description, and may also be demonstrated in a virus yield reduction assay. The *in vivo* antiviral activity against RSV of the present compounds may be demonstrated in a test model using cotton rats as described in Wyde et al. (Antiviral Research (1998), 38, 31-42).

Due to their antiviral properties, particularly their anti-RSV properties, the compounds of Formula (RI) or any embodiment thereof, tautomers and stereoisomeric forms thereof, and the pharmaceutically acceptable addition salts, and the solvates thereof, are useful in the treatment of individuals experiencing a viral infection, particularly a RSV infection, and for the prophylaxis of these infections. In general, the compounds of the present invention may be useful in the treatment of warm-blooded animals infected with viruses, in particular the respiratory syncytial virus.

The compounds of the present invention or any embodiment thereof may therefore be used as medicines. Said use as a medicine or method of treatment comprises the systemic administration to viral infected subjects or to subjects susceptible to viral infections of an amount effective to combat the conditions associated with the viral infection, in particular the RSV infection.

The present invention also relates to the use of the present compounds or any embodiment thereof in the manufacture of a medicament for the treatment or the prevention of viral infections, particularly RSV infection.

The present invention furthermore relates to a method of treating a warm-blooded animal infected by a virus, or being at risk of infection by a virus, in particular by RSV, said method comprising the administration of an anti-virally effective amount of a compound of Formula (RI), as specified herein, or of a compound of any of the embodiments of compounds of Formula (RI), as specified herein.

The exact dosage and frequency of administration depends on the particular compound of Formula (RI) used, the particular condition being treated, the severity of the condition being treated, the age, weight, sex, extent of disorder and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the

compounds of the instant invention. The effective daily amount ranges mentioned hereinabove are therefore only guidelines.

Also, the combination of another antiviral agent and a compound of Formula (RI) can be used as a medicine. Thus, the present invention also relates to a product containing (a) a compound of Formula (RI), and (b) another antiviral compound, as a combined preparation for simultaneous, separate or sequential use in antiviral treatment. The different drugs may be combined in a single preparation together with pharmaceutically acceptable carriers. For instance, the compounds of the present invention may be combined with interferon-beta or tumor necrosis factor-alpha in order to treat or prevent RSV infections.

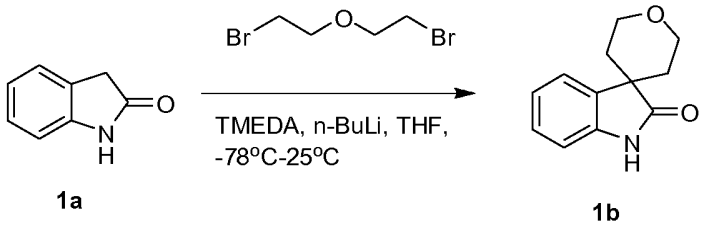
The invention will hereinafter be illustrated with reference to the following, non-limiting examples.

Experimental part

Synthesis of intermediates

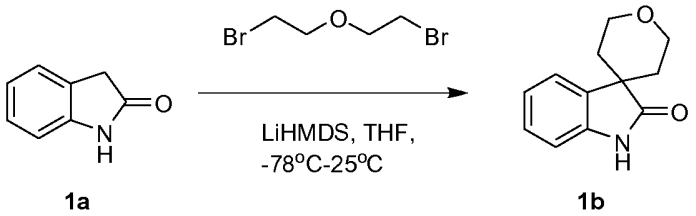
Intermediate 1b: Synthesis of 2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one

Method 1



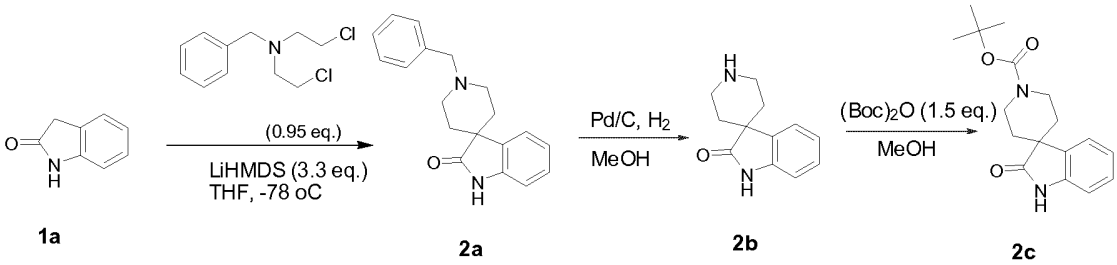
n-BuLi (108 ml, 216 mmol, 2 M in THF) was added to a solution of oxindole **1a** (CAS number: 59-48-3, 11 g, 82.6 mmol) at -78°C in THF (1000 ml). After complete addition, TMEDA (25 g, 214.76 mmol) was added, maintaining the internal temperature <-70 °C. After 1 h at -78 °C, bis(2-bromomethyl)ether (CAS number: 5414-19-7, 57.5 g, 247.8 mmol) was added and the reaction warmed to ambient temperature. After 48 h the reaction was quenched with H_2O and the mixture was partitioned between EtOAc and H_2O. The aqueous solution was extracted with EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by silica gel chromatography, eluting with a gradient of CH_2Cl_2: MeOH=100:0 to 97:3 to give 8% of 2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one **1b**.

Method 2



Oxindole **1a** (CAS number: 59-48-3**,** 40 g, 264.659 mmol) was added to a solution of LiHMDS (800 ml, 800 mmol) at -78°C. The mixture was stirred 1 hour at -78°C. Bis(2-bromomethyl)ether (CAS number: 5414-19-7, 61.378 g, 264.659 mmol) was then added, maintaining the internal temperature <-50°C. The reaction was warmed to ambient temperature. After 18 hours the reaction was quenched with H_2O and the mixture was partitioned between EtOAc and H_2O. The aqueous solution was extracted with EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by silica gel chromatography, eluting with a gradient of petroleum ether: ethyl acetate = 3:1 to give 10.187 g (17%) of 2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one **1b**.

<u>Intermediate 2c:</u> Synthesis of *tert*-butyl 2-oxospiro[indoline-3,4'-piperidine]-1'-carboxylate



Step 1

1'-benzylspiro[indoline-3,4'-piperidin]-2-one **2a** was synthetized with a yield of 59% (52 g) following the method 2 used for the synthesis of 2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one **1b**, using *N,N*-bis(2-chloroethyl)benzenemethanamine (CAS number: 55-51-6, 70 g, 302 mmoles) instead of bis(2-bromomethyl)ether.

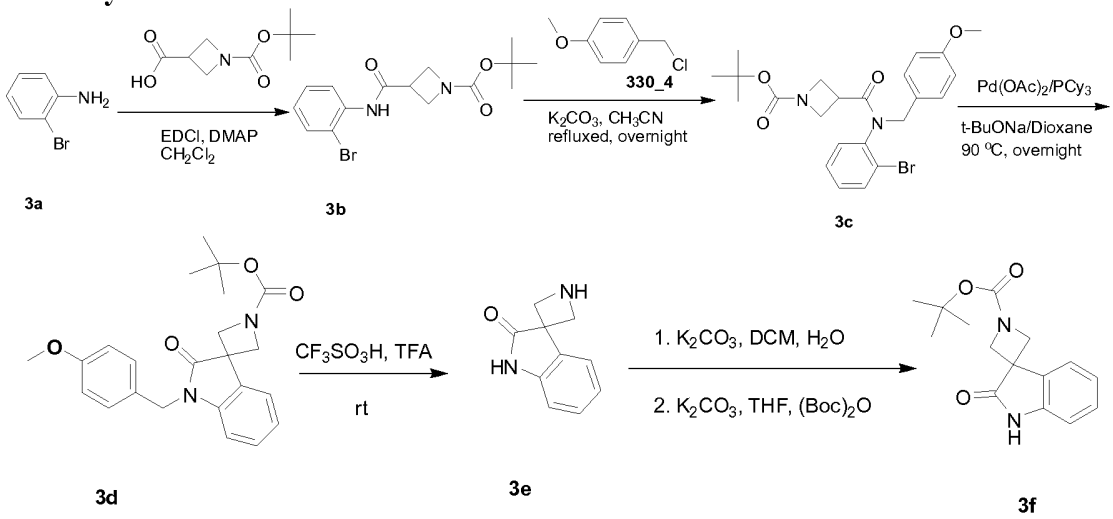
Step 2

A solution of 1'-benzylspiro[indoline-3,4'-piperidin]-2-one **2a** (5 g, 17.10 mmol, 1 eq.) in methanol (100 ml) was hydrogenated at RT with 10% Pd/C (0.18 g) as a catalyst for 15h. The catalyst was filtered off and the solvent was evaporated under vacuum. The residue was then recrystallized from DIPE/acetonitrile to give 2.7 g (78% yield) of spiro[indoline-3,4'-piperidin]-2-one **2b**.

Step 3

To a solution of spiro[indoline-3,4'-piperidin]-2-one **2b** (2.73 g, 11.42 mmol, 1 eq.) in THF (100 ml) were added Boc_2O (2.74 g, 12.57 mmol) and triethylamine (2.38 mL, 17.135 mmoles) at RT. The mixture was stirred at room temperature for 4h. The solvent was then evaporated under vacuum and the residue was treated with a mixture of water and DCM. The aqueous layer was extracted with DCM (3x) and the organic layers were combined, dried over Na_2SO_4, filtered and concentrated to give *tert*-butyl-2-oxospiro[indoline-3,4'-piperidine]-1'-carboxylate **2c** (4.02 g, quantitative yield) as a white foam. 1H NMR (400 MHz, DMSO-d6) δ ppm 1.44 (s, 9 H) 1.56 - 1.73 (m, 4 H) 3.55 - 3.79 (m, 4 H) 6.86 (dd, J=7.70, 0.40 Hz, 1 H) 6.95 (td, J=7.59, 1.10 Hz, 1 H) 7.19 (td, J=7.70, 1.10 Hz, 1 H) 7.43 (dd, J=6.80, 0.70 Hz, 1 H) 10.41 (br. s., 1 H); m/z = 303.05 $(M+H)^+$.

<u>Intermediate 3f</u> : Synthesis of *tert*-butyl 2'-oxospiro[azetidine-3,3'-indoline]-1-carboxylate



Step 1

To a stirred solution of 2-bromoaniline (150 g, 872 mmol, 1 eq.) and DMAP (138.5 g, 1133 mmol, 1.3 eq.) in CH_2Cl_2 (2500 ml) was added N-(*tert*-butoxycarbonyl)azetidine-3-carboxylic acid (CAS number: 142253-55-2, 176 g, 872 mmoles, 1 eq) in one portion followed by the addition of EDCI (217 g, 1133 mmol, 1.3 eq.) in one portion at room temperature. The resulting mixture was stirred at room temperature overnight. It was then successively washed with 10% citric acid aqueous solution, water, saturated Na_2CO_3 aqueous solution, and brine, and dried over Na_2SO_4. After filtration, the solvent was removed under vacuum to give *tert*-butyl 3-((2-bromophenyl)carbamoyl)azetidine-1-carboxylate **3b** (328 g, 85% yield).

Step 2

A mixture of *tert*-butyl 3-((2-bromophenyl)carbamoyl)azetidine-1-carboxylate **3b** (307 g, 864 mmol, 1 eq.), 4-methoxybenzylchloride (203 g, 1296 mmol, 1.5 eq.) and K_2CO_3 (358 g, 2593 mmol, 3 eq.) in CH_3CN (3000 ml) was refluxed overnight. The solution was then filtered, and the solid was washed with CH_3CN (1000 ml). The filtrate was concentrated under vacuum and the crude product was triturated in petroleum ether/ethyl acetate (30:1) to give *tert*-butyl 3-((2-bromophenyl)(4-methoxybenzyl)carbamoyl)azetidine-1-carboxylate **3c** (380 g, 90% yield).

Step 3

$Pd(OAc)_2$ (2.25 g, 10 mmol, 0.025 eq.) and PCy_3 (2.8 g, 10 mmol, 0.025 eq.) were added to the solution of *tert*-butyl 3-((2-bromophenyl)(4-methoxybenzyl)carbamoyl)azetidine-1-carboxylate **3c** (190 g, 400 mmol, 1 eq.) and *t*-BuONa (57.6 g, 600 mmol, 1.5 eq.) in dioxane (960 ml) under N_2 atmosphere. The reaction was stirred at 90 °C overnight under N_2 atmosphere. The solution was then filtered and concentrated under vacuum. The residue was dissolved in CH_2Cl_2, washed with NH_4Cl, brine and dried over Na_2SO_4. The solvent was removed under vacuum to give 158 g (quantitative yield) of *tert*-butyl 1'-(4-methoxybenzyl)-2'-oxospiro[azetidine-3,3'-indoline]-1-carboxylate **3d**.

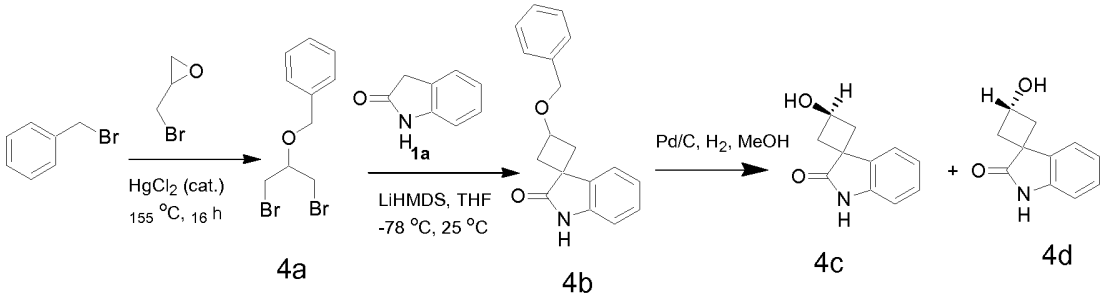
Step 4

CF_3SO_3H (119 ml, 1350 mmol, 3 eq.) was added to a mixture of *tert*-butyl 1'-(4-methoxybenzyl)-2'-oxospiro[azetidine-3,3'-indoline]-1-carboxylate **3d** (178 g, 450 mmol, 1 eq. crude) in TFA (750 ml). The mixture was stirred overnight at 25 °C. The solvent was then removed under vacuum and the residue (78.4 g) was used directly in the next step.

Step 5

A solution of spiro[azetidine-3,3'-indolin]-2'-one **3e** (78.4 g, 450 mmol, 1 eq. crude) in CH_2Cl_2 (1500 ml) was poured into a mixture of K_2CO_3 (186.6 g, 1350 mmol, 3 eq.) in ice water (1500 ml). The aqueous layer was separated and washed with CH_2Cl_2 (3*500 mL). The aqueous layer was diluted in THF (1500 ml) and $(Boc)_2O$ (98.2 g, 450 mmol, 1 eq.) was added. The solution was stirred overnight. 500 mL of a solution of ammonia in MeOH (7M) was then added dropwise to the above solution. The organic solvent was evaporated under vacuum. The aqueous solution was extracted with CH_2Cl_2 (800 ml*3), washed with brine, dried over Na_2SO_4, filtered and then concentrated under vacuum. The resulting residue was washed with t-butyl methyl ether to give the pure product *tert*-butyl 2'-oxospiro[azetidine-3,3'-indoline]-1-carboxylate **3f** (44 g, 37% yield).

<u>Intermediates 4c and 4d</u> : Synthesis of (*3S*) and (*3R*)-hydroxyspiro[cyclobutane-1,3'-indolin]-2'-one



Step 1

In a flask fitted with a condenser, a mixture consisting of benzylbromide (62.43 g, 365.03 mmol, 1eq.), 2-(bromomethyl)oxirane (50 g, 365.03 mmol, 1eq.) and $HgCl_2$ (100 mg) was heated with stirring at 155 °C during 16 hours. The product was isolated via vacuum distillation through a 30 cm Vigreux condenser (110-115, 0.5mm Hg) to provide a colorless liquid. The residue was purified by column chromatography over silica gel (eluent: dichloromethane) to give 65 g of (((1,3-dibromopropan-2-yl)oxy)methyl)benzene **4a**.

Step 2

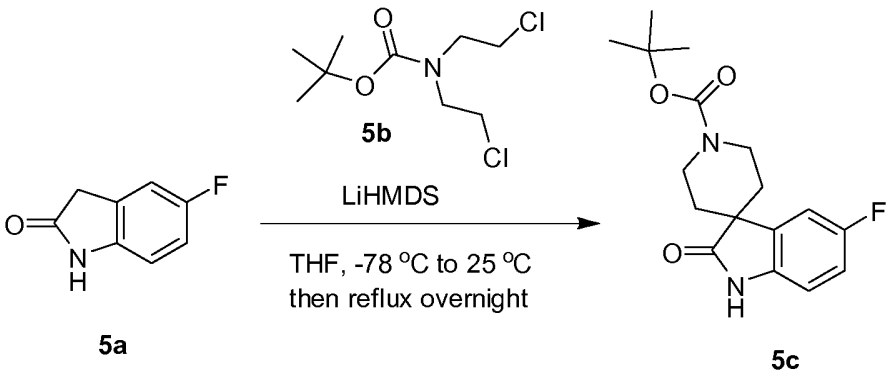
Oxindole **1a** (20 g, 150.210 mmol, 1 eq.) was dissolved in THF (400 ml) and HMPA (40 ml). The reaction mixture was cooled to -78°C, then *n*-BuLi (132.185 ml, 330.462 mmol, 2.2 eq.) was added. The reaction mixture was stirred at -78°C for 1 hour. Then (((1,3-dibromopropan-2-yl)oxy)methyl)benzene **4a** (46.27 g, 150.210 mmol, 1 eq.) was added. The mixture was successively stirred at room temperature for 14 hours, quenched with water and extracted with dichloromethane. The residue was purified by column chromatography over silica gel (eluent: petrolumn ether: ethyl acetate 10:1). The product fractions were collected and the solvent was evaporated to give 15 g of the desired product 3-(benzyloxy)spiro[cyclobutane-1,3'-indolin]-2'-one **4b**.

Step 3

A mixture of 3-(benzyloxy)spiro[cyclobutane-1,3'-indolin]-2'-one **4b** (15 g, 53.699 mmol, 1eq) and Pd/C (1.5 g) in methanol (150 ml) was hydrogenated under a 30 psi pressure for 15 hours. The reaction mixture was filtered on a celite pad which was washed several times with CH_3OH. The combined filtrates were evaporated till dryness. The residue was purified by column chromatography over silica gel (eluent: petroleum ether: ethyl acetate=3: 1) to provide the racemic mixture of (3)-hydroxyspiro[cyclobutane-1,3'-indolin]-2'-one, whose enantiomers **4c** and **4d** were

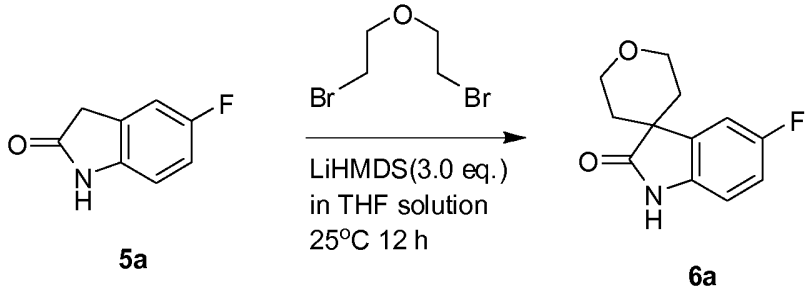
separated by high performance liquid chromatography (HPLC condition: Column: SYNERGI 250*50 10um, Flow rate: 80 ml/min, Mobile Phase A: Purified water (containing 0.075%TFA), Mobile Phase B: Acetonitrile, Gradient: 5-30 %(%B)). The desired fractions were collected, evaporated to remove off CH_3CN in vacuum and made alkaline with a saturated $NaHCO_3$ solution. The aqueous solution was extracted with CH_2Cl_2. The organic layers were dried, filtered and the solvent was evaporated to give 4.59 g of (*3S*)-hydroxyspiro[cyclobutane-1,3'-indolin]-2'-one **4c** and 0.89 g of (*3R*)-hydroxyspiro[cyclobutane-1,3'-indolin]-2'-one **4d**.

<u>Intermediate 5c</u> : Synthesis of *tert*-butyl 5-fluoro-2-oxospiro[indoline-3,4'-piperidine]-1'-carboxylate



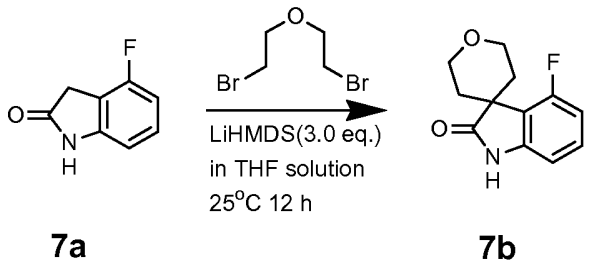
5-fluoroindolin-2-one **5a** (35 g, 231.576 mmol, 1 eq.) was added to a solution of LiHMDS (700 ml, 700 mmol, 3 eq) at -78°C. The mixture was stirred 1 hour at -78°C, then *tert*-butyl bis(2-chloroethyl)carbamate **5b** (56.075 g, 231.576 mmol,1eq) was added, maintaining the internal temperature <-50°C. The reaction was then warmed to ambient temperature during 2 hours, and the reaction was refluxed overnight. The mixture was quenched with H_2O and the mixture was partitioned between EtOAc and H_2O.The aqueous solution was extracted with EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuum. The resulting residue was purified by high performance liquid chromatography (HPLC condition: Column: Synergi-10μm, 250×50mmI.D, Flow rate: 80 ml/min, Mobile Phase A: Purified water (containing 0.1%TFA), Mobile Phase B: Acetonitrile, Gradient: 35-65 %(%B)) to give 5.003 g (7% yield) of *tert*-butyl 5-fluoro-2-oxospiro[indoline-3,4'-piperidine]-1'-carboxylate **5c**.

<u>Intermediate 6a</u> : Synthesis of 5-fluoro-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one



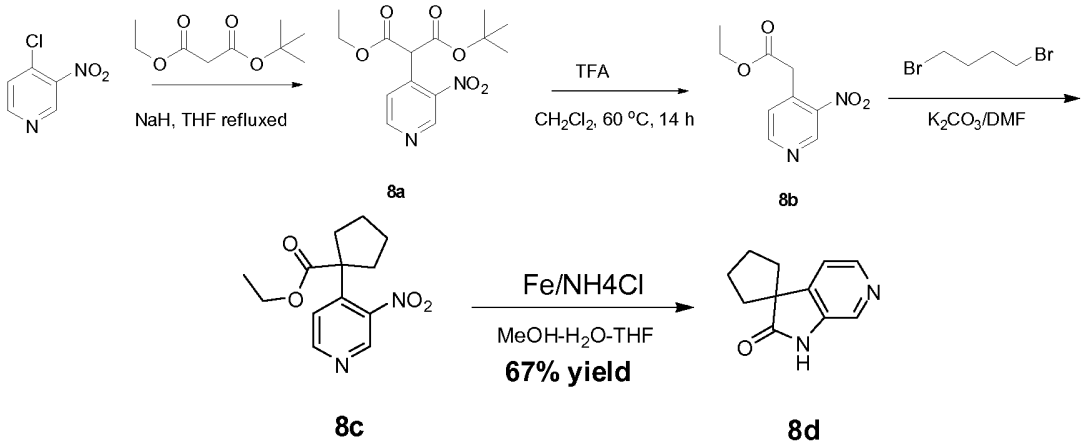
5-fluoroindolin-2-one **5a** (30 g, 198.49 mmol, 1.0 eq.) was added to LiHMDS (1M in THF, 595.48 ml, 595.48 mmol, 3.0 eq.) at -78°C. The mixture was stirred at -78°C for 10 minutes and warmed to 0°C. The mixture was stirred at 0°C for 30 minutes, then bis(2-bromomethyl)ether (CAS number: 5414-19-7, 46.03 g, 198.49 mmol, 1.0 eq.) was added. The mixture was stirred at room temperature overnight. Water (300 ml) was added to the reaction mixture. The resulting precipitate was filtered off and washed with water to give 5-fluoro-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one **6a** (12 g, 13% yield).

<u>Intermediate 7b</u> : Synthesis of 4-fluoro-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one



4-fluoroindolin-2-one **7a** (9.5 g, 62.856 mmol, 1.0 eq.) was added to LiHMDS (1M in THF, 188.568 ml, 188.568 mmol, 3.0 eq.) at -78°C. The mixture was stirred at -78 °C for 10 minutes and warmed to 0°C. The mixture was stirred at 0 °C for 30 minutes, then bis(2-bromomethyl)ether (14.577 g, 62.856 mmol, 1.0 eq.) was added. The mixture was stirred at room temperature overnight. Water (300 ml) was added to the reaction mixture. The resulting solid was filtered off and washed with water to give 4-fluoro-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one **7b** (1.61 g, 12% yield).

<u>Intermediate 8d</u> : Synthesis of spiro[cyclopentane-1,3'-pyrrolo[2,3-c]pyridin]-2'(1'*H*)-one



Step 1

To a solution of *tert*-butyl ethyl malonate (160 g, 850 mmol) in THF (1600 ml) was added NaH (80 g, 2118 mmol) portionwise at 0°C. The mixture was stirred for 1h at 15 °C, then 4-chloro-3-nitropyridine (112 g, 706 mmol) was added portionwise at 0 °C. The mixture was stirred for 1 h at 15 °C. The reaction was quenched with water and 1N HCl was added until pH=5. The mixture was extracted with ethyl acetate twice. The organic layers were washed with brine, dried and evaporated under vacuum to give 1-(*tert*-butyl) 3-ethyl 2-(3-nitropyridin-4-yl)malonate **8a** (250 g), which was used without further purification in the next step.

Step 2

To a solution of 1-(*tert*-butyl) 3-ethyl 2-(3-nitropyridin-4-yl)malonate **8a** (crude, 250 g, 706 mmol) in CH_2Cl_2 (1500 ml) was added TFA (250 mL). After 14h of stirring at 60°C, the mixture was evaporated. A 10% $NaHCO_3$ aqueous solution was then added and the mixture was extracted with ethyl acetate twice. The organic layers were washed with brine, dried and evaporated under vacuum to give ethyl 2-(3-nitropyridin-4-yl)acetate **8b** (180 g), which was used without further purification in the next step.

Step 3

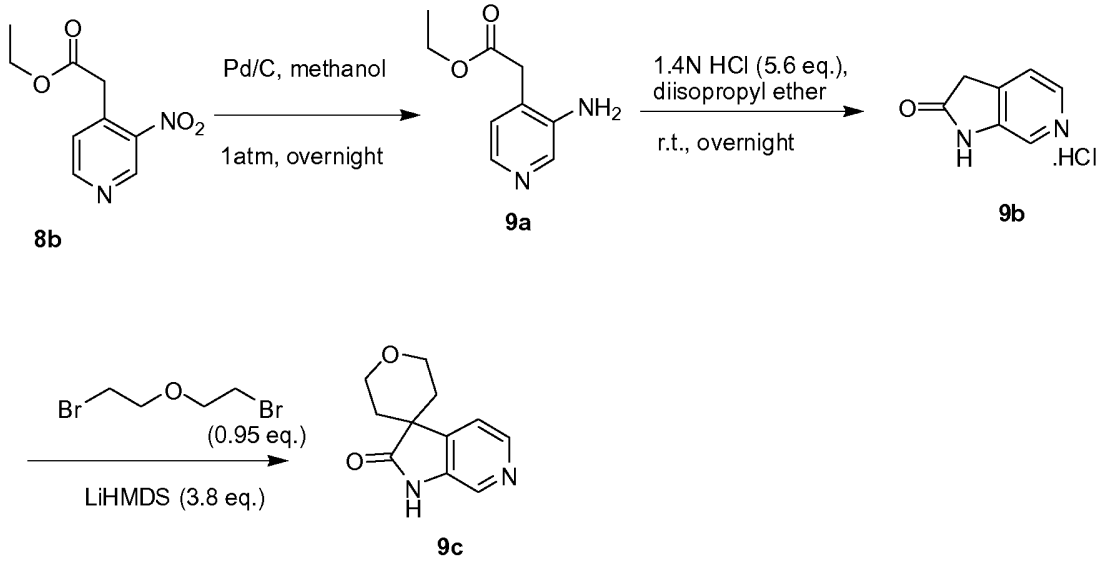
Ethyl 2-(3-nitropyridin-4-yl)acetate **8b** (50 g, 238 mmol), 1,4-dibromobutane (50 g, 238 mmol), K_2CO_3 (100 g, 714 mmol) and 4A molecular sieve (50 g) in DMF (500 ml) were stirred for 14 h at 80°C. 1N HCl was then added and the mixture was extracted with CH_2Cl_2 twice. The organic layers were washed with a 10% $NaHCO_3$ aqueous solution (2x), brine (2x), dried and evaporated under vacuum. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/ethyl acetate = 10/1) to give

8.4 g (15% yield in total for the three steps) of ethyl 1-(3-nitropyridin-4-yl)cyclopentane-1-carboxylate **8c**.

Step 4

Ethyl 1-(3-nitropyridin-4-yl)cyclopentane-1-carboxylate **8c** (8.4 g, 31.8 mmol), Fe (7 g, 127 mmol) and NH_4Cl (7g, 127 mmol) in CH_3OH (80 ml), THF (80 ml) and H_2O (80 ml) were stirred and refluxed for 3 h. The mixture was then filtered off and the solvent was evaporated under vacuum. A 10% $NaHCO_3$ aqueous solution was added and the mixture was extracted with ethyl acetate (3x). The combined organic layers were washed with brine, dried and evaporated under vacuum. The residue was washed with CH_3CN (2x) and the solid was collected and dried to give 4 g (67% yield) of spiro[cyclopentane-1,3'-pyrrolo[2,3-c]pyridin]-2'(1'H)-one **8d**.

<u>Intermediate 9c</u> Synthesis of 2,3,5,6-tetrahydrospiro[pyran-4,3'-pyrrolo[2,3-c]-pyridin]-2'(1'*H*)-one



Step 1: synthesis of ethyl 2-(3-aminopyridin-4-yl)acetate (intermediate 9a)

A mixture of ethyl 2-(3-nitropyridin-4-yl)acetate **8b** (65 g, 309mmol, 90% purity, 1 eq.) in methanol (1500 ml) was hydrogenated at 20°C (atmospheric pressure) with 10% Pd/C (6.5 g) as a catalyst for 16h. After uptake of H_2 (3 equiv), the catalyst was filtered off and the filtrate was evaporated under vacuum to give 50 g (Yield: 90%) of ethyl 2-(3-aminopyridin-4-yl)acetate **9a**, which was used without further purification in the next step.

Step 2: synthesis of 1,3-dihydro-2*H*-pyrrolo[2,3-c]pyridin-2-one (intermediate 9b)

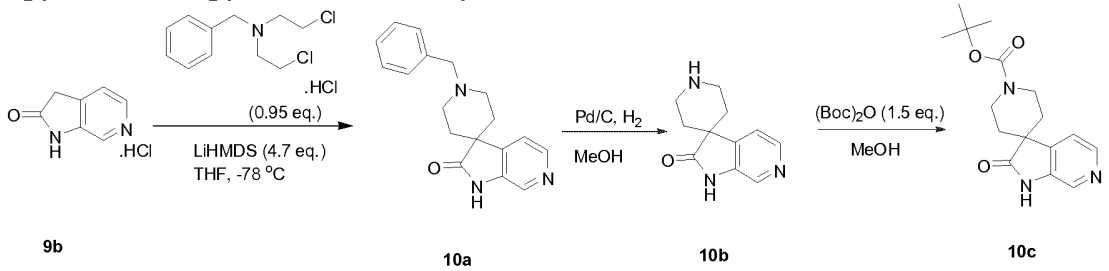
Ethyl 2-(3-aminopyridin-4-yl)acetate **9a** (34 g, 189 mmol, 1 eq.) was dissolved in 1.4 N HCl (1000 ml) and diisopropyl ether (1000 ml). The mixture was stirred at room temperature overnight. The separated organic layer was separated and washed with

H_2O. The combined aqueous layers were washed with CH_2Cl_2 and evaporated to almost dryness. The resulting precipitate was filtered off and dried (vacuum, 60 °C, 2 hours) to give 26 g (Yield: 94%) of 1,3-dihydro-2H-pyrrolo[2,3-c]pyridin-2-one **9b** as a hydrochloric acid salt.

Step 3: synthesis of 2,3,5,6-tetrahydrospiro[pyran-4,3'-pyrrolo[2,3-c]pyridin]-2'(1'*H*)-one (intermediate 9c)

1,3-dihydro-2H-pyrrolo[2,3-c]pyridin-2-one **9b** (12 g, 70.34 mmol, 1.05 eq.) was added to 1M LiHMDS solution in THF (281 ml, 281mmol, 4 eq.) at -78°C. The mixture was stirred at -78°C for 10 min. and warmed to 0°C naturally. After stirring at 0°C for 0.5h, 1-bromo-2-(2-bromoethoxy)ethane (15.54 g, 66.99 mmol, 1 eq.) was added. The mixture was warmed to 20°C and stirred at 20°C for 0.5h, then refluxed overnight. After cooling down to room temperature, the reaction mixture was successively quenched with a 10% NH_4Cl solution (300 ml) and extracted with ethyl acetate (2*300 ml). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and the solvent was evaporated under vacuum. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2: methanol from 1:0 to 20:1) to give 1.735 g (12% yield) of 2,3,5,6-tetrahydrospiro[pyran-4,3'-pyrrolo[2,3-c]pyridin]-2'(1'H)-one **9c**.

<u>Intermediate 10c</u> Synthesis of *tert*-butyl 2'-oxo-1',2'-dihydrospiro[piperidine-4,3'-pyrrolo[2,3-c]pyridine]-1-carboxylate



Step 1: synthesis of 1-benzylspiro[piperidine-4,3'-pyrrolo[2,3-c]pyridin]-2'(1'*H*)-one (intermediate 10a)

The hydrochloric acid salt 1,3-dihydro-2H-pyrrolo[2,3-c]pyridin-2-one **9b** (160 g, 938 mmol, 1 eq.) was added to 1M LiHMDS solution in THF (3751 ml, 3751mmol, 4 eq.) at -78°C. After warming up to 0°C, *N*-benzyl-2-chloro-*N*-(2-chloroethyl)ethan-1-amine hydrochloride (218 g, 938 mmol, 1 eq.) was added. The mixture was warmed to 20°C, then refluxed overnight. After cooling down to room temperature, the reaction mixture was successively quenched with a 10% NH_4Cl solution (300 ml) and extracted with ethyl acetate (2*300 ml). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and the solvent was evaporated under vacuum. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2: methanol from 1:0

to 10:1) to give 70 g (23% yield) of 1-benzylspiro[piperidine-4,3'-pyrrolo[2,3-c]pyridin]-2'(1'H)-one **10a**.

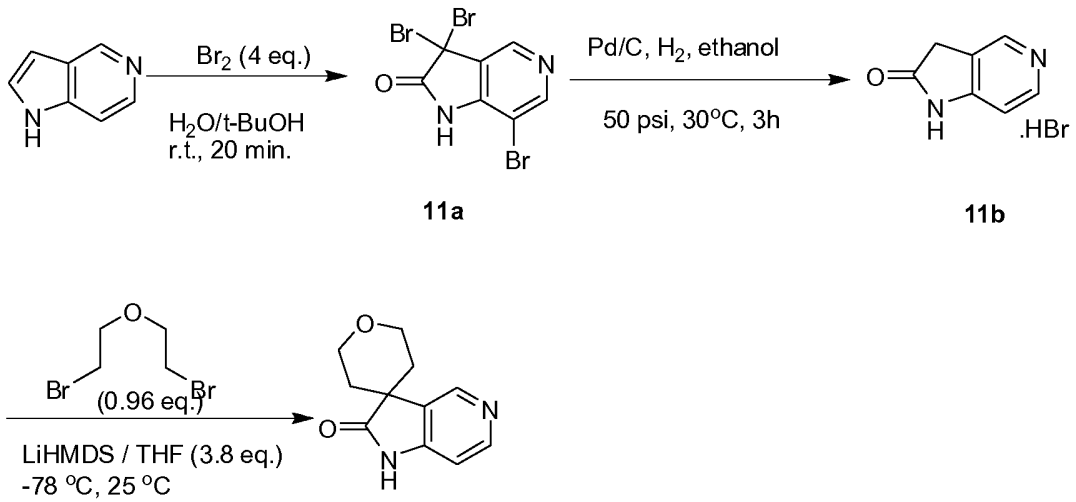
Step 2: synthesis of spiro[piperidine-4,3'-pyrrolo[2,3-c]pyridin]-2'(1'*H*)-one (intermediate 10b)

A mixture of 1-benzylspiro[piperidine-4,3'-pyrrolo[2,3-c]pyridin]-2'(1'H)-one **10a** (70 g, 238.61 mmol, 1 eq.) in methanol (1000 ml) was hydrogenated at 50 °C (50 psi) with 10% Pd/C (50 g) as a catalyst for 15h. The catalyst was filtered off and the solvent was evaporated under vacuum. The residue was purified by flash column chromatography over silica gel (eluent: CH_2Cl_2/ethyl acetate from 1/0 to 0/1) to give 50 g (93% yield) of spiro[piperidine-4,3'-pyrrolo[2,3-c]pyridin]-2'(1'H)-one **10b**.

Step 3: synthesis of *tert*-butyl 2'-oxo-1',2'-dihydrospiro[piperidine-4,3'-pyrrolo[2,3-c]pyridine]-1-carboxylate (intermediate 10c)

To a solution of spiro[piperidine-4,3'-pyrrolo[2,3-c]pyridin]-2'(1'H)-one **10b** (50 g, 246.05 mmol, 1 eq.) in MeOH (1000 ml) was added Boc_2O (64.43 g, 295.22 mmol, 1.2 eq.). The mixture was stirred at room temperature overnight, then evaporated till dryness. The residue was purified by column chromatography over silica gel (eluent: dichloromethane: ethyl acetate from 1:0 to 0:1) to give 43.32 g (58% yield) of *tert*-butyl 2'-$_{oxo}$-1',2'-dihydrospiro[piperidine-4,3'-pyrrolo[2,3-c]pyridine]-1-carboxylate **10c**.

<u>Intermediate 11c</u> Synthesis of 2,3,5,6-tetrahydrospiro[pyran-4,3'-pyrrolo[3,2-c]pyridin]-2'(1'*H*)-one



Step 1: synthesis of 3,3,7-tribromo-1,3-dihydro-2*H*-pyrrolo[3,2-c]pyridin-2-one (intermediate 11a)

Br_2 (26ml, 507mmol, 4eq.) was added dropwise to a solution of 1H-pyrrolo[3,2-c]pyridine (15g, 127mmol, 1eq.) in H_2O (500ml) and *t*-BuOH (500ml) at room temperature over a period of 20 min. Following addition of Br_2, the pH of the mixture was approximately 1. Saturated $NaHCO_3$ solution (800 ml) was added slowly and carefully over 30 min, and the pH of the mixture was adjusted to 6.5-7. The mixture was stirred for 1 h, then filtered off. The resulting solid was further washed with water and co-evaporated with ethanol to give 28.5 g (61% yield) of 3,3,7-tribromo-1,3-dihydro-2H-pyrrolo[3,2-c]pyridin-2-one **11a**.

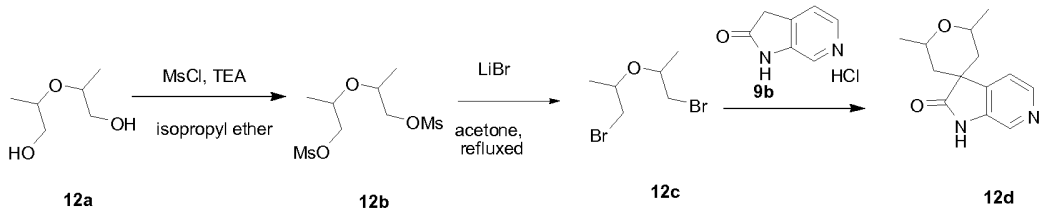
Step 2: synthesis of 1,3-dihydro-2*H*-pyrrolo[3,2-c]pyridin-2-one hydrobromide (intermediate 11b)

The reaction was carried out in three parallel reactors. A mixture of 3,3,7-tribromo-1,3-dihydro-2H-pyrrolo[3,2-c]pyridin-2-one **11a (**28.5g, 76.9mmol, 1 eq.) in ethanol (2850ml) was hydrogenated at 30°C (50 psi) with Pd/C (14g) as a catalyst for 3 h. After uptake of H_2 (3 eq.), the catalyst was filtered off and the filtrate was evaporated under vacuum to give 14 g (85% yield) of 1,3-dihydro-2H-pyrrolo[3,2-c]pyridin-2-one hydrobromide **11b**.

Step 3: synthesis of 2,3,5,6-tetrahydrospiro[pyran-4,3'-pyrrolo[3,2-c]pyridin]-2'(1'*H*)-one (intermediate 11c)

1,3-dihydro-2H-pyrrolo[3,2-c]pyridin-2-one hydrobromide **11b** (11.7g, 54.4 mmol, 1.04 eq.) was added to 1M LiHMDS solution in THF (210 ml, 210mmol, 4 eq.) at -78°C. The mixture was stirred at -78°C for 10 min and warmed to 0°C naturally. After stirring at 0°C for 0.5 h, 1-bromo-2-(2-bromoethoxy)ethane (12.1g, 52.2 mmol, 1 eq.) was added. The mixture was warmed to 20°C, then refluxed overnight. The mixture was then cooled to room temperature, quenched with a saturated NH_4Cl solution (200 ml), filtered over a celite pad and the filtrate was extracted with ethyl acetate (2*200 ml). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and the solvent was evaporated under vacuum. The residue was dissolved in CH_2Cl_2: methanol (5:1) and purified by column chromatography over silica gel (eluent: CH_2Cl_2: methanol from 1:0 to 10:1) to give a residue which was further washed with CH_3CN to give 812 mg (7% yield) of 2,3,5,6-tetrahydrospiro[pyran-4,3'-pyrrolo[3,2-c]pyridin]-2'(1'H)-one **11c**.

<u>Intermediate 12d</u> Synthesis of 2,6-dimethyl-2,3,5,6-tetrahydrospiro[pyran-4,3'-pyrrolo[2,3-c]pyridin]-2'(1'*H*)-one



Step 1: synthesis of oxybis(propane-2,1-diyl) dimethanesulfonate (intermediate 12b)

2,2'-oxybis(propan-1-ol) **12a** (obtained from the reduction of diethyl 2,2'-oxydipropionate with $LiAlH_4$ as described in Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999), (3), 245-50; 1975) was mesylated using mesylchloride and triethylamine in isopropylether, to give oxybis(propane-2,1-diyl) dimethanesulfonate **12b**. Diethyl 2,2'-oxydipropionate was obtained following the procedure reported in Supramolecular Chemistry, 22(11 & 12), 827-837; 2010, by mixing the commercially available ethyl 2-hydroxypropanoate and ethyl 2-bromopropanoate in the presence of NaH in THF.

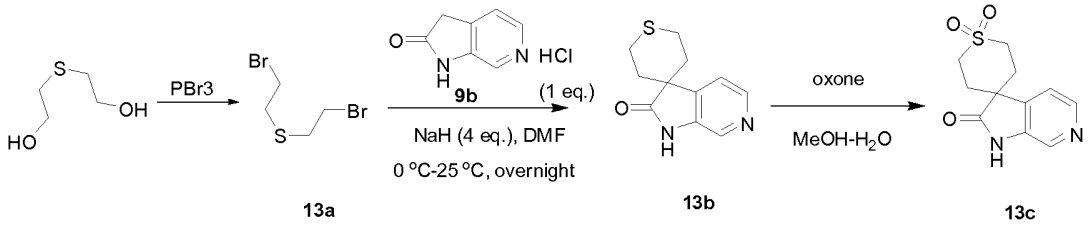
Step 2: synthesis of 1-bromo-2-((1-bromopropan-2-yl)oxy)propane (intermediate 12c)

To a solution of oxybis(propane-2,1-diyl)dimethanesulfonate **12b** in acetone was added LiBr and the reaction mixture was stirred under reflux until completion, to give 1-bromo-2-((1-bromopropan-2-yl)oxy)propane **12c**.

Step 3: synthesis of 2,6-dimethyl-2,3,5,6-tetrahydrospiro[pyran-4,3'-pyrrolo[2,3-c]pyridin]-2'(1'*H*)-one (intermediate 12d)

2,6-dimethyl-2,3,5,6-tetrahydrospiro[pyran-4,3'-pyrrolo[2,3-c]pyridin]-2'(1'H)-one **12d** was synthetized following the protocol used for the synthesis of 2,3,5,6-tetrahydro-spiro[pyran-4,3'-pyrrolo[2,3-c]pyridin]-2'(1'H)-one **9c**, using 1-bromo-2-((1-bromopropan-2-yl)oxy)propane **12c** instead of 1-bromo-2-(2-bromoethoxy)ethane, and NaH in DMF instead of LiHMDS.

<u>Intermediate 13c</u> Synthesis of 2',3',5',6'-tetrahydrospiro[pyrrolo[2,3-c]pyridine-3,4'-thiopyran]-2(1*H*)-one 1',1'-dioxide



Step 1: synthesis of bis(2-bromoethyl)sulfane (intermediate 13a)

To a solution of 2,2'-thiodiethanol (5g, 40.9 mmoles) in dry THF was added phosphorous tribromide (7.75 g, 0.7 eq.) at -15°C, under N_2. After stirring for 30 minutes at -15°C, the reaction mixture was allowed to warm up and stirred for 12 hours at room temperature. It was then diluted with a $NaHCO_3$ aq. solution at 0°C. The organic layer was separated, concentrated and purified by column chromatography over silica gel (eluent: petroleum ether / ethyl acetate = 10/1, v/v) to give 2.5 g (22% yield) of bis(2-bromoethyl)sulfane **13a**.

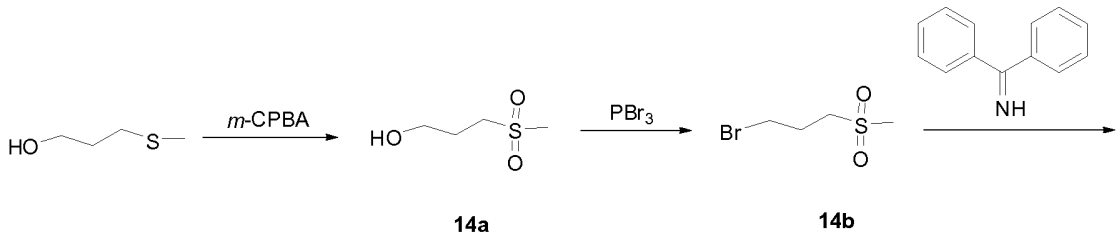
Step 2: synthesis of 2',3',5',6'-tetrahydrospiro[pyrrolo[2,3-c]pyridine-3,4'-thiopyran]-2(1H)-one (intermediate 13b)

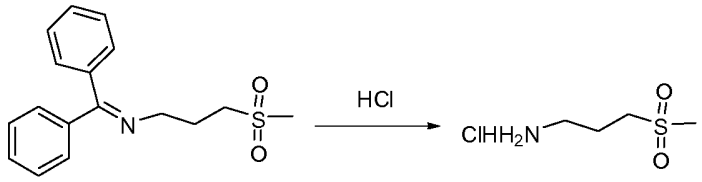
2',3',5',6'-tetrahydrospiro[pyrrolo[2,3-c]pyridine-3,4'-thiopyran]-2(1H)-one **13b** was synthetized following the protocol used for the synthesis of 2,3,5,6-tetrahydrospiro[pyran-4,3'-pyrrolo[2,3-c]pyridin]-2'(1'H)-one **9c**, using bis(2-bromoethyl)sulfane **13a** instead of 1-bromo-2-(2-bromoethoxy)ethane, and NaH (4 eq.) in DMF at 0°C instead of LiHMDS.

Step 3: synthesis of 2',3',5',6'-tetrahydrospiro[pyrrolo[2,3-c]pyridine-3,4'-thiopyran]-2(1H)-one (intermediate 13c)

A solution of 2',3',5',6'-tetrahydrospiro[pyrrolo[2,3-c]pyridine-3,4'-thiopyran]-2(1H)-one **13b** in $MeOH/H_2O$ was oxidized with oxone to give 2',3',5',6'-tetrahydrospiro[pyrrolo[2,3-c]pyridine-3,4'-thiopyran]-2(1H)-one **13c**.

<u>Intermediate 14d</u> Synthesis of 3-(methylsulfonyl)propan-1-amine hydrochloride





Step 1: synthesis of 3-(methylsulfonyl)propan-1-ol (intermediate 14a)
3-(methylthio)propan-1-ol (200 g, 1900 mmol, CAS 505-10-2) was dissolved in CH_2Cl_2 (2000 mL). The mixture was cooled to 0°C, then *m*-CPBA 85% in water (970 g, 5700 mmol, CAS 937-14-4) was added portion wise keeping the temperature between 0 and 5°C. After addition, the mixture was allowed to warm to 25°C and stirred for 15 h. The mixture was filtered through a celite pad and the filtrate was purified by flash column (Eluent: petroleum ether: ethyl acetate = 3:1 and then ethyl acetate: methanol = 10:1) to yield the intermediate **14a** (75 g, 29%).

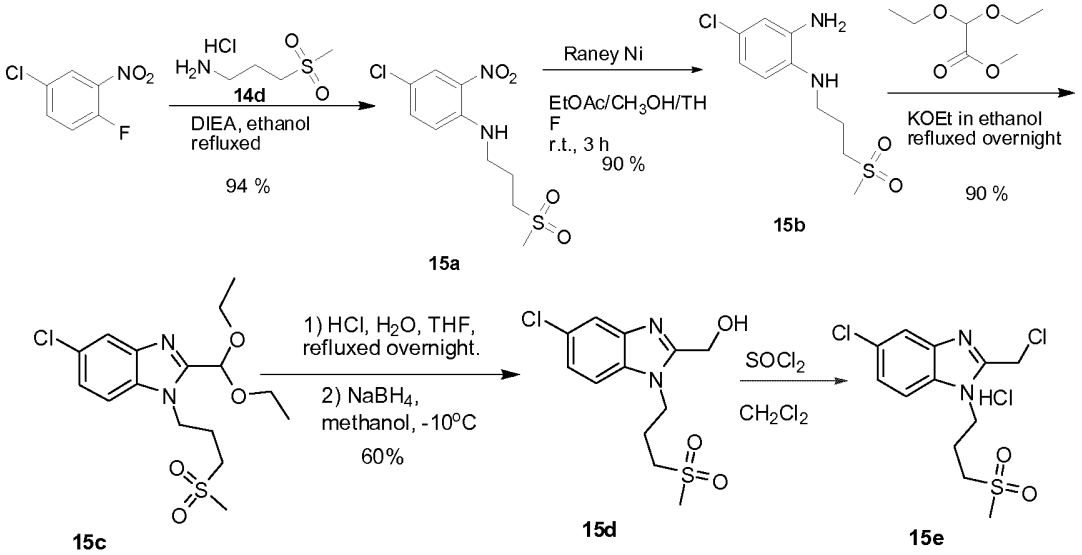
Step 2: synthesis of 1-bromo-3-(methylsulfonyl)propane (intermediate 14b)
To a solution of the intermediate **14a** (75 g, 543 mmol) in CH_2Cl_2 (750 mL), at 0°C, was added dropwise phosphorus tribromide (53.6 mL, 570 mmol), keeping the temperature between 0 and 5°C. After addition, the mixture was allowed to warm to 25°C and stirred for 15 h. The mixture was poured into ice-water, the organic layer was then separated, washed with brine (2 x 500 mL), dried over Na_2SO_4, filtered and evaporated under vacuum to yield the title compound **14b** (77 g, 71%). ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.25 – 2.40 (m, 2 H) 2.91 (s, 3 H) 3.1-3.2 (m, 2H) 3.5-3.6 (m, 2H).

Step 3: synthesis of *N*-(diphenylmethylene)-3-(methylsulfonyl)propan-amines (intermediate 14c)
To a solution of the intermediate **14b** (27 g, 134 mmol) in CH_3CN (60 mL) were added diphenylmethanimine (27 g, 148 mmol) and DIEA (19.6 g, 152 mmol). The mixture was refluxed for 4 h and then cooled to room temperature. The mixture was then neutralized with 50% aqueous acetic acid at 25°C. Water (80 mL) was added and the mixture was extracted with ethyl acetate (2 X 300 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated under vacuum. The residue was washed with petroleum ether (4 X 100 mL). The mixture was treated with methyl *tert*-butyl ether. The solid was collected and washed with petroleum ether. The filtrate was dried under vacuum and the resulting residue was purified by column chromatography (Eluent: CH_2Cl_2: ethyl acetate from 1:0 to 10:1) to give the title compound **14c** (34 g, 85%) as a white solid.

Step 4: synthesis of 3-(methylsulfonyl)propan-1-amine hydrochloride (intermediate 14d)

To a solution of the intermediate **14c** (34 g, 113 mmol) in dioxane (600 mL) was added a solution of 4N HCl/dioxane (120 mL, 480 mmol) dropwise at 0°C. After addition, the mixture was allowed to warm to 25°C and stirred for 15 h. The mixture was filtered. The solid was collected and washed with dioxane to give the title product **14d** (11.5 g, 50%) as a yellow powder.

<u>Intermediate 15e</u> Synthesis of 5-chloro-2-(chloromethyl)-1-(3-(methylsulfonyl)-propyl)-1*H*-benzo[d]imidazole hydrochloride



Step 1: Synthesis of 4-chloro-*N*-(3-(methylsulfonyl)propyl)-2-nitroaniline

A solution of 1-chloro-4-chloro-3-nitrobenzene (7.6 g, 35 mmol), 3-(methylsulfonyl)-propan-1-amine hydrochloride **14d** (6 g, 35 mmol) and diisopropylethylamine (DIEA) (13.5 g, 105 mmol) in ethanol (70 mL) was refluxed for 14 h. The mixture was then cooled to 20°C and the resulting precipitate was filtered and washed with ethanol. 11 g (94%) of intermediate **15a** was obtained as an orange powder.

Step 2: Synthesis of 4-chloro-*N*1-(3-(methylsulfonyl)propyl)benzene-1,2-diamine

Intermediate **15a** (10 g, 29.7 mmol) in methanol (200 mL), EtOAc (200 mL) and THF (200 mL) was hydrogenated with Raney Ni (10 g) as a catalyst at 20°C (1 atm) for 3h. After uptake of H_2 (3 eq), the catalyst was filtered off and the filtrate was evaporated. 10 g (90%) of intermediate **15b** was obtained as a black solid.

Step 3: Synthesis of 5-chloro-2-(diethoxymethyl)-1-(3-(methylsulfonyl)propyl)-1*H*-benzo[d]imidazole

Intermediate **15b** (10 g, 29.7 mmol) and methyl dimethoxyacetate (9.2 g, 68.31 mmol) in 24 wt% KOEt in ethanol (13.5 g, 38.5 mmol) were stirred and refluxed overnight. The mixture was evaporated under vacuum. Water (200 mL) was then added, followed by acetic acid to neutralize the mixture. The mixture was extracted with ethyl acetate (2x100 mL). The combined organic layers were washed with saturated $NaHCO_3$, brine and dried over Na_2SO_4. The solvent was removed under vacuum to yield 12.3 g (90%) of intermediate **15c** as a dark oil.

Step 4: Synthesis of (5-chloro-1-(3-(methylsulfonyl)propyl)-1*H*-benzo[d]imidazol-2-yl)methanol

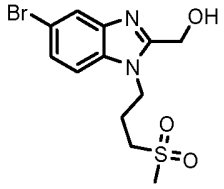
Intermediate **15c** (12.3 g, 29.3 mmol) in THF (100 mL) was stirred for 0.5 h at 20°C until complete dissolution. Conc. HCl (21 mL) and H_2O (42 mL) were then added. The mixture was refluxed for 6 h and then cooled to -10°C. CH_3OH (50 mL) were added, followed by careful addition of $NaBH_4$ (24 g, 629 mmol). The mixture was stirred for 0.5 h at 10°C and concentrated under vacuum. Water (200 mL) was added. The mixture was extracted with ethyl acetate (2x100 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under vacuum. The resulting solid was washed with ethyl acetate (2x5 mL) and dried under vacuum. 6.8 g (60%) of intermediate **15d** was obtained as an off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.20 (dq, *J*=7.8, 7.5 Hz, 2 H), 2.98 (s, 3 H), 3.16 - 3.24 (m, 2 H), 4.42 (t, *J*=7.4 Hz, 2 H), 4.73 (d, *J*=6.0 Hz, 2 H), 5.73 (t, *J*=5.8 Hz, 1 H), 7.42 (dd, *J*=8.7, 1.9 Hz, 1 H), 7.63 (d, *J*=8.5 Hz, 1 H), 7.79 - 7.83 (m, 1 H).

Step 5

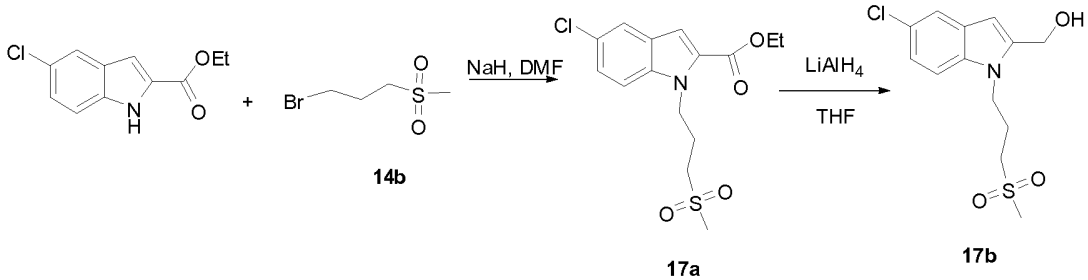
To a solution of alcohol **15d** (363 mg, 1.414 mmole) in 30 mL of dichloromethane was added dropwise a solution of thionyl chloride (336 mg, 2 eq) in 10 mL of dichloromethane. The reaction mixture was stirred for one hour at 45°C. It was then concentrated under vacuum to give the desired intermediate **15e** (440 mg, 99%) as an HCl salt, which was used as such in the next step.

<u>Intermediate 16a</u> Synthesis of (5-bromo-1-(3-(methylsulfonyl)propyl)-1*H*-benzo[d]imidazol-2-yl)methanol



(5-bromo-1-(3-(methylsulfonyl)propyl)-1H-benzo[d]imidazol-2-yl)methanol **16a** was synthetized following the chemical pathway used for the synthesis of (5-chloro-1-(3-(methylsulfonyl)propyl)-1H-benzo[d]imidazol-2-yl)methanol **15d**, using 1-bromo-4-fluoro-3-nitrobenzene (7.6 g, 35 mmol) instead of 1-chloro-4-fluoro-3-nitrobenzene in the first step. 6.8 g of the desired product **16a** were obtained as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.20 (dq, *J*=7.8, 7.5 Hz, 2 H), 2.98 (s, 3 H), 3.16 - 3.24 (m, 2 H), 4.42 (t, *J*=7.4 Hz, 2 H), 4.73 (d, *J*=6.0 Hz, 2 H), 5.73 (t, *J*=5.8 Hz, 1 H), 7.42 (dd, *J*=8.7, 1.9 Hz, 1 H), 7.63 (d, *J*=8.5 Hz, 1 H), 7.79 - 7.83 (m, 1 H); m/z = 347 & 349 (M+H)+Br pattern.

<u>Intermediate 17b</u> Synthesis of (5-chloro-1-(3-(methylsulfonyl)propyl)-1*H*-indol-2-yl)methanol



Step 1: synthesis of ethyl 5-chloro-1-(3-(methylsulfonyl)propyl)-1*H*-indole-2-carboxylate (intermediate 17a)

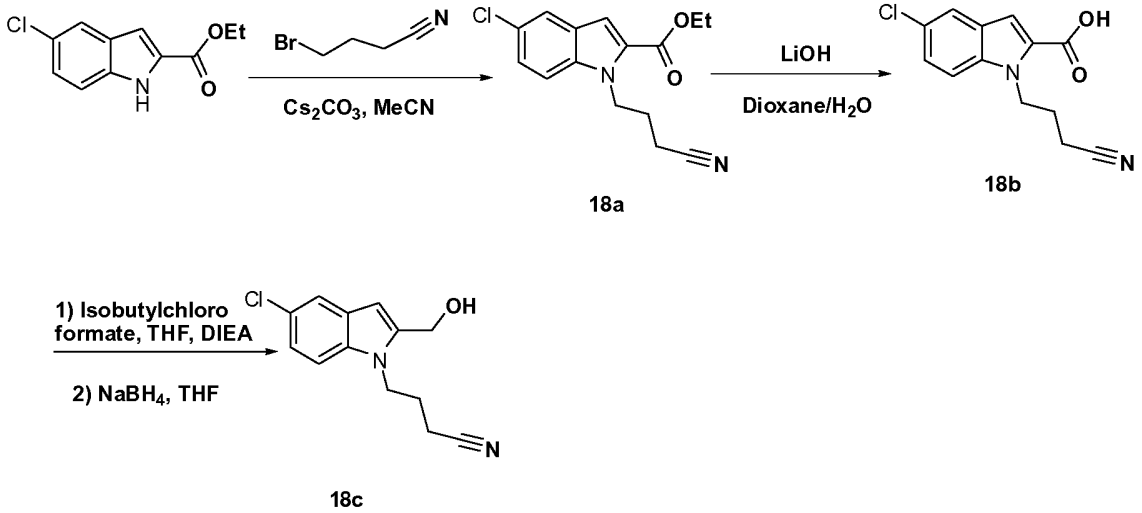
Ethyl 5-bromo-1*H*-indole-2-carboxylate (2.3 g, 8.6 mmol) was dissolved in DMF (50 mL). The mixture was stirred at room temperature, then sodium hydride 60% suspension in mineral oil (0.52 g, 12.8 mmol) was added. The resulting mixture was stirred at room temperature for 1 hour, then 1-bromo-3-(methylsulfonyl)propane **14b** (2.6 g, 12.8 mmol) was added. The resulting mixture was stirred at room temperature overnight. The mixture was poured in ice/water solution and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated to yield a brown crude oil. The crude was purified by column chromatography using dichloro-methane/methanol to yield the title compound ethyl 5-chloro-1-(3-

(methylsulfonyl)propyl)-1*H*-indole-2-carboxylate **17a** (3.2 g, 96%) as a white solid. *m/z* = 344 $(M+H)^+$.

Step 2: synthesis of (5-chloro-1-(3-(methylsulfonyl)propyl)-1*H*-indol-2-yl)methanol (intermediate 17b)

To a solution of intermediate **17a** (3.2 g, 8.24 mmol) in THF (100 mL) was added at room temperature lithium aluminum hydride (2 M solution in THF, 5.2 mL, 10.4 mmol). The resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched by addition of ethyl acetate and ethanol. The resulting mixture was poured in ice/water solution then filtered on celite. The aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using dichloromethane/ methanol as the eluent to give the desired product (5-chloro-1-(3-(methylsulfonyl)propyl)-1*H*-indol-2-yl)methanol **17b** (2.5 g, 88%) as a white solid. *m/z* = 302 $(M+H)^+$.

<u>Intermediate 18c</u> Synthesis of 4-(5-chloro-2-(hydroxymethyl)-1*H*-indol-1-yl)-butanenitrile



Step 1: synthesis of ethyl 5-chloro-1-(3-cyanopropyl)-1*H*-indole-2-carboxylate (intermediate 18a)

Ethyl-5-chloroindol-2-carboxylate (33.55 g, 150 mmol) was dissolved in acetonitrile (600 mL) and stirred at room temperature. Then cesiumcarbonate (73.31 g, 225 mmol) was added and stirring was continued for 30 minutes. 4-Bromobutyronitrile (18.83 mL, 180 mmol) was added in small portions over a period of one hour and stirring was continued overnight at ambient temperature. The reaction mixture was filtered and the filtrate was evaporated to dryness. The residue was dissolved in dichloromethane and

washed with water. The organic layer was dried over $MgSO_4$, filtered and evaporated to give 43.5 g (99% yield) of ethyl 5-chloro-1-(3-cyanopropyl)-1H-indole-2-carboxylate **18a,** which was used as such in the next step. *m/z* = 290 $(M+H)^+$.

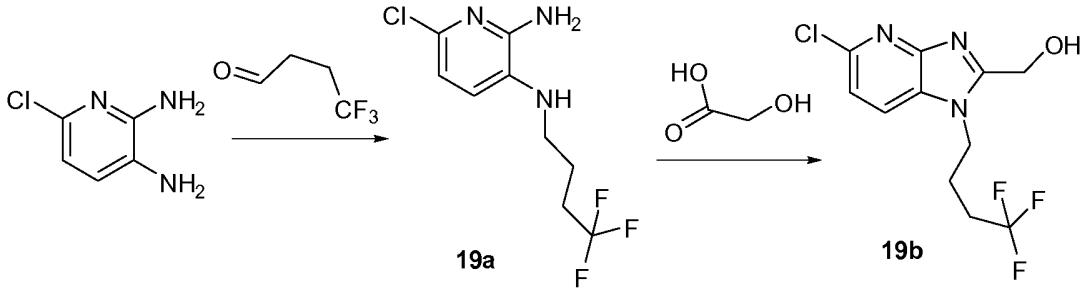
Step 2: synthesis of 5-chloro-1-(3-cyanopropyl)-1*H*-indole-2-carboxylic acid (intermediate 18b)

Ethyl 5-chloro-1-(3-cyanopropyl)indol-2-carboxylate **18a** (43.61 g, 149.97 mmol) was dissolved in 1,4-dioxane (850 mL) and stirred at room temperature. Then a solution of lithiumhydroxide (10.78 g, 450 mmol) in distilled water (150 mL) was added. After stirring overnight at RT, the reaction mixture was evaporated to dryness. The residue was dissolved in 500 mL water and neutralised with aqueous hydrochloric acid 1 N (450 mL). The white precipitate was filtered off and dried *in vacuo* to yield 39.8 g (quantitative yield) of 5-chloro-1-(3-cyanopropyl)-1*H*-indole-2-carboxylic acid **18b**. *m/z* = 262 $(M+H)^+$.

Step 3: synthesis of 4-(5-chloro-2-(hydroxymethyl)-1*H*-indol-1-yl)butanenitrile (intermediate 18c)

5-chloro-1-(3-cyanopropyl)indol-2-carboxylic acid **18b** (39.4 g, 149.98 mmol) and Hunigs base (51.69 mL, 300 mmol) were dissolved in tetrahydrofuran (550 mL) and stirred at -10°C under a nitrogen atmosphere. Then a solution of isobutylchloroformate in tetrahydrofuran (50 ml) was added dropwise and the stirring was continued for one hour at -10°C and one hour at ambient temperature. Then sodiumborohydride (17.02 g, 450 mmol) was added portionwise at -10°C and stirred for one hour, afterwards distilled water (200 mL) was added cautiously to the reaction mixture and stirring was continued for another hour at room temperature under a nitrogen atmosphere. The mixture was neutralised with 10% citric acid in water and then extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered and evaporated. The residue was purified over silica with heptane/ dichloromethane/methanol 50/50/0->0/100/0->0/99/1 as gradient. The corresponding fractions were evaporated to yield 23.9 g (64% yield) of 4-(5-chloro-2-(hydroxymethyl)-1H-indol-1-yl)butanenitrile **18c** as a white powder. *m/z* = 248 $(M+H)^+$.

<u>Intermediate 19b</u> Synthesis of (5-chloro-1-(4,4,4-trifluorobutyl)-1*H*-imidazo[4,5-*b*]pyridin-2-yl)methanol



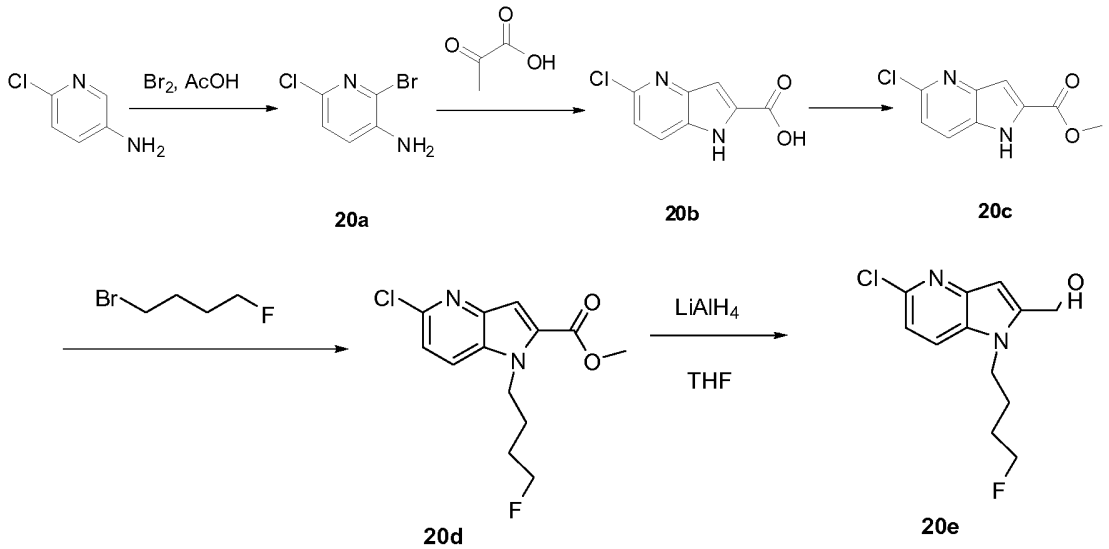
Step 1: 6-chloro-N^3-(4,4,4-trifluorobutyl)-pyridine-2,3-diamine (intermediate 19a)

6-chloropyridine-2,3-diamine (5 g, 34.82 mmol) was dissolved in dichloromethane (200 mL), acetic acid (20 drops) and 4,4,4-trifluorobutanal (4.38 g, 34.8 mmol) were added. The resulting mixture was stirred for 30 minutes and then sodium triacetoxyhydroborate (22.14 g, 104.5 mmol) was added. The reaction mixture was stirred at room temperature overnight and a solution of 50% Na_2CO_3 was added dropwise until gas evolution stopped. The organic layer was separated, dried on $MgSO_4$, filtrated and evaporated to dryness. The residue was purified by column chromatography using heptane/EtOAc 7/3 to pure EtOAc. Intermediate 6-chloro-N^3-(4,4,4-trifluorobutyl)-pyridine-2,3-diamine **19a** was recovered as a white solid and dried *in vacuo* overnight (6.16 g, 70%). *m/z* = 254 $(M+H)^+$.

Step 2: synthesis of (5-chloro-1-(4,4,4-trifluorobutyl)-1*H*-imidazo[4,5-*b*]pyridin-2-yl)methanol (intermediate 19b)

A mixture of intermediate **19a** (5.68 g, 22.46 mmol) and 2-hydroxyacetic acid (4.27 g, 56.2 mmol) was stirred at 150°C for 4 hours. The mixture was allowed to cool down to room temperature and treated carefully with 3N hydrochloric acid. The resulting mixture was made basic with aqueous ammonia and extracted with CH_2Cl_2 (300 mL). The organic layer was dried over $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography on silica using CH_2Cl_2 to EtOAc to give 4.27 g (65%) of (5-chloro-1-(4,4,4-trifluorobutyl)-1*H*-imidazo[4,5-*b*]pyridin-2-yl)methanol **19b** as a brown solid. *m/z* = 294 $(M+H)^+$. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.00 (s, 2 H), 1.12 - 1.23 (m, 2 H), 1.83 - 1.99 (m, 2 H), 2.12 - 2.31 (m, 2 H), 2.91 (spt, *J*=3.50 Hz, 1 H), 4.38 - 4.54 (m, 2 H), 5.38 (s, 2 H), 7.13 (dd, *J*=5.27, 0.50 Hz, 1 H), 7.27 (d, *J*=8.28 Hz, 1 H), 7.61 (d, *J*=8.53 Hz, 1 H), 8.36 (d, *J*=5.27 Hz, 1 H), 8.77 (s, 1 H).

<u>Intermediate 20e</u> Synthesis of (5-chloro-1-(4-fluorobutyl)-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl)methanol



Step 1: synthesis of 2-bromo-6-chloropyridin-3-amine (intermediate 20a)

Bromine (24.86 g, 155.57 mmol) was added to a solution of 6-chloropyridin-3-amine (20.00 g, 155.57 mmol) and sodium acetate (25.52 g, 311.14 mmol) in acetic acid (383 ml). The reaction mixture was stirred at room temperature for 1 hour. Acetic acid was then evaporated. The residue was dissolved in EtOAc, washed with saturated aqueous Na_2CO_3, water and brine. The organic layer was dried over $MgSO_4$, filtered and evaporated, yielding 32.20 g of the desired product **20a** (99.8%). *m/z* = 206.96 $(M+H)^+$, Cl+Br pattern.

Step 2: synthesis of 5-chloro-1*H*-pyrrolo[3,2-*b*]pyridine-2-carboxylic acid (intermediate 20b)

2-oxopropanoic acid (36.22 g, 411.31 mmol), palladium(II)acetate (7.74 g, 34.15 mmol) and Et_3N (69.11 g, 682.94 mmol) were added to a solution of 2-bromo-6-chloropyridin-3-amine **20a** (32.20 g, 155.21 mmol) and TPP (35.83 g, 136.59 mmol) in dry DMF (300 ml). The reaction mixture was stirred at 100°C overnight. The solvent was then evaporated, water was added and the water layer was washed with EtOAc. The water layer was acidified with conc. HCl. The precipitate was filtered off and dried, yielding 25.21 g of the wanted product **20b** (82.6 %). *m/z* = 197.1 $(M+H)^+$, Cl pattern.

Step 3: synthesis of methyl 5-chloro-1*H*-pyrrolo[3,2-b]pyridine-2-carboxylate (intermediate 20c)

5-chloro-1*H*-pyrrolo[3,2-*b*]pyridine-2-carboxylic acid **20b** (25.20 g, 128.18 mmol) was added to a refluxing mixture of sulfuric acid (20 ml) and methanol (400 ml). The

mixture was refluxed overnight. The mixture was then evaporated and a cold $NaHCO_3$ solution was added until basic pH. The precipitate was filtered off and dried, yielding 16.15 g of the desired product **20c** (59.8%). *m/z* = 211.17 $(M+H)^+$, Cl pattern.

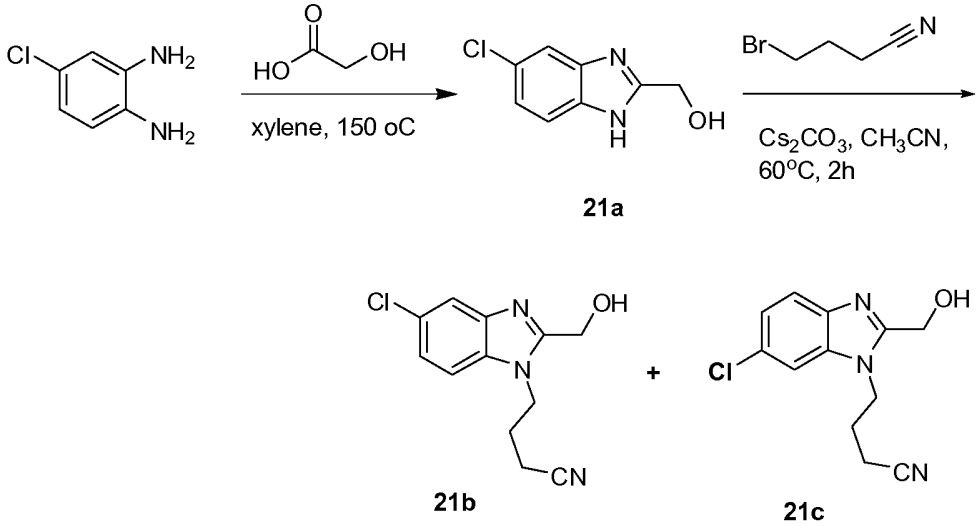
Step 4: synthesis of methyl 5-chloro-1-(4-fluorobutyl)-1*H*-pyrrolo[3,2-b]pyridine-2-carboxylate (intermediate 20d)

To a solution of methyl 5-chloro-1H-pyrrolo[3,2-b]pyridine-2-carboxylate **20c** (2.9 g, 12.2 mmol) in DMF (50 mL) were added successively cesium carbonate (4 g, 12.2 mmol) and 1-bromo-4-fluorobutane (1.3 mL, 12.2 mmol). The resulting mixture was heated at 60°C overnight. The reaction mixture was allowed to cool down to room temperature then poured into iced water and the product was extracted 3 times with DCM. The combined organic layers were dried over Na_2SO_4, filtered and evaporated to give the targeted product **20d** as a yellowish solid. The product was used as such in the next step. *m/z* = 313 $(M+H)^+$, Cl pattern.

Step 5: synthesis of (5-chloro-1-(4-fluorobutyl)-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl)-methanol (intermediate 20e)

To a solution of methyl 5-chloro-1-(4-fluorobutyl)-1H-pyrrolo[3,2-b]pyridine-2-carboxylate **20d** (3.82 g, 10.8 mmol) in dry THF (100 mL) was added a 1M solution of lithium aluminumhydride (11.96 mL, 11.96 mmol) at -75°C. The cooling bath was then removed and the reaction mixture was kept at room temperature for 3 hours. EtOAc was added, followed by a saturated NH_4Cl solution. The mixture was stirred for 30 min. The organic layer was dried over Na_2SO_4, filtered and evaporated to give a yellow oil, which was purified by column chromatography to yield the targeted product (5-chloro-1-(4-fluorobutyl)-1H-pyrrolo[3,2-b]pyridin-2-yl)methanol **20e** (2.8 g, 98%). *m/z* = 257 $(M+H)^+$, Cl pattern.

<u>Intermediates 21 b and 21c</u> Synthesis of 4-(5-chloro-2-(hydroxymethyl)-1*H*-benzo[*d*]imidazol-1-yl)butanenitrile (intermediate 21b) and 4-(6-chloro-2-(hydroxymethyl)-1*H*-benzo[*d*]imidazol-1-yl)butanenitrile (intermediate 21c)



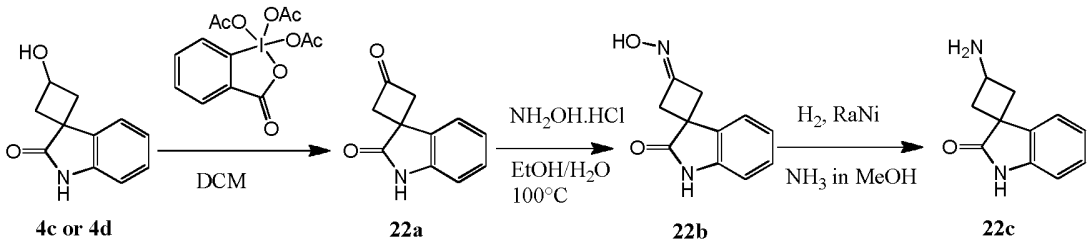
Step 1: synthesis of (5-chloro-1*H*-benzo[d]imidazol-2-yl)methanol (intermediate 21a)

A mixture of 4-chlorobenzene-1,2-diamine (105 g, 736 mmoles, 1 eq.) and hydroxyacetic acid (112 g, 2 eq.) in xylene (1500 mL) was stirred at 150 °C for 4 hours. The mixture was then cooled to 60 °C and treated with 3N HCl (480 ml), then basified to pH=7-8 by the addition of aqueous ammonia. The mixture was filtered and the solid was collected, washed with H_2O and *tert*-butyl methyl ether to give 123 g (82% yield) of (5-chloro-1H-benzo[d]imidazol-2-yl)methanol **21a**.

Step 2: synthesis of 4-(5-chloro-2-(hydroxymethyl)-1*H*-benzo[d]imidazol-1-yl)butanenitrile (intermediate 21b) and 4-(6-chloro-2-(hydroxymethyl)-1*H*-benzo[d]imidazol-1-yl)butanenitrile (intermediate 21c)

A mixture of (5-chloro-1H-benzo[d]imidazol-2-yl)methanol **21a** (500 mg, 2.738 mmoles, 1 eq.), 4-bromobutyronitrile (466 mg, 1.15 eq.), cesium carbonate (1.338 g, 1.5 eq.) and potassium iodide (45 mg, 0.1 eq.) in acetonitrile (5 mL) was refluxed overnight. The mixture was then cooled and filtered. The filtrate was evaporated under vacuum and the residue was treated with ethyl acetate (30 ml) and brine (20 ml). The separated organic layer was dried (Na_2SO_4), filtered and the solvent was evaporated under vacuum. The residue was purified by column chromatography (eluent: CH_2Cl_2: methanol from 1:0 to 15:1) to yield 732 mg (54%) of a mixture containing the two regio-isomers **21b** and **21c** in a 1/1 ratio. This mixture was further separated by SFC to provide the pure regio-isomer **21b**.

<u>Intermediate 22c</u> Synthesis of 3-aminospiro[cyclobutane-1,3'-indolin]-2'-one



Step 1

To alcohol **4c** or **4d** (5 g, 26.425 mmoles) in DCM was added Dess-martin periodinane (16.8 g, 1.5 eq) at 0°C. After 16h at RT, the RM was filtered off and a saturated solution of $NaHCO_3$ (50 mL) and a NaS_2O_3 solution (50 mL) were added. After stirring for 30 minutes, the organic layer was separated, dried over Na_2SO_4, and concentrated in vacuo to provide the desired spiro[cyclobutane-1,3'-indoline]-2',3-dione **22a** as a racemic mixture, which was used without further purification in the next step.

Step 2

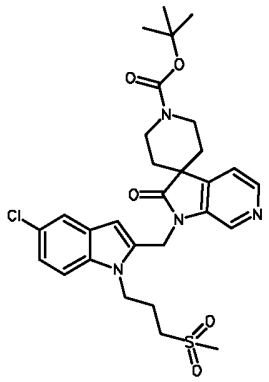
A mixture of ketone **22a** (2 g, 10.68 mmoles), sodium carbonate (3.397 g, 3 eq) and hydroxylamine hydrochloride (1.485 g, 2 eq) in EtOH/H_2O (1/1, 100 mL) was heated at 100°C during 1 h. The RM was then concentrated in vacuo and the resulting precipitate was filtered off, washed with water and dried in the vacuum oven to give 3-(hydroxyimino)spiro[cyclobutane-1,3'-indolin]-2'-one **22b** (1.5 g, 69% yield).

Step 3

The oxime **22b** was hydrogenated over RaNi (435 mg, 1 eq) in NH_3 7N in MeOH (50 mL) overnight. The solution was then filtered over decalite and concentrated in vacuo. The crude was then triturated in Et_2O, and the resulting solid was filtered off and dried in the oven to give aminospiro[cyclobutane-1,3'-indolin]-2'-one **22c** (1.3 g, 85% yield) as a mixture of two isomers.

<u>Synthesis of final compounds</u>

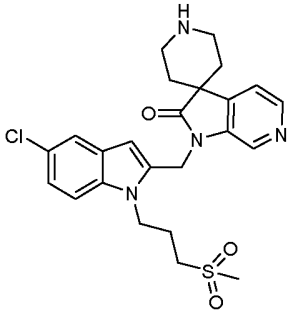
<u>Compound 1</u> Synthesis of *tert*-butyl 1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-indol-2-yl}methyl)-2'-oxo-1',2'-dihydro-1*H*-spiro[piperidine-4,3'-pyrrolo[2,3-*c*]-pyridine]-1-carboxylate



compound 1

To a suspension of {5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-indol-2-yl}methanol **17b** (4000 mg, 13.25 mmols), *tert*-butyl 2'-oxo-1',2'-dihydro-1*H*-spiro[piperidine-4,3'-pyrrolo[2,3-*c*]pyridine]-1-carboxylate **10c** (4423 mg, 14.58 mmols) and TPP (4172 mg, 15.91 mmols) in dry THF (92 ml) was added DIAD (3.869 ml, 19.88 mmols) at room temperature and the reaction mixture was stirred overnight. THF was evaporated and the crude was purified by column chromatography. After evaporation of the relevant fractions, the residue was recrystallized in water. The formed crystals were filtered off and washed with some water and heptane to get the title product **1** as a beige powder (1231 mg, Y = 15.8%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.45 (s, 9 H) 1.80 (t, J=5.50 Hz, 4 H) 2.03 - 2.16 (m, 2 H) 3.01 (s, 3 H) 3.14 - 3.25 (m, 2 H) 3.60 - 3.83 (m, 4 H) 4.37 (t, J=7.48 Hz, 2 H) 5.20 (s, 2 H) 6.37 (s, 1 H) 7.16 (dd, J=8.69, 2.09 Hz, 1 H) 7.53 (d, J=1.98 Hz, 1 H) 7.55 (d, J=8.80 Hz, 1 H) 7.69 (d, J=4.62 Hz, 1 H) 8.33 (d, J=4.84 Hz, 1 H) 8.39 (s, 1 H); m/z = 587.23$(M+H)^+$+Cl pattern.

<u>Compound 2</u> Synthesis of 1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-indol-2-yl}methyl)spiro[piperidine-4,3'-pyrrolo[2,3-*c*]pyridin]-2'(1'*H*)-one

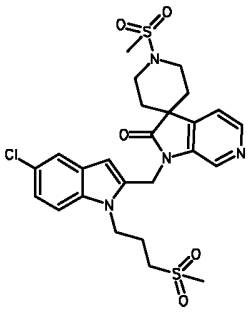


Compound 2

To a solution of *tert*-butyl 1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-indol-2-yl}-methyl)2'-oxo-1',2'-dihydro-1*H*-spiro[piperidine-4,3'-pyrrolo[2,3-*c*]pyridine]-1-carboxylate **1** (3.39 g, 3.75 mmols) in DCM (20 ml) was added TFA (2.872 ml, 37.53 mmols) and the mixture was stirred overnight at room temperature. Then water was

added and the reaction mixture was basified with Na_2CO_3-solution. DCM was evaporated and the remaining aqueous suspension was stirred for 3 hours. The solid was filtered off, washed with water and then purified by column chromatography to obtain a pink glassy oil. The product was triturated in diethyl ether to give the desired product **2** as a pink powder which was dried in the vacuum oven (466 mg, 23.7%); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.62 - 1.88 (m, 4 H) 2.02 - 2.18 (m, 2 H) 2.93 - 3.07 (m, 5 H) 3.11 - 3.24 (m, 4 H) 4.38 (t, *J*=7.48 Hz, 2 H) 5.19 (s, 2 H) 6.33 (s, 1 H) 7.16 (dd, *J*=8.69, 2.09 Hz, 1 H) 7.50 - 7.58 (m, 2 H) 7.64 (d, *J*=4.84 Hz, 1 H) 8.29 - 8.42 (m, 2 H); m/z = 487.27 $(M+H)^+$+Cl pattern.

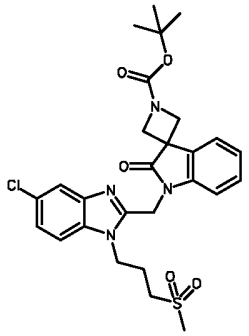
<u>Compound 3</u> Synthesis of 1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-indol-2-yl}methyl)-1-(methylsulfonyl) spiro[piperidine-4,3'-pyrrolo[2,3-*c*]pyridin]-2'(1'*H*)-one



Compound 3

1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-indol-2-yl}methyl)spiro[piperidine-4,3'-pyrrolo[2,3-*c*] pyridin]-2'(1'*H*)-one **2** (500 mg, 0.72 mmols) was dissolved in DCM (5 ml), then methanesulfonyl chloride (0.11 ml, 1.44 mmols) and Et_3N (0.30 ml, 2.16 mmols) were added. The mixture was stirred at room temperature for 30 minutes. Water was added and the reaction mixture was basified with $NaHCO_3$-solution. The product was extracted with DCM (2 times). The organic layers were dried over $MgSO_4$, filtered and evaporated. The residue was purified by preparative column chromatography to give the desired product **3** (172 mg, Y = 42.4%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.88 - 2.16 (m, 6 H) 3.00 (s, 3 H) 3.01 (s, 3 H) 3.17 - 3.26 (m, 2 H) 3.41 - 3.51 (m, 2 H) 3.52 - 3.64 (m, 2 H) 4.38 (t, J=7.48 Hz, 2 H) 5.20 (s, 2 H) 6.38 (s, 1 H) 7.16 (dd, J=8.69, 2.09 Hz, 1 H) 7.53 (d, J=1.98 Hz, 1 H) 7.56 (d, J=8.80 Hz, 1 H) 7.70 (d, J=4.84 Hz, 1 H) 8.36 (d, J=4.84 Hz, 1 H) 8.41 (s, 1 H); m/z = 565.03 $(M+H)^+$+Cl pattern.

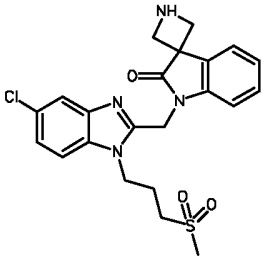
<u>Compound 4</u> Synthesis of *tert*-butyl 1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl}methyl)-2'-oxo-1',2'-dihydro-1*H*-spiro[azetidine-3,3'-indole]-1-carboxylate



Compound 4

Tert-butyl 2'-oxo-1',2'-dihydro-1*H*-spiro[azetidine-3,3'-indole]-1-carboxylate **3f** (1000 mg, 3.65 mmols) was dissolved in dry DMF (23 ml), then 5-chloro-2-(chloromethyl)-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazole hydrochloric acid **15e**(1304 mg, 3.64 mmols) and cesium carbonate (3563 mg, 3.56 mmols) were added. The reaction mixture was stirred at room temperature overnight. Iced water was added and the mixture was stirred overnight. The formed solid was filtered off and washed with water and a little ether. After drying in the vacuum oven the desired product **4** was obtained as a pink solid (1695 mg, Y = 81.5%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.44 (s, 9 H) 2.10 - 2.21 (m, 2 H) 3.00 (s, 3 H) 3.19 - 3.25 (m, 2 H) 4.03 - 4.19 (m, 4 H) 4.47 (t, J=7.48 Hz, 2 H) 5.22 (s, 2 H) 7.13 (td, J=7.48, 0.88 Hz, 1 H) 7.19 (d, J=7.70 Hz, 1 H) 7.27 - 7.34 (m, 2 H) 7.65 - 7.69 (m, 3 H); m/z = 559.21$(M+H)^+$+Cl pattern.

<u>Compound 5</u> Synthesis of 1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl}methyl)spiro[azetidine-3,3'-indol]-2'(1'*H*)-one

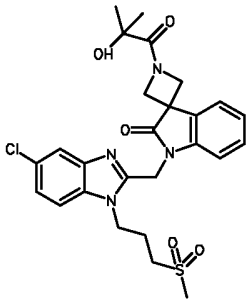


Compound 5

To a solution of *tert*-butyl 1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl}methyl)-2'-oxo-1',2'-dihydro-1*H*-spiro[azetidine-3,3'-indole]-1-carboxylate **4** (1.5 g, 2.63 mmoles) in DCM (20 mL) was added TFA (1 mL, 5 eq.) at RT. After 12h, more TFA (2 mL) was added and the mixture was stirred for 24h. The

reaction was then neutralized by a Na_2CO_3-solution. DCM was evaporated and the formed solid was filtered off and washed with water and ether to give the TFA salt of the desired product **5** as a grey powder (1.303 g, Y = 86.5%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.11 - 2.26 (m, 2 H) 3.01 (s, 3 H) 3.19 - 3.28 (m, 2 H) 4.16 - 4.35 (m, 4 H) 4.48 (t, J=7.48 Hz, 2 H) 5.22 (s, 2 H) 7.18 - 7.28 (m, 2 H) 7.32 (dd, J=8.80, 1.98 Hz, 1 H) 7.36 (td, J=7.90, 0.88 Hz, 1 H) 7.66 (d, J=1.98 Hz, 1 H) 7.69 (d, J=8.80 Hz, 1 H) 7.85 (d, J=6.82 Hz, 1 H) 9.27 (br. s., 2 H); m/z = 459.18$(M+H)^+$+Cl pattern.

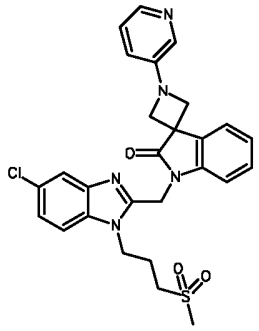
<u>Compound 6</u> Synthesis of 1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl}methyl)-1-(2-hydroxy-2-methylpropanoyl)spiro[azetidine-3,3'-indol]-2'(1'*H*)-one



Compound 6

1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl}methyl)spiro[azetidine-3,3'-indol]-2'(1'*H*)-one **5** (300 mg, 0.50 mmols), 2-hydroxy-2-methylpropanoic acid (117 mg, 1.12 mmols) and Et_3N (0.482 ml, 2.80 mmols) were stirred vigorously at room temperature in dry DMF (4 ml), while DECP (0.188 ml, 1.12 mmols) was added dropwise. Stirring was continued for 1 hour at ambient temperature in a closed vessel. Some ice was added followed by a saturated sodium bicarbonate solution. The resulting suspension was stirred for 2 hours and the solid was filtered off and further purified by column chromatography eluting with a gradient of DCM and MeOH. All pure fractions were evaporated to give a yellowish foam which was further triturated in ether and filtered off to give the title product **6** (121 mg, Y = 42.0%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (s, 3 H) 1.33 (s, 3 H) 2.11 - 2.24 (m, 2 H) 3.00 (s, 3 H) 3.18 - 3.27 (m, 2 H) 4.02 - 4.20 (m, 2 H) 4.47 (t, J=7.37 Hz, 2 H) 4.55 - 4.75 (m, 2 H) 5.23 (s, 2 H) 5.25 (s, 1 H) 7.11 - 7.23 (m, 2 H) 7.27 - 7.35 (m, 2 H) 7.60 - 7.65 (m, 1 H) 7.65 - 7.71 (m, 2 H); m/z = 545.41 $(M+H)^+$+Cl pattern.

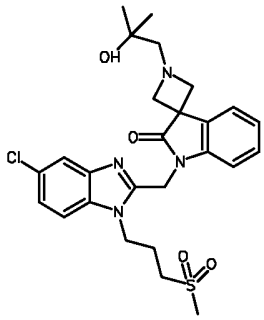
<u>Compound 7</u> Synthesis of 1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl}methyl)-1-(pyridin-3-yl)spiro[azetidine-3,3'-indol]-2'(1'*H*)-one



Compound 7

A mixture of 1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl}methyl)spiro[azetidine-3,3'-indol]-2'(1'*H*)-one **5** (259 mg, 0.43 mmols) and 3-bromopyridine (0.084 ml, 0.87 mmols) in toluene (1.5 ml) was degassed with nitrogen gas during 5 minutes. Then $Pd_2(dba)_3$ (10 mg, 0.01 mmols), NaOtBu (52 mg, 0.54 mmols) and BINAP (20 mg, 0.03 mmols) were added. The mixture was degassed again and then heated in a μ-wave oven for 2 hours at 125°C. The reaction mixture was evaporated, taken up in water and extracted with DCM. Some insolubles were filtered off. The two phases were separated and the organic layer was dried over Na_2SO_4, filtered and evaporated to dry. The crude was purified by preparative column chromatography to give the title product **7** (35 mg, Y = 15.0%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.09 - 2.21 (m, 2 H) 3.00 (s, 3 H) 3.19 - 3.27 (m, 2 H) 4.13 - 4.27 (m, 4 H) 4.47 (t, J=7.48 Hz, 2 H) 5.26 (s, 2 H) 6.99 (ddd, J=8.25, 2.75, 1.32 Hz, 1 H) 7.12 - 7.17 (m, 1 H) 7.20 (d, J=7.70 Hz, 1 H) 7.25 (dd, J=8.14, 4.62 Hz, 1 H) 7.28 - 7.36 (m, 2 H) 7.64 - 7.71 (m, 3 H) 7.98 (d, J=2.64 Hz, 1 H) 8.02 (dd, J=4.62, 1.32 Hz, 1 H); m/z = 536.07 $(M+H)^+$+Cl pattern.

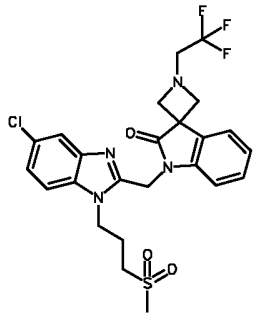
<u>Compound 8</u> Synthesis of 1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl}methyl)-1-(2-hydroxy-2-methylpropyl)spiro[azetidine-3,3'-indol]-2'(1'*H*)-one



Compound 8

To a solution of 1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl}-methyl)spiro[azetidine-3,3'-indol]-2'(1'*H*)-one **5** (150 mg, 0.33 mmols) in EtOH (20 ml) and DMF (5 ml) was added Et_3N (0.227 ml, 1.63 mmols) and 2,2-dimethyloxirane (0.087 ml, 0.98 mmols). The reaction mixture was heated at 60°C for 40 hours. Heating was stopped and iced water was added. EtOH was evaporated. The formed solid was filtered and washed with water and ether to get a grey powder. The crude was purified by column chromatography to get the title product **8** as a white solid after drying in the vacuum oven (74 mg, Y = 39.2%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.12 (s, 6 H) 2.06 - 2.17 (m, 2 H) 2.46 (s, 2 H) 2.99 (s, 3 H) 3.17 - 3.25 (m, 2 H) 3.54 (q, J=7.04 Hz, 4 H) 4.12 (s, 1 H) 4.45 (t, J=7.37 Hz, 2 H) 5.21 (s, 2 H) 7.10 - 7.17 (m, 2 H) 7.23 - 7.28 (m, 1 H) 7.30 (dd, J=8.58, 1.98 Hz, 1 H) 7.64 - 7.68 (m, 2 H) 7.73 - 7.77 (m, 1 H); m/z = 531.09 $(M+H)^+$+Cl pattern.

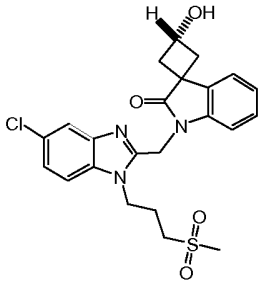
<u>Compound 9</u> Synthesis of 1'-[[5-chloro-1-(3-methylsulfonylpropyl)benzimidazol-2-yl]methyl]-1-(2,2,2-trifluoroethyl)spiro[azetidine-3,3'-indoline]-2'-one



compound 9

A solution of 1'-[[5-chloro-1-(3-methylsulfonylpropyl)benzimidazol-2-yl]methyl]spiro-[azetidine-3,3'-indoline]-2'-one **5** (573 mg, 1 mmol), 2,2,2-trifluoroethyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (382 mg, 1 mmol) and *N*-ethyl-*N*-isopropyl-propan-2-amine (0.52 mL, 3 mmol) were stirred in dioxane (10 mL) at 50°C over weekend. The reaction mixture was then allowed to cool to ambient temperature. The mixture was evaporated to dryness and the residue was crystallised in ethanol/acetonitrile 100/1. The off-white crystals were collected by filtration and dried *in vacuo* to give the title product **9** (420 mg, 77%). ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.13 (m, *J*=8.1 Hz, 2 H), 3.00 (s, 3 H), 3.22 (m, *J*=15.4 Hz, 2 H), 3.42 (q, *J*=10.0 Hz, 2 H), 3.64 (d, *J*=7.0 Hz, 2 H), 3.75 (d, *J*=7.0 Hz, 2 H), 4.46 (t, *J*=7.1 Hz, 2 H), 5.22 (s, 2 H), 7.07 - 7.22 (m, 2 H), 7.31 (d, *J*=8.8 Hz, 1 H), 7.27 (d, *J*=7.3 Hz, 1 H), 7.62 - 7.79 (m, 3 H); m/z = 540.99 $(M+H)^+$+Cl pattern; melting point: 200.68 °C.

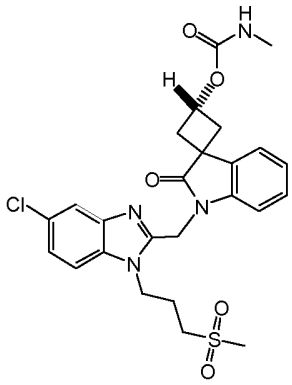
Compound 12 synthesis of (1R,3R)-1'-((5-chloro-1-(3-(methylsulfonyl)propyl)-1*H*-benzo[*d*]imidazol-2-yl)methyl)-3-hydroxyspiro[cyclobutane-1,3'-indolin]-2'-one



compound 12

(3*R*)-1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl}methyl)-3-hydroxyspiro[cyclobutane-1,3'-indol]-2'(1'*H*)-one **12** was synthetized following the reaction conditions used for the synthesis of compound **4**, using (3*R*)-hydroxyspiro-[cyclobutane-1,3'-indolin]-2'-one **4d** instead of *tert*-butyl 2'-oxo-1',2'-dihydro-1*H*-spiro[azetidine-3,3'-indole]-1-carboxylate **3f** and was obtained as a slightly pink solid, with a yield of 82%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.08 - 2.21 (m, 2 H) 2.27 - 2.38 (m, 2 H) 2.60 - 2.72 (m, 2 H) 2.99 (s, 3 H) 3.19 - 3.27 (m, 2 H) 4.46 (t, J=7.48 Hz, 2 H) 4.50 - 4.62 (m, 1 H) 5.20 (s, 2 H) 5.45 (d, J=6.82 Hz, 1 H) 7.05 - 7.14 (m, 2 H) 7.18 - 7.25 (m, 1 H) 7.30 (dd, J=8.80, 1.98 Hz, 1 H) 7.45 - 7.55 (m, 1 H) 7.63 - 7.71 (m, 2 H); m/z = 474.05 (M+H)+; MP = 209.84 °C.

Compound 104 synthesis of (1R,3R)-1'-((5-chloro-1-(3-(methylsulfonyl)propyl)-1*H*-benzo[*d*]imidazol-2-yl)methyl)-2'-oxospiro[cyclobutane-1,3'-indoline]-3-yl methylcarbamate

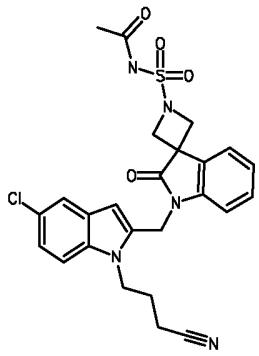


compound 104

A solution of (3*R*)-1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl}-methyl)-3-hydroxyspiro[cyclobutane-1,3'-indol]-2'(1'*H*)-one **12** (100 mg, 0.205 mmole), triethylamine (0.142 mL, 1.023 mmole) and *N,N'*-disuccinimidyl carbonate (210 mg, 0.82 mmole) in DCM (1.5 mL) was stirred at RT for 2h. A 2M solution of methyl amine (1.54 mL, 3.07 mmoles) was then added and the RM was further stirred

for 30 minutes. It was then concentrated and the residue was purified by chromatography on silica gel using a gradient of MeOH (0 to 5%) in DCM to give 110 mg (99% yield) of 1'-({5-Chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl}methyl)-2'-oxo-1',2'-dihydrospiro[cyclobutane-1,3'-indol]-3-yl methylcarbamate **104** as a slightly pink solid. 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.16 (quin, J=7.59 Hz, 2 H) 2.45 - 2.52 (m, 2 H) 2.59 (d, J=4.62 Hz, 3 H) 2.73 - 2.82 (m, 2 H) 3.00 (s, 3 H) 3.20 - 3.27 (m, 2 H) 4.47 (t, J=7.37 Hz, 2 H) 5.22 (s, 2 H) 5.25 - 5.35 (m, 1 H) 7.07 - 7.16 (m, 3 H) 7.22 - 7.28 (m, 1 H) 7.28 - 7.33 (m, 1 H) 7.48 - 7.54 (m, 1 H) 7.64 - 7.70 (m, 2 H); m/z = 531.15 (M+H)+.

Compound 117 synthesis of *N*-[(1'-{[5-Chloro-1-(3-cyanopropyl)-1*H*-indol-2-yl]methyl}-2'-oxo-1',2'-dihydro-1*H*-spiro[azetidine-3,3'-indol]-1-yl)sulfonyl]acetamide

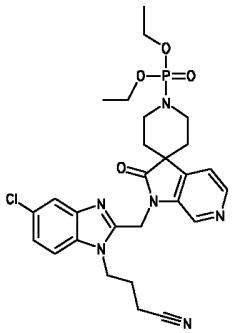


compound 117

A mixture of 4-{5-chloro-2-[(2'-oxospiro[azetidine-3,3'-indol]-1'(2'*H*)-yl)methyl]-1*H*-indol-1-yl}butanenitrile **59** (588 mg, 1.133 mmole) and sulfamide (326 mg, 3.4 mmoles) in dioxane (20 mL) was heated in a microwave oven at 160°C during 40 minutes. After cooling, the RM was concentrated in vacuo and the residue was recrystallized from methanol. This crude material (212 mg, 0.438 mmole) was then redissolved in DCM (30 mL) and acetic anhydride (82 µL, 0.876 mmole), *N*-methylmorpholine (96 µL, 0.876 mmole) and DMAP (3.7 mg, 0.03 mmole) were added. After 3h at RT, two more equivalents of acetic anhydride and *N*-methylmorpholine were added and the RM was stirred overnight. It was then quenched with MeOH (1 mL) and concentrated in vacuo. The resulting residue was purified by chromatography on silica gel using a gradient of MeOH (0 to 5%) in DCM to give 140 mg (58% yield) of *N*-[(1'-{[5-Chloro-1-(3-cyanopropyl)-1*H*-indol-2-yl]methyl}-2'-oxo-1',2'-dihydro-1*H*-spiro[azetidine-3,3'-indol]-1-yl)sulfonyl]acetamide **117** as a white solid. 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.93 - 2.04 (m, 1 H), 2.16 (s, 3 H), 2.58 (t, J=7.4 Hz, 2 H), 4.25 (d, J=8.1 Hz, 2 H), 4.27 - 4.35 (m, 2 H), 4.40 (d, J=8.4 Hz, 2 H), 5.12 (s, 2 H), 6.38 (s, 1 H), 7.08 (d, J=7.9 Hz, 1 H), 7.11 - 7.21 (m, 2 H), 7.26 - 7.35

(m, 1 H), 7.48 - 7.55 (m, 2 H), 7.58 (d, J=7.0 Hz, 1 H), 10.84 - 10.85 (m, 0 H), 11.75 (br. s., 2 H); m/z = 524 $(M-H)^-$; MP = 182.85°C.

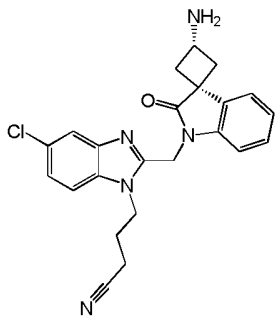
Compound 115 synthesis of Diethyl (1'-{[5-chloro-1-(3-cyanopropyl)-1H-benzimidazol-2-yl]methyl}-2'-oxo-1',2'-dihydro-1H-spiro[piperidine-4,3'-pyrrolo[2,3-c]pyridin]-1-yl)phosphonate



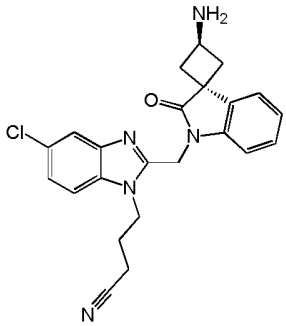
compound 115

A mixture of 4-(5-chloro-2-((2'-oxospiro[piperidine-4,3'-pyrrolo[2,3-c]pyridin]-1'(2'*H*)-yl)methyl)-1*H*-benzo[d]imidazol-1-yl)butanenitrile hydrochloride **84** (500 mg, 0.985 mmole), diethoxycyanophosphonate (0.448 mL, 3 eq) and triethylamine (0.411 mL, 3 eq) in DMF (10 mL) was stirred at RT for 2 hours. The mixture was then extracted with DCM and washed with water. The organics were then dried over $MgSO_4$, concentrated in vacuo and purified by chromatography on silica gel using a gradient of MeOH (0 to 10%) in DCM, followed by a purification by Prep HPLC (Stationary phase: RP Vydac Denali C18 - 10µm, 200g, 5cm), Mobile phase: 0.25% NH_4HCO_3 solution in water, CH_3CN), to give 320 mg (56% yield) of Diethyl (1'-{[5-chloro-1-(3-cyanopropyl)-1H-benzimidazol-2-yl]methyl}-2'-oxo-1',2'-dihydro-1H-spiro[piperidine-4,3'-pyrrolo[2,3-c]**pyridin**]-1-yl)phosphonate **115.** m/z = 571 $(M+H)^+$.

Compounds 148 and 149 Synthesis of 4-(2-(((1r,3r)-3-amino-2'-oxospiro[cyclobutane-1,3'-indolin]-1'-yl)methyl)-5-chloro-1H-benzo[d]imidazol-1-yl)butanenitrile and 4-(2-(((1s,3s)-3-amino-2'-oxospiro[cyclobutane-1,3'-indolin]-1'-yl)methyl)-5-chloro-1H-benzo[d]imidazol-1-yl)butanenitrile



148

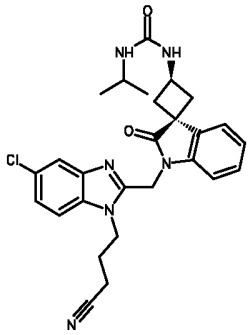


149

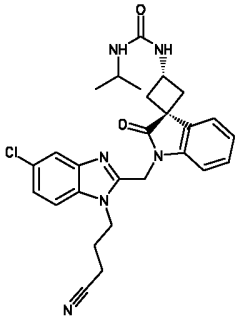
To a solution of amine **22c** (194 mg, 1.035 mmole) in dry DMF (10 mL) was added sodium hydride (79 mg, 2 eq) at RT. After 30 minutes, 4-(5-chloro-2-(chloromethyl)-1H-benzo[d]imidazol-1-yl)butanenitrile hydrochloric acid (332 mg, 1 eq) was added and the RM was stirred at RT for 2 h. The crude was then filtered off and the filtrate was concentrated in vacuo. The resulting crude was further purified by preparative SFC (Stationary phase: Chiralcel Diacel OJ 20 x 250 mm, Mobile phase: CO_2, iPrOH with 0.2% $iPrNH_2$), to give the pure isomers **148** (85 mg, 19% yield) and **149** (158 mg, 35% yield).

For **148**: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.91 - 2.10 (m, 2 H) 2.13 - 2.27 (m, 2 H) 2.55 - 2.71 (m, 4 H) 3.78 (quin, *J*=8.03 Hz, 1 H) 4.38 (t, *J*=7.59 Hz, 2 H) 5.20 (s, 2 H) 7.08 (td, *J*=8.10, 1.54 Hz, 2 H) 7.20 (td, *J*=7.70, 1.32 Hz, 1 H) 7.29 (dd, *J*=8.58, 1.98 Hz, 1 H) 7.53 - 7.70 (m, 3 H); m/z = 420 $[M+H]^+$. For **149**: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.80 - 2.20 (m, 4 H) 2.20 - 2.34 (m, 2 H) 2.36 - 2.47 (m, 2 H) 2.59 (t, *J*=7.48 Hz, 2 H) 3.77 - 3.95 (m, 1 H) 4.36 (t, *J*=7.50 Hz, 2 H) 5.21 (s, 2 H) 7.00 - 7.14 (m, 2 H) 7.16 - 7.25 (m, 1 H) 7.29 (dd, *J*=8.58, 1.98 Hz, 1 H) 7.55 (d, *J*=6.82 Hz, 1 H) 7.64 (d, *J*=8.80 Hz, 1 H) 7.66 (d, *J*=1.76 Hz, 1 H).

Compounds 143 and 144 Synthesis of 1-((1s,3s)-1'-((5-chloro-1-(3-cyanopropyl)-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxospiro[cyclobutane-1,3'-indolin]-3-yl)-3-isopropylurea and 1-((1r,3r)-1'-((5-chloro-1-(3-cyanopropyl)-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxospiro[cyclobutane-1,3'-indolin]-3-yl)-3-isopropylurea.



143

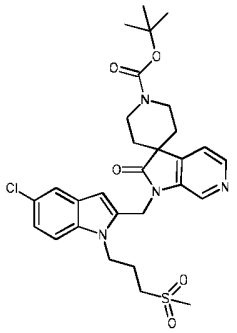
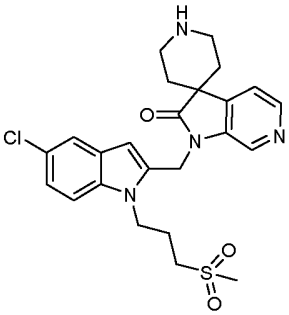
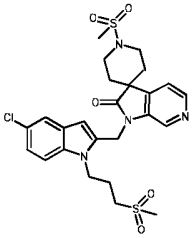


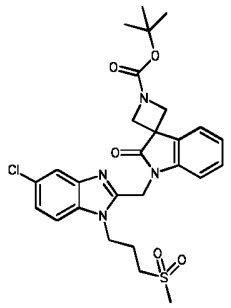
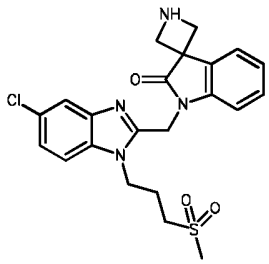
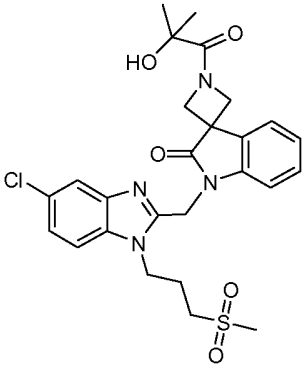
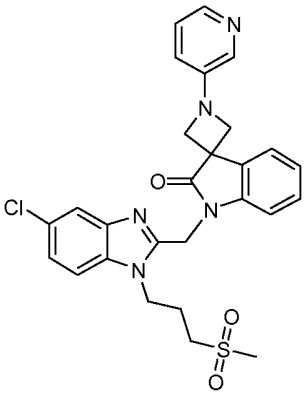
144

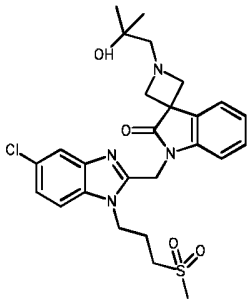
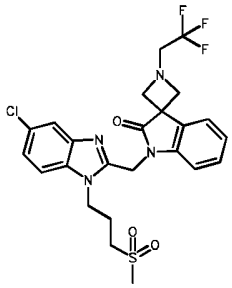
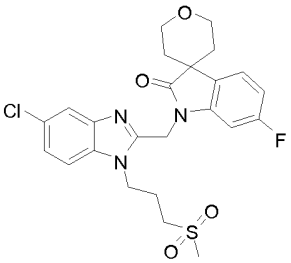
A mixture of 4-(2-(3-amino-2'-oxospiro[cyclobutane-1,3'-indolin]-1'-yl)methyl)-5-chloro-1H-benzo[d]imidazol-1-yl)butanenitrile (racemic mixture, 500 mg, 1.191 mmole), 2-isocyanatopropane (0.14 mL, 1.2 eq) and DIPEA (3.175 mL, 2 eq) was stirred at RT for 1h. The RM was then concentrated in vacuo and purified by preparative HPLC (Stationary phase: RP Vydac Denali C18 - 10μm, 200g, 5cm),

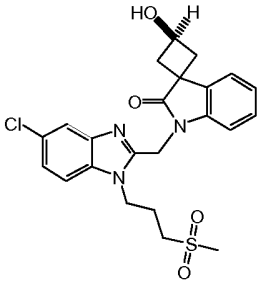
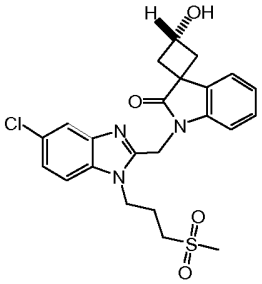
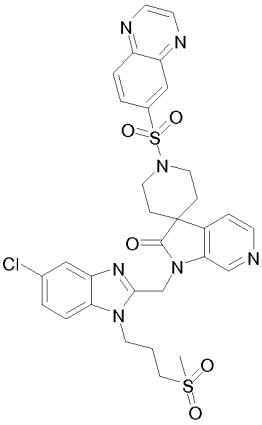
Mobile phase: 0.25% NH_4HCO_3 solution in water, CH_3CN) to give the pure mixture of enantiomers, which were subsequently separated by preparative SFC (Stationary phase: Chiralpak Diacel AD 30 x 250 mm), Mobile phase: CO_2, MeOH with 0.2% $iPrNH_2$), yielding 240 mg (40% yield) of **143** and 122 mg (20% yield) of **144**.

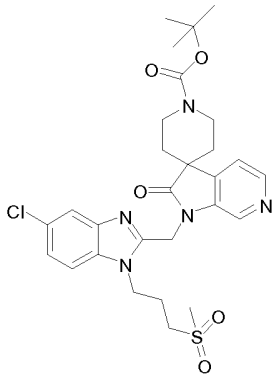
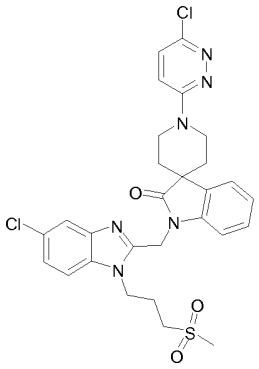
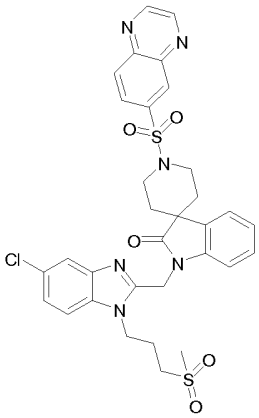
The compounds in the following table were synthetized according to the protocols described above, and to methods known in the art by the skilled chemist.

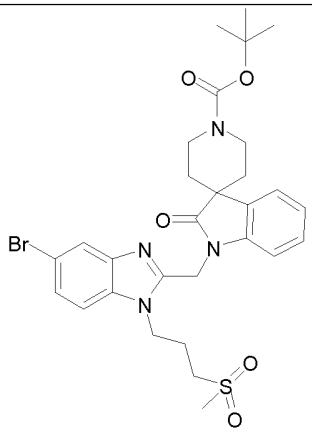
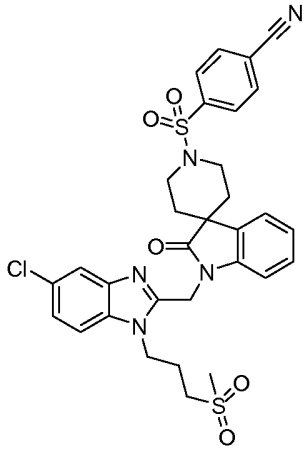
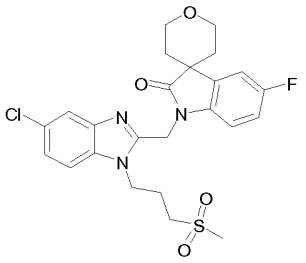
N°	structure	Name / analytical details
1		*tert*-butyl 1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-indol-2-yl}methyl)-2'-oxo-1',2'-dihydro-1*H*-spiro[piperidine-4,3'-pyrrolo[2,3-*c*]pyridine]-1-carboxylate ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.45 (s, 9 H) 1.80 (t, J=5.50 Hz, 4 H) 2.03 - 2.16 (m, 2 H) 3.01 (s, 3 H) 3.14 - 3.25 (m, 2 H) 3.60 - 3.83 (m, 4 H) 4.37 (t, J=7.48 Hz, 2 H) 5.20 (s, 2 H) 6.37 (s, 1 H) 7.16 (dd, J=8.69, 2.09 Hz, 1 H) 7.53 (d, J=1.98 Hz, 1 H) 7.55 (d, J=8.80 Hz, 1 H) 7.69 (d, J=4.62 Hz, 1 H) 8.33 (d, J=4.84 Hz, 1 H) 8.39 (s, 1 H); m/z = 587.23$(M+H)^+$+Cl pattern.
2		1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-indol-2-yl}-methyl)spiro[piperidine-4,3'-pyrrolo[2,3-*c*]pyridin]-2'(1'*H*)-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.62 - 1.88 (m, 4 H) 2.02 - 2.18 (m, 2 H) 2.93 - 3.07 (m, 5 H) 3.11 - 3.24 (m, 4 H) 4.38 (t, *J*=7.48 Hz, 2 H) 5.19 (s, 2 H) 6.33 (s, 1 H) 7.16 (dd, *J*=8.69, 2.09 Hz, 1 H) 7.50 - 7.58 (m, 2 H) 7.64 (d, *J*=4.84 Hz, 1 H) 8.29 - 8.42 (m, 2 H); m/z = 487.27 $(M+H)^+$+Cl pattern.
3		1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-indol-2-yl}-methyl)spiro[piperidine-4,3'-pyrrolo[2,3-*c*]pyridin]-2'(1'*H*)-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.88 - 2.16 (m, 6 H) 3.00 (s, 3 H) 3.01 (s, 3 H) 3.17 - 3.26 (m, 2 H) 3.41 - 3.51 (m, 2 H) 3.52 - 3.64 (m, 2 H) 4.38 (t, J=7.48 Hz, 2 H) 5.20 (s, 2 H) 6.38 (s, 1 H) 7.16 (dd, J=8.69, 2.09 Hz, 1 H) 7.53 (d, J=1.98 Hz, 1 H) 7.56 (d, J=8.80 Hz, 1 H) 7.70 (d, J=4.84 Hz, 1 H) 8.36 (d, J=4.84 Hz, 1 H) 8.41 (s, 1 H); m/z = 565.03 $(M+H)^+$+Cl pattern.

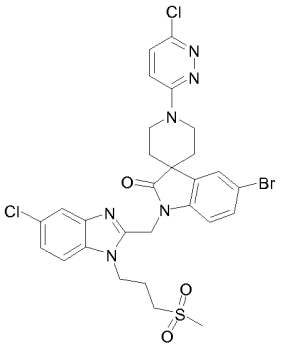
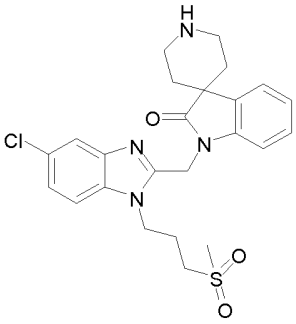
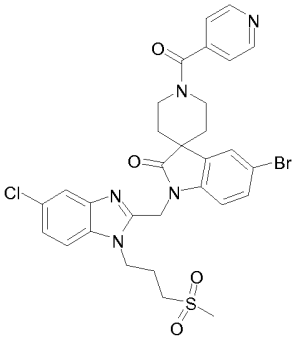
N°	structure	Name / analytical details
4		*tert*-butyl 1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl}methyl)-2'-oxo-1',2'-dihydro-1*H*-spiro[azetidine-3,3'-indole]-1-carboxylate ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.44 (s, 9 H) 2.10 - 2.21 (m, 2 H) 3.00 (s, 3 H) 3.19 - 3.25 (m, 2 H) 4.03 - 4.19 (m, 4 H) 4.47 (t, J=7.48 Hz, 2 H) 5.22 (s, 2 H) 7.13 (td, J=7.48, 0.88 Hz, 1 H) 7.19 (d, J=7.70 Hz, 1 H) 7.27 - 7.34 (m, 2 H) 7.65 - 7.69 (m, 3 H); m/z = 559.21$(M+H)^+$+Cl pattern.
5		1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl}methyl)spiro[azetidine-3,3'-indol]-2'(1'*H*)-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.11 - 2.26 (m, 2 H) 3.01 (s, 3 H) 3.19 - 3.28 (m, 2 H) 4.16 - 4.35 (m, 4 H) 4.48 (t, J=7.48 Hz, 2 H) 5.22 (s, 2 H) 7.18 - 7.28 (m, 2 H) 7.32 (dd, J=8.80, 1.98 Hz, 1 H) 7.36 (td, J=7.90, 0.88 Hz, 1 H) 7.66 (d, J=1.98 Hz, 1 H) 7.69 (d, J=8.80 Hz, 1 H) 7.85 (d, J=6.82 Hz, 1 H) 9.27 (br. s., 2 H); m/z = 459.18$(M+H)^+$+Cl pattern.
6		1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl}methyl)-1-(2-hydroxy-2-methyl-propanoyl)spiro[azetidine-3,3'-indol]-2'(1'*H*)-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (s, 3 H) 1.33 (s, 3 H) 2.11 - 2.24 (m, 2 H) 3.00 (s, 3 H) 3.18 - 3.27 (m, 2 H) 4.02 - 4.20 (m, 2 H) 4.47 (t, J=7.37 Hz, 2 H) 4.55 - 4.75 (m, 2 H) 5.23 (s, 2 H) 5.25 (s, 1 H) 7.11 - 7.23 (m, 2 H) 7.27 - 7.35 (m, 2 H) 7.60 - 7.65 (m, 1 H) 7.65 - 7.71 (m, 2 H); m/z = 545.41 $(M+H)^+$+Cl pattern
7		1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl}methyl)-1-(pyridin-3-yl)spiro[azetidine-3,3'-indol]-2'(1'*H*)-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.09 - 2.21 (m, 2 H) 3.00 (s, 3 H) 3.19 - 3.27 (m, 2 H) 4.13 - 4.27 (m, 4 H) 4.47 (t, J=7.48 Hz, 2 H) 5.26 (s, 2 H) 6.99 (ddd, J=8.25, 2.75, 1.32 Hz, 1 H) 7.12 - 7.17 (m, 1 H) 7.20 (d, J=7.70 Hz, 1 H) 7.25 (dd, J=8.14, 4.62 Hz, 1 H) 7.28 - 7.36 (m, 2 H) 7.64 - 7.71 (m, 3 H) 7.98 (d, J=2.64 Hz, 1 H) 8.02 (dd, J=4.62, 1.32 Hz, 1 H); m/z = 536.07 $(M+H)^+$+Cl pattern

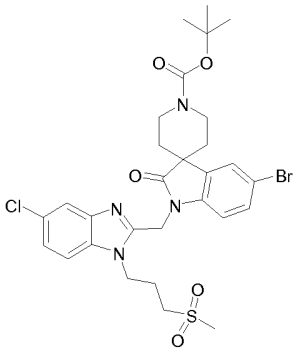
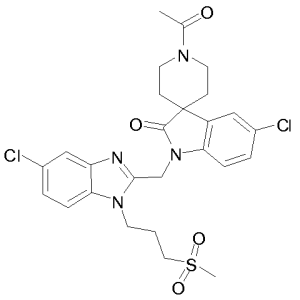
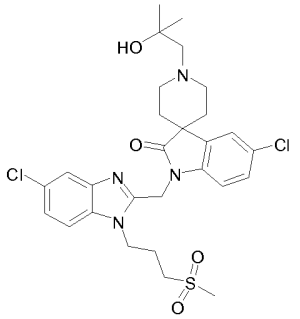
N°	structure	Name / analytical details
8		1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl}methyl)-1-(2-hydroxy-2-methyl-propyl)spiro[azetidine-3,3'-indol]-2'(1'*H*)-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.12 (s, 6 H) 2.06 - 2.17 (m, 2 H) 2.46 (s, 2 H) 2.99 (s, 3 H) 3.17 - 3.25 (m, 2 H) 3.54 (q, J=7.04 Hz, 4 H) 4.12 (s, 1 H) 4.45 (t, J=7.37 Hz, 2 H) 5.21 (s, 2 H) 7.10 - 7.17 (m, 2 H) 7.23 - 7.28 (m, 1 H) 7.30 (dd, J=8.58, 1.98 Hz, 1 H) 7.64 - 7.68 (m, 2 H) 7.73 - 7.77 (m, 1 H); m/z = 531.09 $(M+H)^+$+Cl pattern
9		1'-[[5-chloro-1-(3-methylsulfonylpropyl)benzimidazol-2-yl]-methyl]-1-(2,2,2-trifluoroethyl)spiro[azetidine-3,3'-indoline]-2'-one ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 2.13 (m, *J*=8.1 Hz, 2 H), 3.00 (s, 3 H), 3.22 (m, *J*=15.4 Hz, 2 H), 3.42 (q, *J*=10.0 Hz, 2 H), 3.64 (d, *J*=7.0 Hz, 2 H), 3.75 (d, *J*=7.0 Hz, 2 H), 4.46 (t, *J*=7.1 Hz, 2 H), 5.22 (s, 2 H), 7.07 - 7.22 (m, 2 H), 7.31 (d, *J*=8.8 Hz, 1 H), 7.27 (d, *J*=7.3 Hz, 1 H), 7.62 - 7.79 (m, 3 H); m/z = 540.99 $(M+H)^+$+Cl pattern; melting point: 200.68 °C
10		1-((5-chloro-1-(3-(methylsulfonyl)propyl)-1*H*-benzo[*d*]-imidazol-2-yl)methyl)-6-fluoro-2',3',5',6'-tetrahydro-spiro[indoline-3,4'-pyran]-2-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.63 - 1.92 (m, 4 H) 2.12 - 2.26 (m, 2 H) 3.01 (s, 3 H) 3.21 - 3.28 (m, 2 H) 3.76 - 3.90 (m, 2 H) 3.98 - 4.13 (m, 2 H) 4.46 (t, J=6.93 Hz, 2 H) 5.24 (s, 2 H) 6.82 - 6.91 (m, 1 H) 7.14 (dd, J= 9.57, 1.65 Hz, 1 H) 7.31 (dd, J=8.36, 1.32 Hz, 1 H) 7.60 (dd, J=7.92, 5.72 Hz, 1 H) 7.65 (d, J=1.32 Hz, 1 H) 7.67 (d, J=8.80 Hz, 1 H); m/z = 506.13 (M+H)+Cl pattern MP = 207.14°C

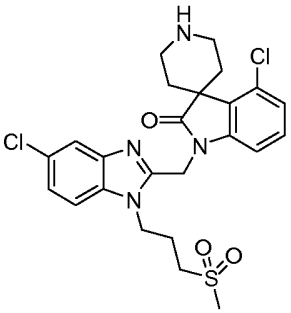
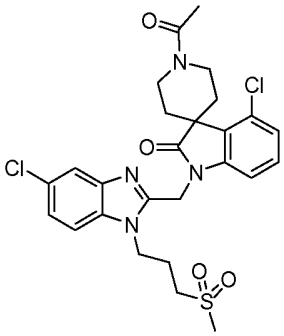
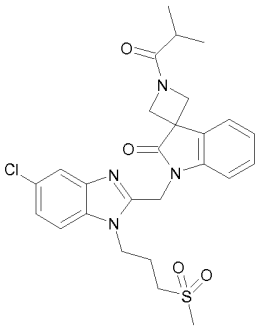
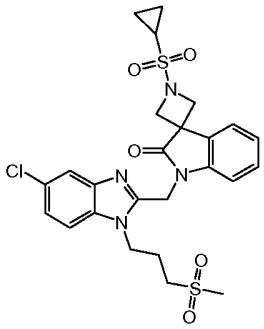
N°	structure	Name / analytical details
11		(3S)-1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl}methyl)-3-hydroxyspiro[cyclobutane-1,3'-indol]-2'(1'*H*)-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.00 - 2.17 (m, 2 H) 2.38 - 2.48 (m, 4 H) 2.99 (s, 3 H) 3.15 - 3.25 (m, 2 H) 4.45 (t, J=7.26 Hz, 2 H) 4.63 - 4.79 (m, 1 H) 5.23 (s, 2 H) 5.57 (br. s., 1 H) 7.00 - 7.16 (m, 2 H) 7.17 - 7.26 (m, 1 H) 7.30 (dd, J=8.69, 1.87 Hz, 1 H) 7.50 (d, J=7.26 Hz, 1 H) 7.62 - 7.71 (m, 2 H) m/z = 474.05(M+H)+Cl pattern; MP = 232.91 °C
12		(3R)-1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl}methyl)-3-hydroxyspiro[cyclobutane-1,3'-indol]-2'(1'*H*)-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.08 - 2.21 (m, 2 H) 2.27 - 2.38 (m, 2 H) 2.60 - 2.72 (m, 2 H) 2.99 (s, 3 H) 3.19 - 3.27 (m, 2 H) 4.46 (t, J=7.48 Hz, 2 H) 4.50 - 4.62 (m, 1 H) 5.20 (s, 2 H) 5.45 (d, J=6.82 Hz, 1 H) 7.05 - 7.14 (m, 2 H) 7.18 - 7.25 (m, 1 H) 7.30 (dd, J=8.80, 1.98 Hz, 1 H) 7.45 - 7.55 (m, 1 H) 7.63 - 7.71 (m, 2 H); m/z = 474.05 (M+H)+Cl pattern; MP = 209.84 °C
13		1'-((5-chloro-1-(3-(methylsulfonyl)propyl)-1*H*-benzo[*d*]-imidazol-2-yl)methyl)-1-(quinoxalin-6-ylsulfonyl)spiro-[piperidine-4,3'-pyrrolo[2,3-*c*]pyridin]-2'(1'*H*)-one ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.91 - 2.02 (m, 2 H), 2.04 - 2.16 (m, 2 H), 2.21 - 2.35 (m, 2 H), 2.89 (s, 3 H), 3.00 (t, *J*=7.2 Hz, 2 H), 3.44 - 3.56 (m, 2 H), 3.70 - 3.81 (m, 2 H), 4.36 - 4.47 (m, 2 H), 5.11 (s, 2 H), 7.10 (d, *J*=4.4 Hz, 1 H), 7.24 (m, *J*=1.8 Hz, 2 H), 7.69 (d, *J*=1.1 Hz, 1 H), 8.15 (dd, *J*=8.8, 2.0 Hz, 1 H), 8.33 (d, *J*=8.8 Hz, 1 H), 8.40 (d, *J*=4.8 Hz, 1 H), 8.66 (d, *J*=1.8 Hz, 1 H), 8.70 (s, 1 H), 8.99 - 9.07 (m, 2 H); m/z = 681 (M+H)+Cl pattern

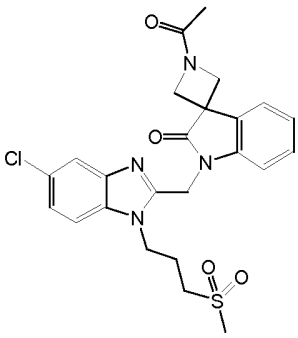
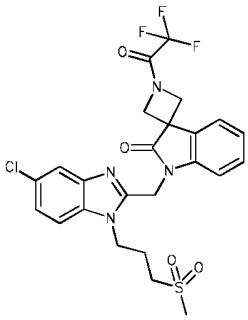
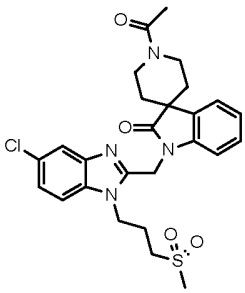
N°	structure	Name / analytical details
14		*tert*-butyl 1'-((5-chloro-1-(3-(methylsulfonyl)propyl)-1*H*-benzo[*d*] imidazol-2-yl)methyl)-2'-oxo-1',2'-dihydrospiro-[piperidine-4,3'-pyrrolo[2,3-*c*]pyridine]-1-carboxylate ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.44 (s, 9 H), 1.79 (m, *J*=5.6, 5.6 Hz, 4 H), 2.18 (m, *J*=7.6, 7.6 Hz, 2 H), 3.01 (s, 3 H), 3.20 - 3.29 (m, 2 H), 3.61 - 3.81 (m, 4 H), 4.47 (t, *J*=7.4 Hz, 2 H), 5.30 (s, 2 H), 7.31 (dd, *J*=8.6, 2.0 Hz, 1 H), 7.62 - 7.72 (m, 3 H), 8.33 (d, *J*=4.8 Hz, 1 H), 8.48 (s, 1 H); m/z = 589 (M+H)+Cl pattern
15		1-((5-chloro-1-(3-(methylsulfonyl)propyl)-1*H*-benzo[*d*]-imidazol-2-yl)methyl)-1'-(6-chloropyridazin-3-yl)spiro-[indoline-3,4'-piperidin]-2-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.83 - 1.98 (m, 4 H), 2.13 - 2.25 (m, 2 H), 3.01 (s, 3 H), 3.20 - 3.29 (m, 2 H), 3.92 - 4.13 (m, 4 H), 4.48 (t, *J*=7.4 Hz, 2 H), 5.26 (s, 2 H), 7.05 (t, *J*=7.4 Hz, 1 H), 7.17 - 7.23 (m, 1 H), 7.23 - 7.35 (m, 2 H), 7.43 - 7.51 (m, 1 H), 7.51 - 7.59 (m, 2 H), 7.63 - 7.72 (m, 2 H) m/z = 600 (M+H)+Cl pattern
16		1-((5-chloro-1-(3-(methylsulfonyl)propyl)-1*H*-benzo[*d*]-imidazol-2-yl)methyl)-1'-(quinoxalin-6-ylsulfonyl)spiro-[indoline-3,4'-piperidin]-2-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.85 (m, *J*=14.1 Hz, 2 H), 2.03 - 2.15 (m, 4 H), 2.93 (s, 3 H), 3.11 - 3.19 (m, 2 H), 3.28 (td, *J*=11.6, 2.9 Hz, 2 H), 3.62 - 3.74 (m, 2 H), 4.36 (t, *J*=7.5 Hz, 2 H), 5.12 (s, 2 H), 5.75 (s, 1 H), 7.02 (td, *J*=7.5, 0.9 Hz, 1 H), 7.12 (d, *J*=7.5 Hz, 1 H), 7.19 - 7.25 (m, 1 H), 7.27 (dd, *J*=8.6, 2.0 Hz, 1 H), 7.36 (d, *J*=7.3 Hz, 1 H), 7.59 (d, *J*=1.8 Hz, 1 H), 7.62 (d, *J*=8.6 Hz, 1 H), 8.20 (dd, *J*=8.8, 2.0 Hz, 1 H), 8.39 (d, *J*=8.8 Hz, 1 H), 8.51 (d, *J*=2.0 Hz, 1 H), 9.10 - 9.19 (m, 2 H); m/z = 680 (M+H)+Cl pattern

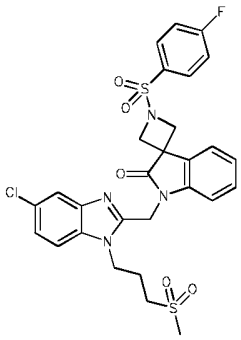
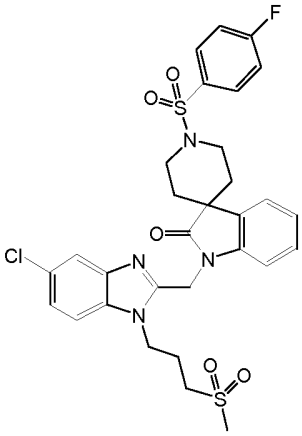
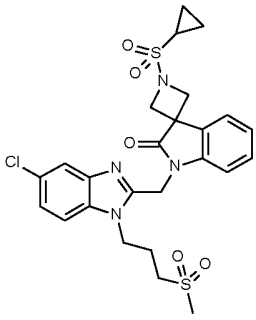
N°	structure	Name / analytical details
17		*tert*-butyl 1-((5-bromo-1-(3-(methylsulfonyl)propyl)-1*H*-benzo[*d*] imidazol-2-yl)methyl)-2-oxospiro[indoline-3,4'-piperidine]-1'-carboxylate ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.51 (s, 9 H), 1.73 - 1.91 (m, 4 H), 2.23 - 2.35 (m, 2 H), 2.96 (s, 3 H), 3.11 (t, *J*=7.2 Hz, 2 H), 3.72 - 3.91 (m, 4 H), 4.49 (t, *J*=7.8 Hz, 2 H), 5.19 (s, 2 H), 7.05 - 7.11 (m, 1 H), 7.26 (s, 1 H), 7.29 (m, *J*=8.5 Hz, 2 H), 7.28 - 7.28 (m, 1 H), 7.41 (dd, *J*=8.7, 1.6 Hz, 1 H), 7.49 (d, *J*=7.8 Hz, 1 H), 7.92 (d, *J*=1.5 Hz, 1 H); m/z = 632 (M+H)+Br pattern
18		4-(1-((5-chloro-1-(3-(methylsulfonyl)propyl)-1*H*-benzo[*d*]-imidazol-2-yl)methyl)-2-oxospiro[indoline-3,4'-piperidine]-1'-ylsulfonyl) benzonitrile ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.83 (d, *J*=14.1 Hz, 2 H), 1.98 - 2.22 (m, 4 H), 2.97 (s, 3 H), 3.13 - 3.28 (m, 4 H), 3.53 - 3.63 (m, 2 H), 4.40 (t, *J*=7.5 Hz, 1 H), 5.15 (s, 2 H), 6.99 - 7.08 (m, 1 H), 7.13 (d, *J*=7.8 Hz, 1 H), 7.20 - 7.26 (m, 1 H), 7.28 (dd, *J*=8.7, 1.9 Hz, 1 H), 7.36 (d, *J*=7.3 Hz, 1 H), 7.60 (d, *J*=1.5 Hz, 1 H), 7.62 - 7.67 (m, 1 H), 7.99 (d, *J*=8.5 Hz, 1 H), 8.15 (d, *J*=8.3 Hz, 1 H); m/z = 653 (M+H)+Cl pattern
19		1-((5-chloro-1-(3-(methylsulfonyl)propyl)-1*H*-benzo[*d*]-imidazol-2-yl) methyl)-5-fluoro-2',3',5',6'-tetrahydrospiro-[indoline-3,4'-pyran]-2-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.72 - 1.82 (m, 2 H), 1.89 (m, *J*=18.2, 4.2, 4.2 Hz, 1 H), 2.17 (m, *J*=7.6, 7.6, 7.6, 7.6 Hz, 1 H), 3.01 (s, 3 H), 3.20 - 3.28 (m, 2 H), 3.78 - 3.90 (m, 2 H), 4.07 (ddd, *J*=11.7, 8.9, 3.2 Hz, 2 H), 4.46 (t, *J*=7.5 Hz, 2 H), 5.23 (s, 2 H), 7.06 - 7.14 (m, 1 H), 7.17 - 7.22 (m, 1 H), 7.31 (dd, *J*=8.6, 2.0 Hz, 1 H), 7.53 (dd, *J*=8.7, 2.5 Hz, 1 H), 7.64 (d, *J*=2.0 Hz, 1 H), 7.67 (d, *J*=8.6 Hz, 1 H); m/z = 506 (M+H)+Cl pattern

N°	structure	Name / analytical details
20		5-bromo-1-((5-chloro-1-(3-(methylsulfonyl)propyl)-1*H*-benzo[*d*] imidazol-2-yl)methyl)-1'-(6-chloropyridazin-3-yl)spiro[indoline-3,4'-piperidin]-2-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.81 - 1.90 (m, 2 H), 1.94 - 2.04 (m, 2 H), 2.18 (m, *J*=7.3, 7.3 Hz, 2 H), 3.01 (s, 3 H), 3.21 - 3.28 (m, 2 H), 3.87 - 3.99 (m, 2 H), 4.06 - 4.17 (m, 2 H), 4.47 (t, *J*=7.5 Hz, 2 H), 5.26 (s, 2 H), 7.16 (d, *J*=8.4 Hz, 1 H), 7.31 (dd, *J*=8.6, 2.0 Hz, 1 H), 7.42 - 7.49 (m, 2 H), 7.52 - 7.57 (m, 1 H), 7.64 (d, *J*=2.0 Hz, 1 H), 7.67 (d, *J*=8.6 Hz, 1 H), 7.77 (d, *J*=2.0 Hz, 1 H); m/z = 679 (M+H)+Cl/Br pattern
21		1-((5-chloro-1-(3-(methylsulfonyl)propyl)-1*H*-benzo[*d*]-imidazol-2-yl)methyl)spiro[indoline-3,4'-piperidin]-2-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.91 - 2.10 (m, 4 H), 2.21 - 2.32 (m, 2 H), 2.97 (s, 3 H), 3.17 (br. s., 2 H), 3.20 - 3.28 (m, 2 H), 3.41 (br. s., 2 H), 4.49 (t, *J*=7.3 Hz, 2 H), 5.22 (s, 2 H), 7.04 - 7.13 (m, 1 H), 7.16 - 7.22 (m, 1 H), 7.23 - 7.30 (m, 2 H), 7.44 (d, *J*=6.9 Hz, 1 H), 7.58 (s, 1 H), 7.61 (d, *J*=8.5 Hz, 1 H); m/z = 488 (M+H)+Cl/Br pattern
22		5-bromo-1-((5-chloro-1-(3-(methylsulfonyl)propyl)-1*H*-benzo[*d*] imidazol-2-yl)methyl)-1'-isonicotinoylspiro-[indoline-3,4'-piperidin]-2-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.72 (d, *J*=13.2 Hz, 1 H), 1.86 (d, *J*=13.9 Hz, 1 H), 2.02 (m, *J*=13.9 Hz, 2 H), 2.12 - 2.24 (m, 2 H), 3.01 (s, 3 H), 3.20 - 3.28 (m, 2 H), 3.45 (d, *J*=13.6 Hz, 1 H), 3.74 (m, *J*=10.3 Hz, 1 H), 4.28 (d, *J*=13.4 Hz, 1 H), 4.46 (t, *J*=7.5 Hz, 2 H), 5.24 (s, 2 H), 7.15 (d, *J*=8.4 Hz, 1 H), 7.30 (dd, *J*=8.7, 2.1 Hz, 1 H), 7.46 (dd, *J*=8.4, 2.0 Hz, 1 H), 7.49 - 7.54 (m, 2 H), 7.62 (d, *J*=2.0 Hz, 1 H), 7.67 (d, *J*=8.6 Hz, 1 H), 7.88 (d, *J*=2.0 Hz, 1 H), 8.66 - 8.73 (m, 2 H); m/z = 672 (M+H)+Cl pattern

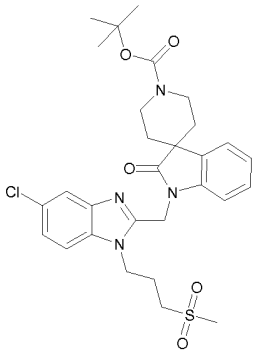
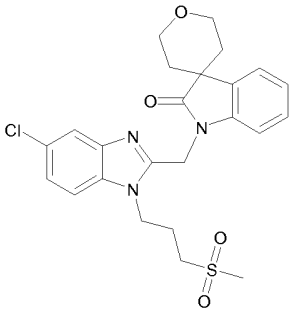
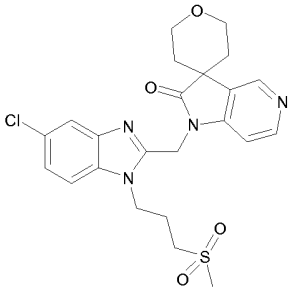
N°	structure	Name / analytical details
23		*tert*-butyl 5-bromo-1-((5-chloro-1-(3-(methyl-sulfonyl)propyl)-1*H*-benzo[*d*]imidazol-2-yl)methyl)-2-oxospiro[indoline-3,4'-piperidine]-1'-carboxylate ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.45 (s, 9 H), 1.69 - 1.79 (m, 2 H), 1.80 - 1.90 (m, 2 H), 2.17 (t, *J*=7.4 Hz, 2 H), 3.01 (s, 3 H), 3.21 - 3.28 (m, 2 H), 3.63 (br. s., 2 H), 3.70 - 3.79 (m, 2 H), 4.45 (t, *J*=7.5 Hz, 2 H), 5.24 (s, 2 H), 7.15 (d, *J*=8.6 Hz, 1 H), 7.31 (dd, *J*=8.6, 2.0 Hz, 1 H), 7.45 (dd, *J*=8.4, 2.0 Hz, 1 H), 7.63 (d, *J*=1.8 Hz, 1 H), 7.67 (d, *J*=8.6 Hz, 1 H), 7.75 (d, *J*=2.0 Hz, 1 H); m/z = 667 (M+H)+Cl pattern
24		1'-acetyl-5-chloro-1-((5-chloro-1-(3-(methylsulfonyl)-propyl)-1*H*-benzo[*d*]imidazol-2-yl)methyl)spiro[indoline-3,4'-piperidin]-2-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.68 - 1.87 (m, 3 H), 1.91 - 2.02 (m, 1 H), 2.07 (s, 3 H), 2.18 (quin, *J*=7.6 Hz, 2 H), 3.01 (s, 3 H), 3.21 - 3.29 (m, 2 H), 3.53 - 3.64 (m, 1 H), 3.69 - 3.77 (m, 1 H), 3.80 (dd, *J*=9.7, 3.3 Hz, 1 H), 3.99 - 4.08 (m, 1 H), 4.46 (t, *J*=7.5 Hz, 2 H), 5.25 (s, 2 H), 7.19 (d, *J*=8.6 Hz, 1 H), 7.28 - 7.35 (m, 1 H), 7.64 (dd, *J*=4.3, 2.1 Hz, 1 H), 7.67 (d, *J*=8.6 Hz, 1 H); m/z = 564 (M+H)+Cl pattern
25		5-chloro-1-((5-chloro-1-(3-(methylsulfonyl)propyl)-1*H*-benzo[*d*] imidazol-2-yl)methyl)-1'-(2-hydroxy-2-methylpropyl)spiro[indoline-3,4'-piperidin]-2-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.13 (s, 6 H), 1.74 - 1.90 (m, 4 H), 2.16 (m, *J*=7.3, 7.3 Hz, 2 H), 2.35 (s, 2 H), 2.69 - 2.78 (m, 2 H), 2.94 - 3.00 (m, 2 H), 3.01 (s, 3 H), 3.20 - 3.28 (m, 2 H), 4.08 (s, 1 H), 4.45 (t, *J*=7.5 Hz, 2 H), 5.23 (s, 2 H), 7.18 (d, *J*=8.4 Hz, 1 H), 7.31 (ddd, *J*=8.5, 6.5, 2.1 Hz, 1 H), 7.59 (d, *J*=2.0 Hz, 1 H), 7.63 (d, *J*=1.8 Hz, 1 H), 7.66 (d, *J*=8.6 Hz, 1 H); m/z = 594 (M+H)+Cl pattern

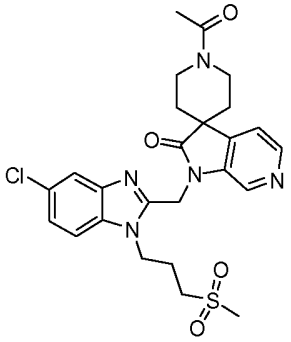
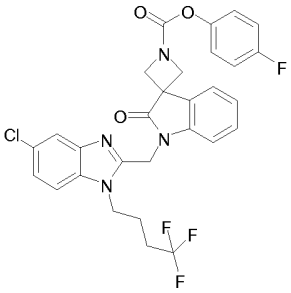
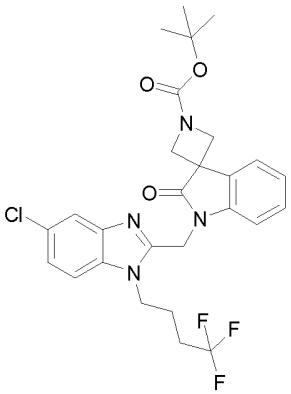
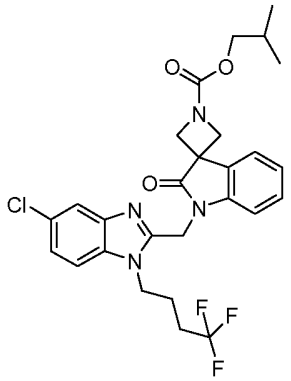
N°	structure	Name / analytical details
26		4-chloro-1-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl}methyl)spiro[indole-3,4'-piperidin]-2(1*H*)-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.51 (br. s, 2 H) 2.11 - 2.26 (m, 2 H) 2.42 - 2.54 (m, 2 H) 2.73 - 2.86 (m, 2 H) 3.02 (s, 3 H) 3.21 - 3.28 (m, 2 H) 3.28 - 3.39 (m, 2 H) 4.47 (t, J=7.37 Hz, 2 H) 5.23 (s, 2 H) 7.04 (d, J=8.14 Hz, 1 H) 7.12 (d, J=7.48 Hz, 1 H) 7.25 (t, J=7.92 Hz, 1 H) 7.30 (dd, J=8.69, 1.87 Hz, 1 H) 7.63 (d, J=1.98 Hz, 1 H) 7.67 (d, J=8.80 Hz, 1 H); m/z = 521.01 (M+H)+2*Cl pattern
27		1'-acetyl-4-chloro-1-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl}methyl)spiro[indole-3,4'-piperidin]-2(1*H*)-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.61 - 1.79 (m, 2 H) 2.07 (s, 3 H) 2.14 - 2.26 (m, 2 H) 2.37 - 2.64 (m, 2 H) 3.02 (s, 3 H) 3.21 - 3.29 (m, 2 H) 3.31 - 3.39 (m, 1 H) 3.77 - 3.88 (m, 2 H) 4.35 - 4.43 (m, 1 H) 4.47 (t, J=7.37 Hz, 2 H) 5.26 (s, 2 H) 7.07 (d, J=8.14 Hz, 1 H) 7.18 (d, J=7.70 Hz, 1 H) 7.25 - 7.34 (m, 2 H) 7.64 (d, J=1.76 Hz, 1 H) 7.68 (d, J=8.80 Hz, 1 H); m/z = 563.05 (M+H)+2*Cl pattern
28		1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl}methyl)-1-(2-methylpropanoyl)-spiro[azetidine-3,3'-indol]-2'(1'*H*)-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.00 - 1.10 (m, 6 H) 2.08 - 2.22 (m, 2 H) 2.52 - 2.60 (m, 1 H) 3.00 (s, 3 H) 3.19 - 3.26 (m, 2 H) 4.01 - 4.20 (m, 2 H) 4.37 - 4.55 (m, 4 H) 5.17 - 5.31 (m, 2 H) 7.10 - 7.24 (m, 2 H) 7.27 - 7.36 (m, 2 H) 7.62 - 7.74 (m, 3 H); m/z = 529.11 (M+H)+Cl pattern; MP = 133.12°C and 226.64°C
29		1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl}methyl)-1-(cyclopropylsulfonyl)-spiro[azetidine-3,3'-indol]-2'(1'*H*)-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.00 - 1.19 (m, 4 H) 2.09 - 2.21 (m, 2 H) 2.93 - 3.03 (m, 4 H) 3.20 - 3.27 (m, 2 H) 4.12 - 4.34 (m, 4 H) 4.47 (t, J=7.37 Hz, 2 H) 5.23 (s, 2 H) 7.14 - 7.25 (m, 2 H) 7.28 - 7.37 (m, 2 H) 7.63 - 7.71 (m, 3 H); m/z = 563.05 (M+H)+Cl pattern; MP = 191.15°C

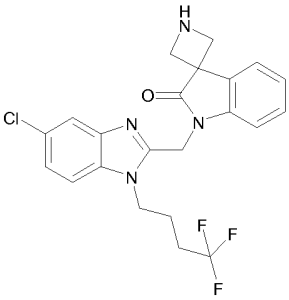
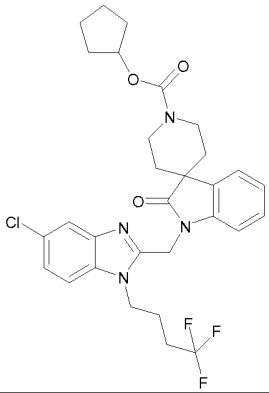
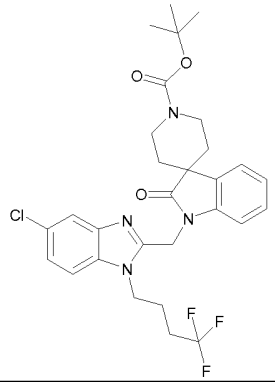
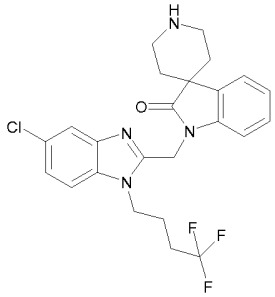
N°	structure	Name / analytical details
30		1-acetyl-1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl}methyl)spiro[azetidine-3,3'-indol]-2'(1'*H*)-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.87 (s, 3 H) 2.10 - 2.22 (m, 2 H) 3.00 (s, 3 H) 3.19 - 3.27 (m, 2 H) 4.02 - 4.17 (m, 2 H) 4.36 - 4.44 (m, 2 H) 4.47 (t, J=7.59 Hz, 2 H) 5.16 - 5.31 (m, 2 H) 7.10 - 7.17 (m, 1 H) 7.18 - 7.23 (m, 1 H) 7.27 - 7.36 (m, 2 H) 7.64 - 7.73 (m, 3 H); m/z = 501.11(M+H)+Cl pattern; MP = 221.24°C
31		1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl} methyl)-1-(trifluoroacetyl)spiro-[azetidine-3,3'-indol]-2'(1'*H*)-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.10 - 2.22 (m, 2 H) 3.00 (s, 3 H) 3.20 - 3.27 (m, 2 H) 4.29 - 4.36 (m, 1 H) 4.36 - 4.41 (m, 1 H) 4.48 (t, J=7.37 Hz, 2 H) 4.61 - 4.68 (m, 1 H) 4.70 - 4.77 (m, 1 H) 5.23 (s, 2 H) 7.11 - 7.19 (m, 1 H) 7.22 - 7.27 (m, 1 H) 7.29 - 7.37 (m, 2 H) 7.64 - 7.72 (m, 2 H) 7.82 - 7.88 (m, 1 H); m/z = 554.99 (M+H)+Cl pattern; MP = 249.58°C
32		1'-acetyl-1-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl}methyl)spiro[indole-3,4'-piperidin]-2(1*H*)-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.67 - 1.94 (m, 4 H) 2.08 (s, 3 H) 2.12 - 2.24 (m, 2 H) 3.01 (s, 3 H) 3.20 - 3.28 (m, 2 H) 3.62 - 4.04 (m, 4 H) 4.47 (t, J=7.48 Hz, 2 H) 5.24 (s, 2 H) 7.06 (t, J=7.50 Hz, 1 H) 7.19 (d, J=7.48 Hz, 1 H) 7.26 (t, J=7.50 Hz, 1 H) 7.31 (dd, J=8.58, 1.98 Hz, 1 H) 7.51 (d, J=7.26 Hz, 1 H) 7.65 (d, J=1.76 Hz, 1 H) 7.67 (d, J=8.80 Hz, 1 H); m/z = 529.11 (M+H)+Cl pattern; MP = 247.98°C

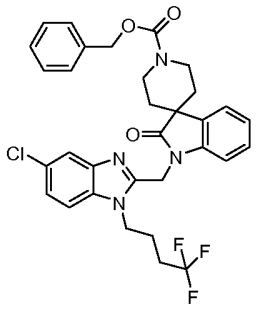
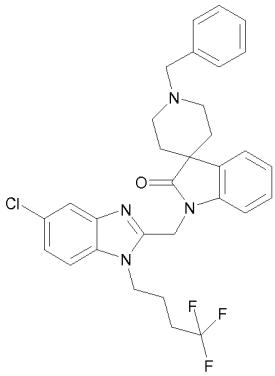
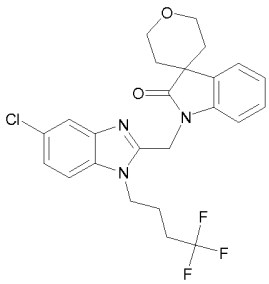
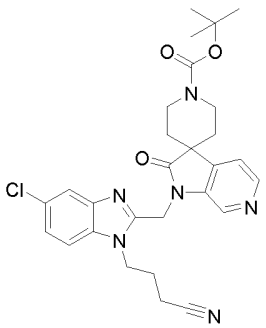
N°	structure	Name / analytical details
33		1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl}methyl)-1-[(4-fluorophenyl)-sulfonyl]spiro[azetidine-3,3'-indol]-2'(1'*H*)-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.02 - 2.17 (m, 2 H) 2.99 (s, 3 H) 3.12 - 3.24 (m, 2 H) 3.91 - 4.12 (m, 4 H) 4.40 (t, J=7.37 Hz, 2 H) 5.13 (s, 2 H) 6.98 (d, J=7.26 Hz, 1 H) 7.06 (t, J=7.30 Hz, 1 H) 7.16 (d, J=7.70 Hz, 1 H) 7.23 - 7.35 (m, 2 H) 7.56 - 7.72 (m, 4 H) 7.97 - 8.07 (m, 2 H); m/z = 617.40 (M+H)+Cl pattern
34		1-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl}methyl)-1'-[(4-fluorophenyl)-sulfonyl]spiro[indole-3,4'-piperidin]-2(1*H*)-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.77 - 1.90 (m, 2 H) 1.99 - 2.18 (m, 4 H) 2.97 (s, 3 H) 3.08 - 3.23 (m, 4 H) 3.46 - 3.59 (m, 2 H) 4.40 (t, J=7.37 Hz, 2 H) 5.15 (s, 2 H) 6.99 - 7.08 (m, 1 H) 7.14 (d, J=7.70 Hz, 1 H) 7.20 - 7.26 (m, 1 H) 7.29 (dd, J=8.58, 1.98 Hz, 1 H) 7.35 (d, J=7.26 Hz, 1 H) 7.48 - 7.57 (m, 2 H) 7.61 (d, J=1.76 Hz, 1 H) 7.65 (d, J=8.80 Hz, 1 H) 7.83 - 7.94 (m, 2 H); m/z = 645.47 (M+H)+Cl pattern; MP = 183.97°C
35		1-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl}methyl)-1'-(cyclopropylsulfonyl)-spiro[indole-3,4'-piperidin]-2(1*H*)-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.93 - 1.10 (m, 4 H) 1.84 - 2.04 (m, 4 H) 2.10 - 2.24 (m, 2 H) 2.68 - 2.81 (m, 1 H) 3.01 (s, 3 H) 3.19 - 3.28 (m, 2 H) 3.49 - 3.73 (m, 4 H) 4.47 (t, J=7.04 Hz, 2 H) 5.24 (s, 2 H) 7.03 - 7.12 (m, 1 H) 7.17 - 7.35 (m, 3 H) 7.50 (d, J=7.48 Hz, 1 H) 7.60 - 7.73 (m, 2 H); m/z = 591.04 (M+H)+Cl pattern; MP = 194.85°C

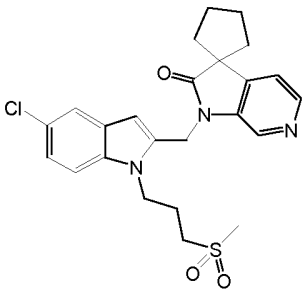
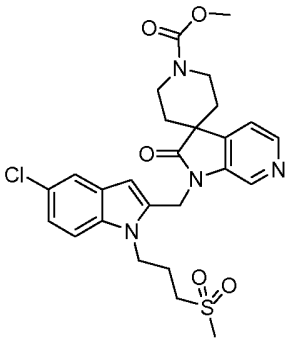
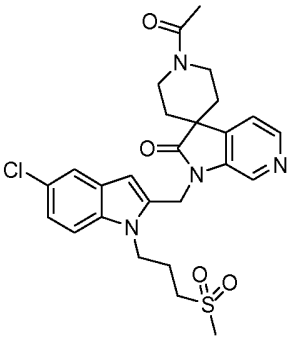
N°	structure	Name / analytical details
36		1-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl}methyl)-1'-[(4-methoxyphenyl)-sulfonyl]spiro[indole-3,4'-piperidin]-2(1*H*)-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.74 - 1.87 (m, 2 H) 1.98 - 2.18 (m, 4 H) 2.96 (s, 3 H) 3.06 - 3.23 (m, 4 H) 3.43 - 3.55 (m, 2 H) 3.87 (s, 3 H) 4.40 (t, J=7.48 Hz, 2 H) 5.15 (s, 2 H) 7.03 (t, J=7.37 Hz, 1 H) 7.13 (d, J=7.92 Hz, 1 H) 7.15 - 7.20 (m, 2 H) 7.20 - 7.26 (m, 1 H) 7.29 (dd, J=8.58, 1.76 Hz, 1 H) 7.33 (d, J=7.48 Hz, 1 H) 7.61 (d, J=1.98 Hz, 1 H) 7.65 (d, J=8.80 Hz, 1 H) 7.70 - 7.77 (m, 2 H); m/z = 657.05 (M+H)+Cl pattern; MP = 237.33°C
37		1'-((5-chloro-1-(3-(methylsulfonyl)propyl)-1*H*-benzo[d]-imidazol-2-yl)methyl)spiro[cyclopentane-1,3'-pyrrolo[2,3-c]pyridin]-2'(1'*H*)-one ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.79 - 2.30 (m, 10 H) 2.91 (s, 3 H) 3.10 (t, *J*=7.15 Hz, 2 H) 4.38 - 4.51 (m, 2 H) 5.18 (s, 2 H) 7.10 (dd, *J*=4.77, 0.75 Hz, 1 H) 7.17 - 7.23 (m, 1 H) 7.27 - 7.32 (m, 1 H) 7.68 (d, *J*=1.76 Hz, 1 H) 8.32 (d, *J*=4.77 Hz, 1 H) 8.68 (s, 1 H); m/z = 473 $(M+H)^+$
38		1'-((5-chloro-1-(3-(methylsulfonyl)propyl)-1*H*-benzo[d]-imidazol-2-yl)methyl)-2,3,5,6-tetrahydrospiro[pyran-4,3'-pyrrolo[2,3-c]pyridin]-2'(1'*H*)-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.83 (t, *J*=5.39 Hz, 4 H) 2.19 (quin, *J*=7.65 Hz, 2 H) 3.02 (s, 3 H) 3.21 - 3.29 (m, 2 H) 3.78 - 3.91 (m, 2 H) 4.04 (dt, *J*=11.72, 5.69 Hz, 2 H) 4.48 (t, *J*=7.48 Hz, 2 H) 5.30 (s, 2 H) 7.31 (dd, *J*=8.58, 1.98 Hz, 1 H) 7.65 (d, *J*=1.76 Hz, 1 H) 7.68 (d, *J*=8.58 Hz, 1 H) 7.70 (d, *J*=4.84 Hz, 1 H) 8.35 (d, *J*=4.84 Hz, 1 H) 8.48 (s, 1 H); m/z = 489 $(M+H)^+$

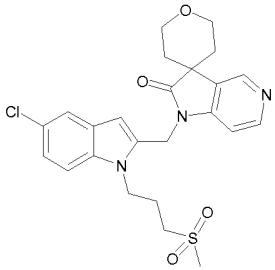
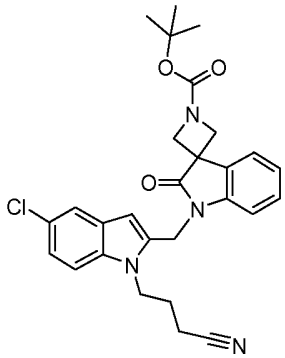
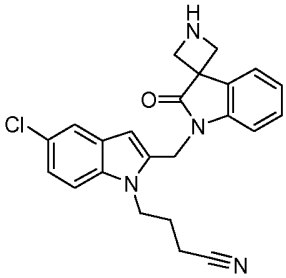
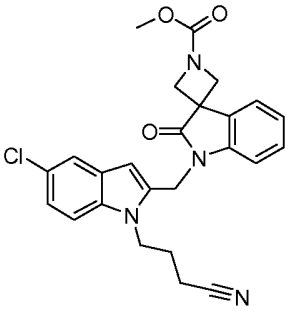
N°	structure	Name / analytical details
39		*tert*-butyl 1-((5-chloro-1-(3-(methylsulfonyl)propyl)-1*H*-benzo[*d*]imida zol-2-yl)methyl)-2-oxospiro[indoline-3,4'-piperidine]-1'-carboxylate ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.51 (s, 9 H), 1.73 - 1.91 (m, 4 H), 2.22 - 2.36 (m, 2 H), 2.96 (d, *J*=0.75 Hz, 3 H), 3.11 (t, *J*=7.15 Hz, 2 H), 3.72 - 3.92 (m, 4 H), 4.49 (t, *J*=7.78 Hz, 2 H), 5.19 (s, 2 H), 7.05 - 7.11 (m, 1 H), 7.30 (s, 4 H), 7.49 (d, *J*=7.78 Hz, 1 H), 7.75 (d, *J*=2.01 Hz, 1 H) m/z = 587 $(M+H)^+$, Cl pattern
40		1-((5-chloro-1-(3-(methylsulfonyl)propyl)-1*H*-benzo[*d*]-imidazol-2-yl)methyl)-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.80 - 1.96 (m, 4 H), 2.29 (quin, *J*=7.47 Hz, 2 H), 2.95 (s, 3 H), 3.12 (t, *J*=7.28 Hz, 2 H), 3.88 - 4.02 (m, 2 H), 4.23 (ddd, *J*=11.80, 7.28, 4.52 Hz, 2 H), 4.44 - 4.56 (m, 2 H), 5.19 (s, 2 H), 7.05 - 7.13 (m, 1 H), 7.27 - 7.36 (m, 3 H), 7.39 (d, *J*=7.28 Hz, 1 H), 7.50 (d, *J*=7.78 Hz, 1 H), 7.76 (d, *J*=1.76 Hz, 1 H); m/z = 488 $(M+H)^{+,}$ Cl pattern
41		1'-((5-chloro-1-(3-(methylsulfonyl)propyl)-1*H*-benzo[*d*]-imidazol-2-yl)methyl)-2,3,5,6-tetrahydrospiro[pyran-4,3'-pyrrolo[3,2-*c*]pyridin]-2'(1'*H*)-one ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.76 - 1.89 (m, 2 H), 2.01 (ddd, *J*=13.64, 7.37, 3.63 Hz, 2 H), 2.27 - 2.39 (m, 2 H), 2.99 (s, 3 H), 3.14 (d, *J*=14.30 Hz, 2 H), 3.94 (ddd, *J*=11.72, 7.54, 3.63 Hz, 2 H), 4.19 (ddd, *J*=11.66, 7.37, 3.85 Hz, 2 H), 4.45 - 4.57 (m, 2 H), 5.17 (s, 2 H), 7.27 - 7.31 (m, 1 H), 7.31 - 7.36 (m, 1 H), 7.46 (d, *J*=5.28 Hz, 1 H), 7.73 (d, *J*=1.76 Hz, 1 H), 8.51 (d, *J*=5.28 Hz, 1 H), 8.63 (s, 1 H); m/z = 489 $(M+H)^+$, Cl pattern

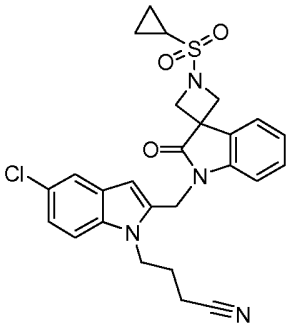
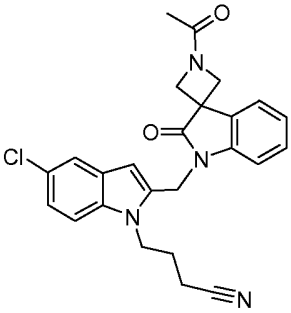
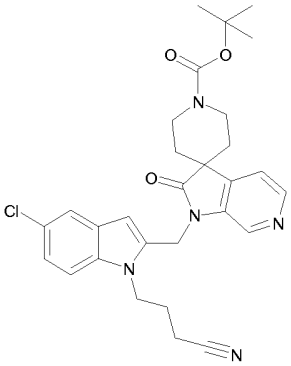
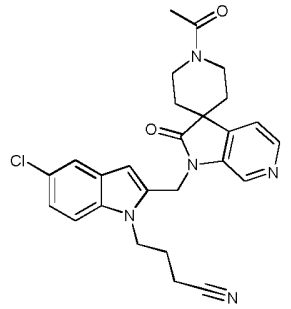
N°	structure	Name / analytical details
42		1-acetyl-1'-((5-chloro-1-(3-(methylsulfonyl)propyl)-1*H*-benzo[d]imida zol-2-yl)methyl)spiro[piperidine-4,3'-pyrrolo-[2,3-c]pyridin]-2'(1'H)-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.72 - 1.82 (m, 2 H), 1.83 - 1.92 (m, 2 H), 2.08 (s, 3 H), 2.19 (m, *J*=7.4, 7.4 Hz, 2 H), 3.02 (s, 3 H), 3.22 - 3.29 (m, 2 H), 3.66 - 3.79 (m, 2 H), 3.80 - 3.93 (m, 2 H), 4.48 (t, *J*=7.5 Hz, 2 H), 5.31 (s, 2 H), 7.31 (dd, *J*=8.7, 1.9 Hz, 1 H), 7.65 (d, *J*=2.0 Hz, 2 H), 7.68 (d, *J*=8.6 Hz, 1 H), 8.34 (d, *J*=4.8 Hz, 1 H), 8.49 (s, 1 H)
43		4-fluorophenyl 1'-((5-chloro-1-(4,4,4-trifluorobutyl)-1*H*-benzo[*d*]imida zol-2-yl)methyl)-2'-oxospiro[azetidine-3,3'-indoline]-1-carboxylate ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.89 - 2.04 (m, 2 H), 2.33 - 2.48 (m, 2 H), 4.27 (br. s., 2 H), 4.44 (t, *J*=7.5 Hz, 3 H), 5.25 (s, 2 H), 7.17 (td, *J*=7.5, 0.8 Hz, 1 H), 7.21 - 7.28 (m, 5 H), 7.28 - 7.38 (m, 2 H), 7.65 - 7.73 (m, 2 H), 7.80 - 7.86 (m, 1 H); m/z = 587 $(M+H)^+$, Cl pattern
44		*tert*-butyl 1'-((5-chloro-1-(4,4,4-trifluorobutyl)-1*H*-benzo[*d*]imidazol-2-yl)methyl)-2'-oxospiro[azetidine-3,3'-indoline]-1-carboxylate ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.47 - 1.53 (m, 9 H), 1.95 (m, *J*=7.8, 7.8 Hz, 2 H), 2.14 - 2.29 (m, 2 H), 4.08 (d, *J*=8.3 Hz, 2 H), 4.33 - 4.41 (m, 4 H), 5.19 (s, 2 H), 7.13 - 7.19 (m, 1 H), 7.20 - 7.29 (m, 2 H), 7.29 - 7.35 (m, 1 H), 7.51 (d, *J*=7.8 Hz, 1 H), 7.54 (d, *J*=7.3 Hz, 1 H), 7.76 (d, *J*=1.8 Hz, 1 H); m/z = 587 $(M+H)^+$, Cl pattern
45		isobutyl 1'-((5-chloro-1-(4,4,4-trifluorobutyl)-1*H*-benzo[*d*]-imidazol-2-yl)methyl)-2'-oxospiro[azetidine-3,3'-indoline]-1-carboxylate ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.95 (d, *J*=6.5 Hz, 6 H), 1.88 - 2.03 (m, 3 H), 2.14 - 2.29 (m, 2 H), 3.92 (d, *J*=6.8 Hz, 2 H), 4.14 (d, *J*=8.3 Hz, 2 H), 4.37 (t, *J*=7.8 Hz, 2 H), 4.42 (d, *J*=8.3 Hz, 2 H), 5.19 (s, 2 H), 7.12 - 7.20 (m, 1 H), 7.21 - 7.30 (m, 2 H), 7.33 (td, *J*=7.8, 1.3 Hz, 1 H), 7.53 (t, *J*=7.2 Hz, 2 H), 7.76 (d, *J*=1.5 Hz, 1 H); m/z = 549 $(M+H)^+$, Cl pattern

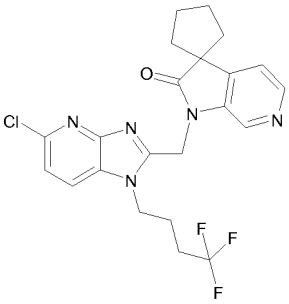
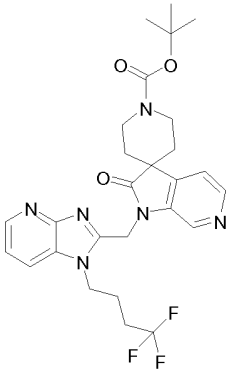
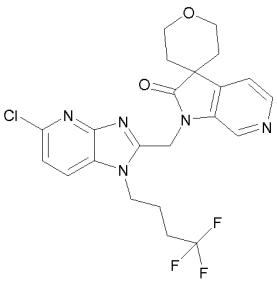
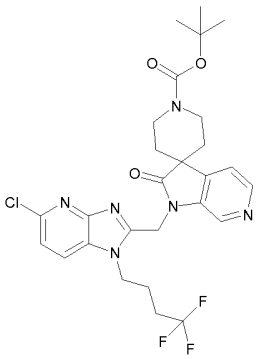
N°	structure	Name / analytical details
46		1'-((5-chloro-1-(4,4,4-trifluorobutyl)-1*H*-benzo[*d*]imidazol-2-yl) methyl)spiro[azetidine-3,3'-indolin]-2'-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.92 - 2.05 (m, 2 H), 2.35 - 2.46 (m, 2 H), 4.19 - 4.26 (m, 2 H), 4.26 - 4.33 (m, 2 H), 4.43 (t, *J*=7.7 Hz, 2 H), 5.21 (s, 2 H), 7.20 (t, *J*=7.4 Hz, 1 H), 7.26 (d, *J*=7.8 Hz, 1 H), 7.31 (dd, *J*=8.8, 2.0 Hz, 1 H), 7.33 - 7.40 (m, 1 H), 7.65 (d, *J*=2.0 Hz, 1 H), 7.70 (d, *J*=8.5 Hz, 1 H), 7.85 (d, *J*=7.3 Hz, 1 H), 9.39 (br. s., 1 H); m/z = 449 $(M+H)^+$, Cl pattern
47		Cyclopentyl 1-((5-chloro-1-(4,4,4-trifluorobutyl)-1*H*-benzo[*d*]imidazol -2-yl)methyl)-2-oxospiro[indoline-3,4'-piperidine]-1'-carboxylate ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.54 - 1.67 (m, 2 H), 1.68 - 2.06 (m, 12 H), 2.22 (m, *J*=10.2, 8.1, 8.1 Hz, 2 H), 3.75 - 3.96 (m, 4 H), 4.32 - 4.41 (m, 2 H), 5.14 - 5.23 (m, 3 H), 7.05 - 7.11 (m, 1 H), 7.19 - 7.25 (m, 1 H), 7.27 - 7.32 (m, 2 H), 7.52 - 7.61 (m, 1 H), 7.77 (d, *J*=1.8 Hz, 1 H) m/z = 590 $(M+H)^+$, Cl pattern
48		*tert*-butyl 1-((5-chloro-1-(4,4,4-trifluorobutyl)-1*H*-benzo[*d*]-imidazol-2-yl)methyl)-2-oxospiro[indoline-3,4'-piperidine]-1'-carboxylate ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.51 (s, 10 H), 1.73 - 1.89 (m, 4 H), 1.91 - 2.02 (m, 2 H), 2.15 - 2.30 (m, 2 H), 3.74 - 3.91 (m, 4 H), 4.32 - 4.40 (m, 2 H), 5.19 (s, 2 H), 7.05 - 7.11 (m, 1 H), 7.20 - 7.24 (m, 1 H), 7.26 - 7.31 (m, 2 H), 7.55 (d, *J*=7.5 Hz, 1 H), 7.77 (d, *J*=1.8 Hz, 1 H) m/z = 577 $(M+H)^+$, Cl pattern
49		1-((5-chloro-1-(4,4,4-trifluorobutyl)-1*H*-benzo[*d*]imidazol-2-yl)methyl) spiro[indoline-3,4'-piperidin]-2-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.89 - 2.03 (m, 4 H), 2.04 - 2.17 (m, 2 H), 2.34 - 2.47 (m, 2 H), 3.35 - 3.41 (m, 2 H), 3.52 (br. s., 2 H), 4.42 (t, *J*=7.7 Hz, 2 H), 5.24 (s, 2 H), 7.13 (t, *J*=7.5 Hz, 1 H), 7.21 - 7.27 (m, 1 H), 7.27 - 7.35 (m, 1 H), 7.41 (d, *J*=7.3 Hz, 1 H), 7.63 (d, *J*=2.0 Hz, 1 H), 7.69 (d, *J*=8.8 Hz, 1 H), 8.76 (br. s., 1 H); m/z = 477 $(M+H)^+$, Cl pattern

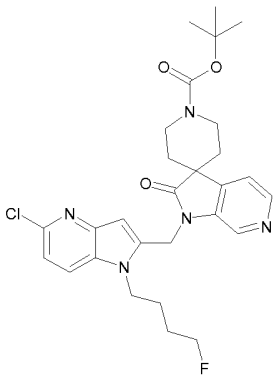
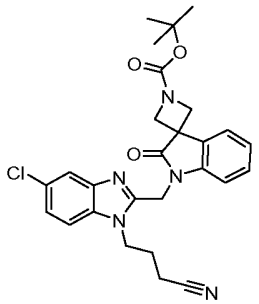
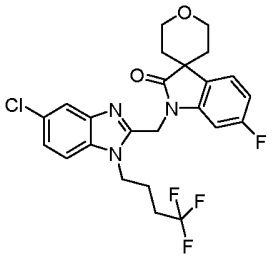
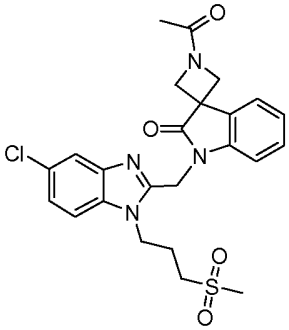
N°	structure	Name / analytical details
50		benzyl 1-((5-chloro-1-(4,4,4-trifluorobutyl)-1*H*-benzo[*d*]-imidazol-2-yl)methyl)-2-oxospiro[indoline-3,4'-piperidine]-1'-carboxylate ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.75 - 1.91 (m, 4 H), 1.91 - 2.03 (m, 2 H), 2.21 (m, *J*=10.4, 8.0, 8.0 Hz, 2 H), 3.84 - 4.01 (m, 4 H), 4.31 - 4.42 (m, 2 H), 5.15 - 5.25 (m, 4 H), 7.04 - 7.11 (m, 1 H), 7.20 - 7.30 (m, 4 H), 7.30 - 7.37 (m, 2 H), 7.37 - 7.43 (m, 3 H), 7.55 (d, *J*=8.0 Hz, 1 H), 7.77 (d, *J*=1.8 Hz, 1 H) m/z = 612 $(M+H)^+$, Cl pattern
51		1'-benzyl-1-((5-chloro-1-(4,4,4-trifluorobutyl)-1*H*-benzo[*d*]-imidazol-2-yl)methyl)spiro[indoline-3,4'-piperidin]-2-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.71 - 1.80 (m, 2 H), 1.81 - 1.89 (m, 2 H), 1.93 (t, *J*=7.7 Hz, 2 H), 2.31 - 2.47 (m, 3 H), 2.58 - 2.69 (m, 2 H), 2.83 (m, *J*=7.7, 7.7, 3.8, 3.8 Hz, 2 H), 3.63 (s, 2 H), 4.40 (t, *J*=7.7 Hz, 2 H), 5.22 (s, 2 H), 7.01 - 7.08 (m, 1 H), 7.17 - 7.41 (m, 8 H), 7.53 (d, *J*=7.5 Hz, 1 H), 7.65 (d, *J*=2.0 Hz, 1 H), 7.67 (d, *J*=8.8 Hz, 1 H); m/z = 568 $(M+H)^+$, Cl pattern
52		1-((5-chloro-1-(4,4,4-trifluorobutyl)-1*H*-benzo[*d*]imidazol-2-yl)methyl) -2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.87 (t, *J*=5.52 Hz, 4 H), 1.91 - 2.02 (m, 2 H), 2.14 - 2.33 (m, 2 H), 3.95 (dt, *J*=11.73, 4.93 Hz, 2 H), 4.24 (dt, *J*=11.86, 5.99 Hz, 2 H), 4.32 - 4.43 (m, 2 H), 5.19 (s, 2 H), 7.04 - 7.14 (m, 1 H), 7.19 - 7.25 (m, 1 H), 7.25 - 7.32 (m, 2 H), 7.37 (d, *J*=7.28 Hz, 1 H), 7.55 (d, *J*=7.78 Hz, 1 H), 7.77 (d, *J*=1.76 Hz, 1 H); m/z = 478 $(M+H)^+$, Cl pattern
53		tert-butyl 1'-((5-chloro-1-(3-cyanopropyl)-1*H*-benzo[d]-imidazol-2-yl) methyl)-2'-oxo-1',2'-dihydrospiro[piperidine-4,3'-pyrrolo[2,3-c]pyridine]-1-carboxylate ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.44 (s, 9 H), 1.79 (m, *J*=5.7, 5.7 Hz, 4 H), 2.02 - 2.16 (m, 2 H), 2.63 (t, *J*=7.4 Hz, 2 H), 3.61 - 3.78 (m, 2 H), 4.39 (t, *J*=7.5 Hz, 1 H), 5.30 (s, 1 H), 7.30 (dd, *J*=8.6, 2.0 Hz, 1 H), 7.64 (d, *J*=2.0 Hz, 1 H), 7.65 (d, *J*=5.5 Hz, 1 H), 7.67 (s, 1 H), 8.32 (d, *J*=4.6 Hz, 1 H), 8.47 (s, 1 H)

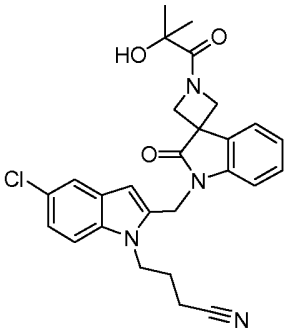
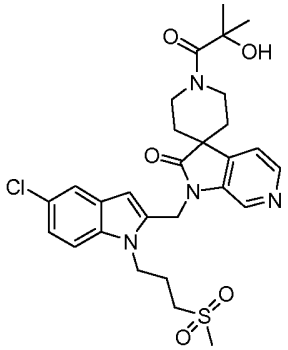
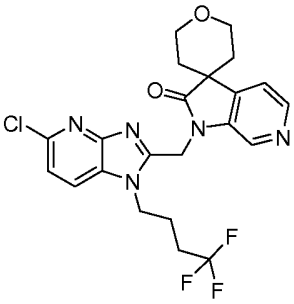
N°	structure	Name / analytical details
54		1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-indol-2-yl}methyl)spiro [cyclopentane-1,3'-pyrrolo[2,3-*c*]pyridin]-2'(1'*H*)-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.81 - 2.16 (m, 10 H) 3.00 (s, 3 H) 3.14 - 3.24 (m, 2 H) 4.37 (t, *J*=7.40 Hz, 2 H) 5.19 (s, 2 H) 6.37 (s, 1 H) 7.16 (dd, *J*=8.78, 2.01 Hz, 1 H) 7.43 (d, *J*=4.77 Hz, 1 H) 7.55 (m, *J*=5.40, 3.40 Hz, 2 H) 8.31 (d, *J*=4.77 Hz, 1 H) 8.34 (s, 1 H); m/z = 472.44 $(M+H)^+$, Cl pattern
55		1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-indol-2-yl}-methyl)-2'-oxo-1',2'-dihydro-1*H*-spiro[piperidine-4,3'-pyrrolo[2,3-*c*]pyridine]-1-carboxylate ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.73 - 1.92 (m, 4 H) 2.03 - 2.15 (m, 2 H) 3.01 (s, 3 H) 3.16 - 3.24 (m, 2 H) 3.66 (s, 3 H) 3.70 - 3.85 (m, 4 H) 4.38 (t, J=7.59 Hz, 2 H) 5.20 (s, 2 H) 6.37 (s, 1 H) 7.16 (dd, J=8.69, 2.09 Hz, 1 H) 7.53 (d, J=2.20 Hz, 1 H) 7.55 (d, J=8.80 Hz, 1 H) 7.68 - 7.71 (m, 1 H) 8.34 (d, J=4.84 Hz, 1 H) 8.39 (s, 1 H); m/z = 545.04 $(M+H)^+$, Cl pattern; MP = 234.28°C
56		1-acetyl-1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-indol-2-yl}methyl)spiro[piperidine-4,3'-pyrrolo[2,3-*c*]pyridin]-2'(1'*H*)-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.75 - 1.82 (m, 2 H) 1.84 - 1.96 (m, 2 H) 2.04 - 2.17 (m, 5 H) 3.01 (s, 3 H) 3.17 - 3.24 (m, 2 H) 3.64 - 3.95 (m, 4 H) 4.38 (t, J=7.59 Hz, 2 H) 5.21 (s, 2 H) 6.38 (s, 1 H) 7.16 (dd, J=8.69, 2.09 Hz, 1 H) 7.53 (d, J=1.98 Hz, 1 H) 7.56 (d, J=8.80 Hz, 1 H) 7.68 (d, J=4.62 Hz, 1 H) 8.34 (d, J=4.62 Hz, 1 H) 8.39 (s, 1 H); m/z = 529.07 $(M+H)^+$, Cl pattern; MP = 258.32°C

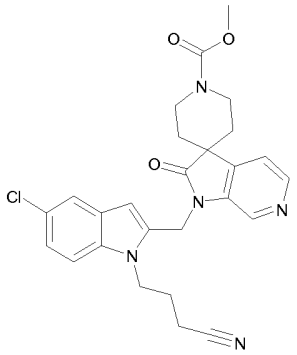
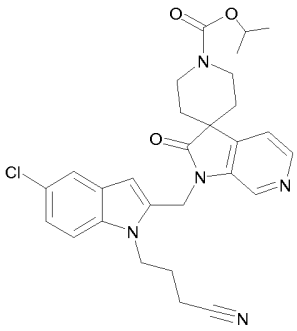
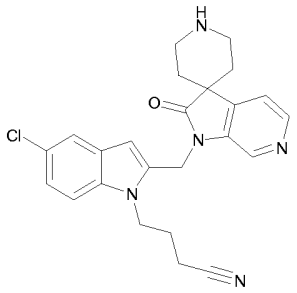
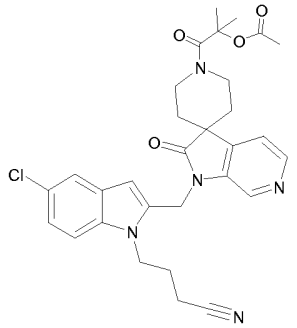
N°	structure	Name / analytical details
57		1'-((5-chloro-1-(3-(methylsulfonyl)propyl)-1*H*-indol-2-yl)-methyl)-2,3,5,6-tetrahydrospiro[pyran-4,3'-pyrrolo[3,2-*c*]-pyridin]-2'(1'*H*)-one ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.85 (ddd, *J*=13.64, 7.15, 3.63 Hz, 2 H), 2.01 (ddd, *J*=13.59, 7.10, 3.74 Hz, 2 H), 2.31 (quin, *J*=7.26 Hz, 2 H), 2.96 (s, 3 H), 3.07 (t, *J*=7.15 Hz, 2 H), 3.95 (ddd, *J*=11.72, 7.43, 3.74 Hz, 2 H), 4.16 - 4.26 (m, 2 H), 4.40 (t, *J*=7.37 Hz, 2 H), 5.07 (s, 2 H), 6.37 (s, 1 H), 6.99 (d, *J*=5.28 Hz, 1 H), 7.14 - 7.21 (m, 1 H), 7.23 - 7.29 (m, 1 H), 7.50 (d, *J*=1.76 Hz, 1 H), 8.47 (d, *J*=5.28 Hz, 1 H), 8.64 (s, 1 H); m/z = 488 $(M+H)^+$, Cl pattern
58		*tert*-butyl 1'-{[5-chloro-1-(3-cyanopropyl)-1*H*-indol-2-yl]-methyl}-2'-oxo-1',2'-dihydro-1*H*-spiro[azetidine-3,3'-indole]-1-carboxylate ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.45 (s, 9 H) 1.87 - 2.03 (m, 2 H) 2.57 (t, J=7.37 Hz, 2 H) 4.03 - 4.21 (m, 4 H) 4.30 (t, J=7.59 Hz, 2 H) 5.13 (s, 2 H) 6.36 (s, 1 H) 7.08 (d, J=7.92 Hz, 1 H) 7.11 - 7.18 (m, 2 H) 7.25 - 7.31 (m, 1 H) 7.49 - 7.55 (m, 2 H) 7.68 (d, J=6.82 Hz, 1 H) ; m/z = 505.42 $(M+H)^+$, Cl pattern
59		4-{5-chloro-2-[(2'-oxospiro[azetidine-3,3'-indol]-1'(2'*H*)-yl)-methyl]-1*H*-indol-1-yl}butanenitrile ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.83 - 2.00 (m, 2 H) 2.53 - 2.65 (m, 2 H) 3.45 (s, 1 H) 3.51 - 3.85 (m, 4 H) 4.21 - 4.39 (m, 2 H) 5.13 (s, 2 H) 6.25 - 6.45 (m, 1 H) 6.99 - 7.20 (m, 3 H) 7.21 - 7.32 (m, 1 H) 7.44 - 7.61 (m, 2 H) 7.78 (d, J=6.82 Hz, 1 H); m/z = 405.03 $(M+H)^+$, Cl pattern
60		1'-{[5-chloro-1-(3-cyanopropyl)-1*H*-indol-2-yl]methyl}-2'-oxo-1',2'-dihydro-1*H*-spiro[azetidine-3,3'-indole]-1-carboxylate ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 1.97 (quin, J=7.48 Hz, 2 H) 2.57 (t, J=7.37 Hz, 2 H) 3.65 (s, 3 H) 4.11 - 4.36 (m, 6 H) 5.13 (s, 2 H) 6.37 (s, 1 H) 7.08 (d, J=7.92 Hz, 1 H) 7.11 - 7.18 (m, 2 H) 7.29 (td, J=7.81, 1.10 Hz, 1 H) 7.48 - 7.55 (m, 2 H) 7.70 - 7.76 (m, 1 H) ; m/z = 463.09 $(M+H)^+$, Cl pattern

N°	structure	Name / analytical details
61		4-(5-chloro-2-{[1-(cyclopropylsulfonyl)-2'-oxospiro-[azetidine-3,3'-indol]-1'(2'*H*)-yl]methyl}-1*H*-indol-1-yl)-butanenitrile ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.99 - 1.08 (m, 2 H) 1.12 - 1.20 (m, 2 H) 1.90 - 2.02 (m, 2 H) 2.58 (t, J=7.26 Hz, 2 H) 2.93 - 3.04 (m, 1 H) 4.13 - 4.37 (m, 6 H) 5.13 (s, 2 H) 6.38 (s, 1 H) 7.07 - 7.21 (m, 3 H) 7.27 - 7.35 (m, 1 H) 7.48 - 7.55 (m, 2 H) 7.67 (d, J=7.04 Hz, 1 H); m/z = 509.07 $(M+H)^+$, Cl pattern
62		4-{2-[(1-acetyl-2'-oxospiro[azetidine-3,3'-indol]-1'(2'*H*)-yl)-methyl]-5-chloro-1*H*-indol-1-yl}butanenitrile ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.88 (s, 3 H) 1.91 - 2.03 (m, 2 H) 2.58 (t, J=7.48 Hz, 2 H) 4.03 - 4.19 (m, 2 H) 4.31 (t, J=7.59 Hz, 2 H) 4.37 - 4.47 (m, 2 H) 5.14 (s, 2 H) 6.37 (s, 1 H) 7.05 - 7.19 (m, 3 H) 7.29 (td, J=7.70, 1.10 Hz, 1 H) 7.48 - 7.56 (m, 2 H) 7.71 (dd, J=6.82, 0.70 Hz, 1 H) ; m/z = 447.42 $(M+H)^+$, Cl pattern; MP = 195.25°C
63		tert-butyl 1'-((5-chloro-1-(3-cyanopropyl)-1*H*-indol-2-yl)-methyl)-2'-oxo-1',2'-dihydrospiro[piperidine-4,3'-pyrrolo-[2,3-c]pyridine]-1-carboxylate ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.45 (s, 9 H) 1.80 (t, *J*=5.61 Hz, 4 H) 1.92 - 2.04 (m, 2 H) 2.58 (t, *J*=7.26 Hz, 2 H) 3.58 - 3.82 (m, 4 H) 4.29 (t, *J*=7.59 Hz, 2 H) 5.20 (s, 2 H) 6.36 (s, 1 H) 7.10 - 7.18 (m, 1 H) 7.48 - 7.57 (m, 2 H) 7.69 (d, *J*=4.62 Hz, 1 H) 8.33 (d, *J*=4.84 Hz, 1 H) 8.39 (s, 1 H); m/z = 534 $(M+H)^+$
64		4-(2-((1-acetyl-2'-oxospiro[piperidine-4,3'-pyrrolo[2,3-c]-pyridin]-1'(2'*H*)-yl)methyl)-5-chloro-1*H*-indol-1-yl)butane-nitrile ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.71 - 1.82 (m, 2 H) 1.83 - 1.93 (m, 2 H) 1.99 (t, *J*=7.48 Hz, 2 H) 2.09 (s, 3 H) 2.59 (t, *J*=7.37 Hz, 2 H) 3.60 - 3.96 (m, 4 H) 4.20 - 4.37 (m, 2 H) 5.20 (s, 2 H) 6.36 (s, 1 H) 7.09 - 7.19 (m, 1 H) 7.46 - 7.57 (m, 2 H) 7.68 (d, *J*=4.62 Hz, 1 H) 8.34 (d, *J*=4.62 Hz, 1 H) 8.39 (s, 1 H) m/z = 476 $(M+H)^+$

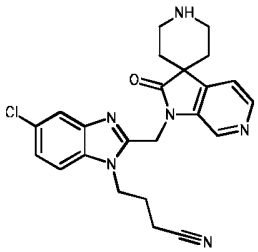
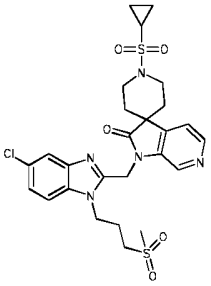
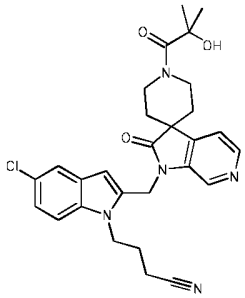
N°	structure	Name / analytical details
65		1’-((5-chloro-1-(4,4,4-trifluorobutyl)-1*H*-imidazo[4,5-*b*]-pyridin-2-yl)methyl)spiro[cyclopentane-1,3’-pyrrolo[2,3-*c*]-pyridin]-2’(1’*H*)-one ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.81 - 1.92 (m, 2 H), 1.94 - 2.06 (m, 4 H), 2.07 - 2.32 (m, 7 H), 4.39 - 4.47 (m, 2 H), 5.26 (s, 2 H), 7.12 (dd, *J*=4.8, 1.0 Hz, 1 H), 7.27 (d, *J*=8.5 Hz, 1 H), 7.62 (d, *J*=8.3 Hz, 1 H), 8.40 (d, *J*=4.8 Hz, 1 H), 8.83 (d, *J*=0.5 Hz, 1 H); m/z = 464 $(M+H)^+$
66		*tert*-butyl-2'-oxo-1'-((1-(4,4,4-trifluorobutyl)-1*H*-imidazo-[4,5-b]pyridine-2-yl)methyl)-1',2'-dihydrospiro[piperidine-4,3'-pyrrolo[2,3-c]pyridine]-1-carboxylate ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.44 (s, 9 H) 1.79 (t, *J*=5.61 Hz, 4 H) 1.94 - 2.11 (m, 2 H) 2.34 - 2.46 (m, 2 H) 3.51 - 3.83 (m, 4 H) 4.45 (t, *J*=7.59 Hz, 2 H) 5.35 (s, 2 H) 7.28 (dd, *J*=8.03, 4.73 Hz, 1 H) 7.69 (d, *J*=4.84 Hz, 1 H) 8.11 (dd, *J*=8.14, 1.32 Hz, 1 H) 8.34 (d, *J*=4.84 Hz, 1 H) 8.37 (dd, *J*=4.62, 1.32 Hz, 1 H) 8.52 (s, 1 H); m/z = 476 $(M+H)^+$
67		1'-((5-chloro-1-(4,4,4-trifluorobutyl)-1*H*-imidazo[4,5-b]-pyridin-2-yl)methyl)-2,3,5,6-tetrahydrospiro[pyran-4,3'-pyrrolo[2,3-c]pyridin]-2'(1'*H*)-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.69 - 1.89 (m, 4 H) 1.92 - 2.08 (m, 2 H) 2.28 - 2.45 (m, 2 H) 3.75 - 3.91 (m, 2 H) 3.96 - 4.09 (m, 2 H) 4.45 (t, *J*=7.59 Hz, 2 H) 5.34 (s, 2 H) 7.36 (d, *J*=8.36 Hz, 1 H) 7.70 (dd, *J*=4.73, 0.55 Hz, 1 H) 8.19 (d, *J*=8.36 Hz, 1 H) 8.35 (d, *J*=4.84 Hz, 1 H) 8.46 (s, 1 H); m/z = 480 $(M+H)^+$
68		*tert*-butyl-1’-((5-chloro-1-(4,4,4-trifluorobutyl)-1*H*-imidazo-[4,5-*b*] pyridin-2-yl)methyl)-2’-oxo-1’,2’-dihydrospiro-[piperidine-4,3’-pyrrolo[2,3-*c*]pyridine]-1-carboxylate ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.51 (s, 9 H), 1.72 - 1.82 (m, 2 H), 1.82 - 1.92 (m, 2 H), 1.97 - 2.10 (m, 2 H), 2.19 - 2.36 (m, 2 H), 3.67 - 3.80 (m, 2 H), 3.80 - 3.91 (m, 2 H), 4.44 (t, *J*=7.90 Hz, 2 H), 5.24 (s, 2 H), 7.24 (dd, *J*=4.84, 0.66 Hz, 1 H), 7.27 (d, *J*=8.36 Hz, 1 H), 7.63 (d, *J*=8.58 Hz, 1 H), 8.42 (d, *J*=4.84 Hz, 1 H), 8.84 (s, 1 H); m/z = 480 $(M+H)^+$, Cl pattern

N°	structure	Name / analytical details
69		*tert*-butyl 1'-((5-chloro-1-(4-fluorobutyl)-1*H*-pyrrolo[3,2-*b*]-pyridin-2-yl)methyl)-2'-oxo-1',2'-dihydrospiro[piperidine-4,3'-pyrrolo[2,3-*c*]pyridine]-1-carboxylate ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.51 (s, 9 H), 1.68 - 1.95 (m, 8 H), 3.69 - 3.82 (m, 2 H), 3.83 - 3.93 (m, 2 H), 4.20 - 4.29 (m, 2 H), 4.43 (t, *J*=5.61 Hz, 1 H), 4.55 (t, *J*=5.50 Hz, 1 H), 5.13 (s, 2 H), 6.61 (s, 1 H), 7.12 (d, *J*=8.58 Hz, 1 H), 7.27 (d, *J*=0.66 Hz, 1 H), 7.55 (dd, *J*=8.58, 0.66 Hz, 1 H), 8.33 (s, 1 H), 8.40 (d, *J*=4.84 Hz, 1 H); m/z = 542 $(M+H)^+$, Cl pattern
70		tert-butyl 1'-((5-chloro-1-(3-cyanopropyl)-1*H*-benzo[d]-imidazol-2-yl)methyl)-2'-oxospiro[azetidine-3,3'-indoline]-1-carboxylate 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.44 (s, 9 H) 2.06 (quin, J=7.48 Hz, 2 H) 2.62 (t, J=7.37 Hz, 2 H) 3.97 - 4.23 (m, 4 H) 4.39 (t, J=7.48 Hz, 2 H) 5.22 (s, 2 H) 7.08 - 7.22 (m, 2 H) 7.26 - 7.36 (m, 2 H) 7.60 - 7.73 (m, 3 H) m/z = 506.14 (M+H)+Cl pattern; MP: 144.10°C
71		1-((5-chloro-1-(4,4,4-trifluorobutyl)-1*H*-benzo[d]imidazol-2-yl)methyl) -6-fluoro-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.68 - 1.89 (m, 4 H) 1.90 - 2.04 (m, 2 H) 2.34 - 2.47 (m, 2 H) 3.78 - 3.87 (m, 2 H) 3.99 - 4.13 (m, 2 H) 4.41 (t, J=7.48 Hz, 2 H) 5.23 (s, 2 H) 6.80 - 6.91 (m, 1 H) 7.16 (dd, J=9.46, 2.20 Hz, 1 H) 7.30 (dd, J=8.58, 1.76 Hz, 1 H) 7.59 (dd, J=8.14, 5.50 Hz, 1 H) 7.66 (d, J=1.76 Hz, 1 H) 7.68 (d, J=8.58 Hz, 1 H); m/z = 496.11(M+H)+Cl pattern; MP = 172.70°C
72		1-acetyl-1'-((5-chloro-1-(3-(methylsulfonyl)propyl)-1*H*-benzo[d]imidazol-2-yl)methyl)spiro[azetidine-3,3'-indolin]-2'-one 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.87 (s, 3 H) 2.08 - 2.23 (m, 2 H) 3.00 (s, 3 H) 3.19 - 3.27 (m, 2 H) 4.03 - 4.18 (m, 2 H) 4.36 - 4.44 (m, 2 H) 4.47 (t, J=7.48 Hz, 2 H) 5.13 - 5.35 (m, 2 H) 7.09 - 7.17 (m, 1 H) 7.20 (d, J=7.48 Hz, 1 H) 7.25 - 7.36 (m, 2 H) 7.64 - 7.74 (m, 3 H); m/z = 501.03 (M+H)+Cl pattern; MP = 226.51°C

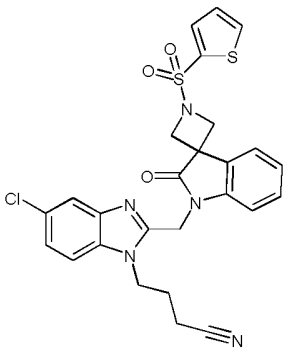
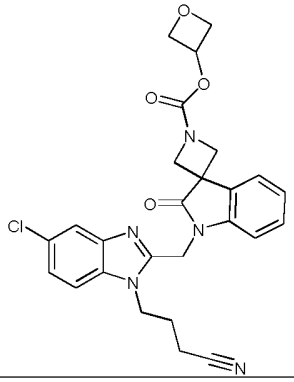
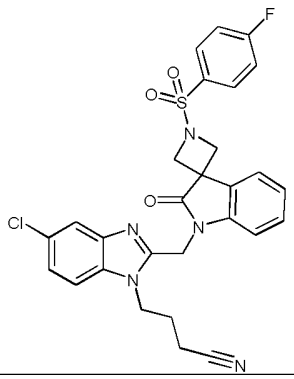
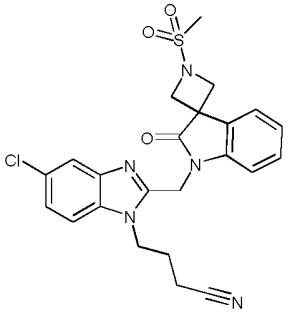
N°	structure	Name / analytical details
73		4-(5-chloro-2-((1-(2-hydroxy-2-methylpropanoyl)-2'-oxospiro [azetidine-3,3'-indolin]-1'-yl)methyl)-1*H*-indol-1-yl)butanenitrile 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (s, 3 H) 1.34 (s, 3 H) 1.98 (quin, J=7.21 Hz, 2 H) 2.57 (t, J=7.26 Hz, 2 H) 4.07 (d, J=9.46 Hz, 1 H) 4.18 (d, J=9.46 Hz, 1 H) 4.31 (t, J=7.37 Hz, 2 H) 4.60 (d, J=9.68 Hz, 1 H), 4.73 (d, J=9.68 Hz, 1 H) 5.14 (s, 2 H) 5.27 (s, 1 H) 6.34 (s, 1 H) 7.08 (d, J=7.70 Hz, 1 H) 7.11 - 7.20 (m, 2 H) 7.24 - 7.34 (m, 1 H) 7.46 - 7.56 (m, 2 H) 7.64 (d, J=7.26 Hz, 1 H); m/z = 491.13 (M+H)+Cl pattern; MP = 89.86°C
74		1'-((5-chloro-1-(3-(methylsulfonyl)propyl)-1H-indol-2-yl)-methyl)-1-(2-hydroxy-2-methylpropanoyl)spiro[piperidine-4,3'-pyrrolo[2,3-c]pyridin]-2'(1'*H*)-one 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.38 (s, 6 H) 1.72 - 1.97 (m, 4 H) 2.03 - 2.16 (m, 2 H) 3.01 (s, 3 H) 3.15 - 3.25 (m, 2 H) 3.69 - 4.04 (m, 2 H) 4.07 - 4.33 (m, 2 H) 4.38 (t, J=7.59 Hz, 2 H) 5.21 (s, 2 H) 5.49 (s, 1 H) 6.37 (s, 1 H) 7.16 (dd, J=8.69, 2.09 Hz, 1 H) 7.53 (d, J=1.98 Hz, 1 H) 7.56 (d, J=8.80 Hz, 1 H) 7.68 (d, J=4.62 Hz, 1 H) 8.35 (d, J=4.84 Hz, 1 H) 8.40 (s, 1 H); m/z = 573.08 (M+H)+Cl pattern
75		1'-((5-chloro-1-(4,4,4-trifluorobutyl)-1*H*-imidazo[4,5-b]-pyridin-2-yl)methyl)-2,3,5,6-tetrahydrospiro[pyran-4,3'-pyrrolo[2,3-c]pyridin]-2'(1'*H*)-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.69 - 1.89 (m, 4 H) 1.92 - 2.08 (m, 2 H) 2.28 - 2.45 (m, 2 H) 3.75 - 3.91 (m, 2 H) 3.96 - 4.09 (m, 2 H) 4.45 (t, *J*=7.59 Hz, 2 H) 5.34 (s, 2 H) 7.36 (d, *J*=8.36 Hz, 1 H) 7.70 (dd, *J*=4.73, 0.55 Hz, 1 H) 8.19 (d, *J*=8.36 Hz, 1 H) 8.35 (d, *J*=4.84 Hz, 1 H) 8.46 (s, 1 H); m/z = 480 (M+H)+Cl pattern; MP = 188.67°C

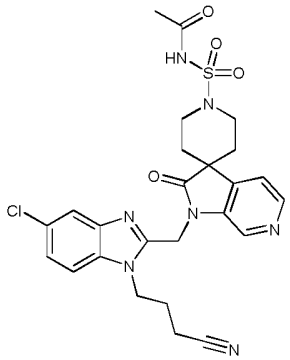
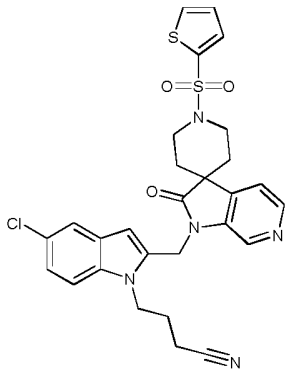
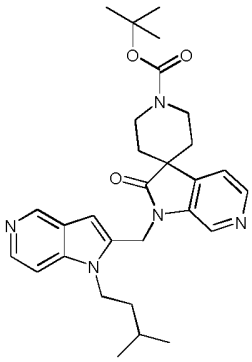
N°	structure	Name / analytical details
76		methyl 1'-((5-chloro-1-(3-cyanopropyl)-1*H*-indol-2-yl)-methyl)-2'-oxo-1',2'-dihydrospiro[piperidine-4,3'-pyrrolo-[2,3-c]pyridine]-1-carboxylate ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.71 - 1.90 (m, 4 H) 1.98 (dt, *J*=14.96, 7.48 Hz, 2 H) 2.58 (t, *J*=7.37 Hz, 2 H) 3.66 (s, 3 H) 3.69 - 3.84 (m, 4 H) 4.21 - 4.34 (m, 2 H) 5.19 (s, 2 H) 6.36 (s, 1 H) 7.08 - 7.18 (m, 1 H) 7.48 - 7.57 (m, 2 H) 7.70 (d, *J*=4.18 Hz, 1 H) 8.34 (d, *J*=4.84 Hz, 1 H) 8.39 (s, 1 H); m/z = 492 (M+H)+Cl pattern
77		isopropyl 1'-((5-chloro-1-(3-cyanopropyl)-1*H*-indol-2-yl)-methyl)-2'-oxo-1',2'-dihydrospiro[piperidine-4,3'-pyrrolo-[2,3-c]pyridine]-1-carboxylate ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.23 (d, *J*=6.38 Hz, 6 H) 1.69 - 1.90 (m, 4 H) 1.92 - 2.05 (m, 2 H) 2.58 (t, *J*=7.90 Hz, 2 H) 3.57 - 3.90 (m, 4 H) 4.15 - 4.40 (m, 2 H) 4.72 - 4.91 (m, 1 H) 5.20 (s, 2 H) 6.36 (s, 1 H) 7.09 - 7.20 (m, 1 H) 7.49 - 7.57 (m, 2 H) 7.71 (d, *J*=5.06 Hz, 1 H) 8.34 (d, *J*=4.84 Hz, 1 H) 8.39 (s, 1 H); m/z = 520 (M+H)+Cl pattern
78		4-(5-chloro-2-((2'-oxospiro[piperidine-4,3'-pyrrolo[2,3-c]-pyridin]-1'(2'*H*)-yl)methyl)-1*H*-indol-1-yl)butanenitrile hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.97 - 2.12 (m, 4 H) 2.16 - 2.30 (m, 2 H) 2.52 - 2.58 (m, 2 H) 3.27 - 3.42 (m, 2 H) 3.47 - 3.64 (m, 2 H) 4.29 (t, *J*=7.70 Hz, 2 H) 5.19 (s, 2 H) 6.17 - 6.51 (m, 1 H) 7.13 (dd, *J*=8.58, 2.20 Hz, 1 H) 7.38 - 7.63 (m, 3 H) 8.38 (s, 1 H) 8.42 (d, *J*=5.06 Hz, 1 H) 9.08 (br. s, 2 H); m/z = 434 (M+H)+Cl pattern; MP = 82.02°C
79		1-(1'-((5-chloro-1-(3-cyanopropyl)-1*H*-indol-2-yl)methyl)-2'-oxo-1',2'-dihydrospiro[piperidine-4,3'-pyrrolo[2,3-c]pyridin]-1-yl)-2-methyl-1-oxopropan-2-yl acetate ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 1.55 (s, 6 H), 1.80 (br. s., 4 H), 1.91 - 2.04 (m, 2 H), 2.08 (s, 3 H), 2.59 (t, *J*=7.3 Hz, 2 H), 3.93 (br. s., 4 H), 4.29 (t, *J*=7.7 Hz, 2 H), 5.20 (s, 2 H), 6.37 (s, 1 H), 7.16 (dd, *J*=8.6, 2.0 Hz, 1 H), 7.47 - 7.60 (m, 2 H), 7.65 (d, *J*=4.8 Hz, 1 H), 8.23 - 8.50 (m, 2 H); m/z = 562 (M+H)+Cl pattern

N°	structure	Name / analytical details
80		oxetan-3-yl 1'-((5-chloro-1-(3-cyanopropyl)-1*H*-indol-2-yl)-methyl)-2'-oxo-1',2'-dihydrospiro[piperidine-4,3'-pyrrolo-[2,3-c]pyridine]-1-carboxylate ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.84 (br. s., 4 H) 1.99 (quin, *J*=7.54 Hz, 2 H) 2.59 (t, *J*=7.37 Hz, 2 H) 3.60 - 3.97 (m, 4 H) 4.21 - 4.35 (m, 2 H) 4.48 - 4.60 (m, 2 H) 4.80 (t, *J*=7.04 Hz, 2 H) 5.20 (s, 2 H) 5.31 - 5.40 (m, 1 H) 6.37 (s, 1 H) 7.15 (dd, *J*=8.80, 2.42 Hz, 1 H) 7.48 - 7.56 (m, 2 H) 7.71 (d, *J*=4.84 Hz, 1 H) 8.34 (d, *J*=4.84 Hz, 1 H) 8.39 (s, 1 H); m/z = 534 (M+H)+Cl pattern; MP = 208.24°C
81		4-(5-chloro-2-((1-(cyclopropylsulfonyl)-2'-oxospiro-[piperidine-4,3'-pyrrolo[2,3-c]pyridin]-1'(2'*H*)-yl)methyl)-1*H*-indol-1-yl)butanenitrile ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 0.94 - 1.11 (m, 4 H), 1.86 - 2.11 (m, 6 H), 2.59 (t, *J*=7.3 Hz, 2 H), 2.69 - 2.82 (m, 1 H), 3.46 - 3.60 (m, 2 H), 3.61 - 3.76 (m, 2 H), 4.20 - 4.39 (m, 2 H), 5.20 (s, 2 H), 6.37 (s, 1 H), 7.10 - 7.20 (m, 1 H), 7.49 - 7.58 (m, 2 H), 7.66 (d, *J*=4.4 Hz, 1 H), 8.31 - 8.44 (m, 2 H); m/z = 538 (M+H)+Cl pattern; MP = 93.04°C
82		oxetan-3-yl 1'-((5-chloro-1-(3-cyanopropyl)-1H-benzo[d]-imidazol-2-yl)methyl)-2'-oxo-1',2'-dihydrospiro[piperidine-4,3'-pyrrolo[2,3-c]pyridine]-1-carboxylate ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.84 (d, *J*=13.4 Hz, 4 H), 2.02 - 2.19 (m, 2 H), 2.63 (t, *J*=7.4 Hz, 2 H), 3.65 - 3.93 (m, 4 H), 4.39 (t, *J*=7.5 Hz, 2 H), 4.48 - 4.60 (m, 2 H), 4.79 (t, *J*=7.0 Hz, 2 H), 5.30 (s, 2 H), 5.32 - 5.40 (m, 1 H), 7.30 (dd, *J*=8.6, 2.0 Hz, 1 H), 7.59 - 7.73 (m, 3 H), 8.34 (d, *J*=4.6 Hz, 1 H), 8.47 (s, 1 H); m/z = 535 (M+H)+Cl pattern; MP = 203.41°C
83		4-(2-((1-acetyl-2'-oxospiro[piperidine-4,3'-pyrrolo[2,3-c]-pyridin]-1'(2'*H*)-yl)methyl)-5-chloro-1*H*-benzo[d]imidazol-1-yl)butanenitrile ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.71 - 1.82 (m, 2 H), 1.82 - 1.95 (m, 2 H), 2.08 (s, 3 H), 2.09 - 2.15 (m, 2 H), 2.63 (t, *J*=7.4 Hz, 2 H), 3.67 - 3.79 (m, 2 H), 3.80 - 3.94 (m, 2 H), 4.39 (t, *J*=7.6 Hz, 2 H), 5.30 (s, 2 H), 7.30 (dd, *J*=8.6, 2.0 Hz, 1 H), 7.62 - 7.69 (m, 3 H), 8.33 (d, *J*=4.6 Hz, 1 H), 8.47 (s, 1 H); m/z = 477 (M+H)+Cl pattern; MP = 223.53°C

N°	structure	Name / analytical details
84		4-(5-chloro-2-((2'-oxospiro[piperidine-4,3'-pyrrolo[2,3-c]-pyridin]-1'(2'*H*)-yl)methyl)-1*H*-benzo[d]imidazol-1-yl)butanenitrile hydrochloride ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.15 - 2.35 (m, 4 H), 2.41 - 2.48 (m, 2 H), 2.74 (t, *J*=7.3 Hz, 2 H), 3.41 (br. s., 4 H), 4.53 (t, *J*=7.0 Hz, 2 H), 5.22 (br. s., 10 H), 5.62 (br. s., 3 H), 7.49 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.71 (d, *J*=1.8 Hz, 1 H), 7.93 (d, *J*=8.6 Hz, 1 H), 8.14 (d, *J*=5.3 Hz, 1 H), 8.77 (d, *J*=5.3 Hz, 1 H), 9.00 (s, 1 H), 9.67 (br. s., 2 H); m/z = 435 (M+H)+Cl pattern
85		1'-((5-chloro-1-(3-(methylsulfonyl)propyl)-1*H*-benzo[d]-imidazol-2-yl)methyl)-1-(cyclopropylsulfonyl)spiro-[piperidine-4,3'-pyrrolo[2,3-c]pyridin]-2'(1'*H*)-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.93 - 1.01 (m, 2 H) 1.01 - 1.08 (m, 2 H) 1.86 - 1.95 (m, 2 H) 1.97 - 2.07 (m, 2 H) 2.13 - 2.26 (m, 2 H) 2.67 - 2.78 (m, 1 H) 3.02 (s, 3 H) 3.22 - 3.29 (m, 2 H) 3.47 - 3.58 (m, 2 H) 3.60 - 3.70 (m, 2 H) 4.48 (t, *J*=7.48 Hz, 2 H) 5.30 (s, 2 H) 7.31 (dd, *J*=8.58, 1.98 Hz, 1 H) 7.64 (d, *J*=4.84 Hz, 1 H) 7.65 (d, *J*=1.76 Hz, 1 H) 7.68 (d, *J*=8.58 Hz, 1 H) 8.36 (d, *J*=4.84 Hz, 1 H) 8.50 (s, 1 H); m/z = 592 (M+H)+Cl pattern; MP = 150.42°C
86		4-(5-chloro-2-((1-(2-hydroxy-2-methylpropanoyl)-2'-oxospiro [piperidine-4,3'-pyrrolo[2,3-c]pyridin]-1'(2'*H*)-yl)methyl)-1*H*-indol-1-yl)butanenitrile ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 1.37 (s, 6 H), 1.71 - 1.90 (m, 4 H), 1.90 - 2.08 (m, 2 H), 2.59 (t, *J*=7.3 Hz, 2 H), 4.09 - 4.43 (m, 4 H), 5.21 (s, 2 H), 5.51 (s, 1 H), 6.36 (s, 1 H), 7.15 (m, *J*=10.6 Hz, 1 H), 7.48 - 7.59 (m, 2 H), 7.69 (d, *J*=4.8 Hz, 1 H), 8.35 (d, *J*=4.8 Hz, 1 H), 8.41 (s, 1 H); m/z = 520 (M+H)+Cl pattern

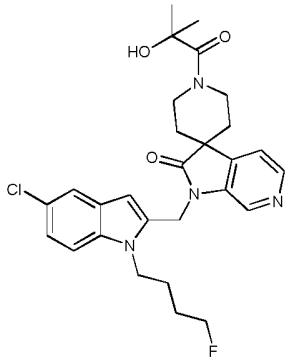
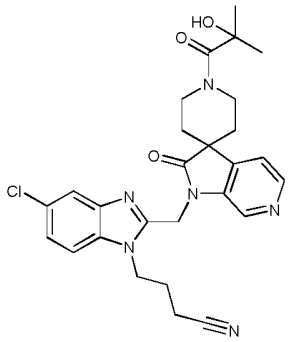
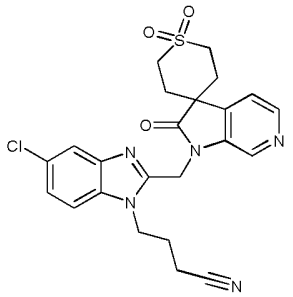
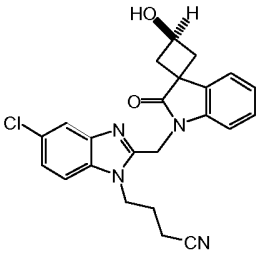
N°	structure	Name / analytical details
87		isopropyl 1'-((5-chloro-1-(3-(methylsulfonyl)propyl)-1*H*-benzo[d]imidazol-2-yl)methyl)-2'-oxo-1',2'-dihydrospiro-[piperidine-4,3'-pyrrolo[2,3-c]pyridine]-1-carboxylate ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.23 (d, *J*=6.16 Hz, 6 H) 1.65 - 1.90 (m, 4 H) 2.19 (quin, *J*=7.59 Hz, 2 H) 3.02 (s, 3 H) 3.18 - 3.30 (m, 2 H) 3.62 - 3.83 (m, 4 H) 4.48 (t, *J*=7.48 Hz, 2 H) 4.84 (quin, *J*=6.22 Hz, 1 H) 5.31 (s, 2 H) 7.31 (dd, *J*=8.58, 1.98 Hz, 1 H) 7.64 - 7.68 (m, 2 H) 7.69 (d, *J*=2.42 Hz, 1 H) 8.33 (d, *J*=4.84 Hz, 1 H) 8.49 (s, 1 H); m/z = 574 (M+H)+Cl pattern
88		4-(2-((1-acetyl-2'-oxospiro[azetidine-3,3'-indolin]-1'-yl)-methyl)-5-chloro-1H-benzo[d]imidazol-1-yl)butanenitrile 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.87 (s, 3 H) 2.07 (quin, J=7.59 Hz, 2 H) 2.63 (t, J=7.37 Hz, 2 H) 3.98 - 4.18 (m, 2 H) 4.34 - 4.47 (m, 4 H) 5.16 - 5.31 (m, 2 H) 7.14 (td, J=7.48, 0.88 Hz, 1 H) 7.18 (d, J=7.70 Hz, 1 H) 7.27 - 7.34 (m, 2 H) 7.64 - 7.68 (m, 2 H) 7.68 - 7.72 (m, 1 H); m/z = 448.04 (M+H)+Cl pattern
89		1'-((5-chloro-1-(3-cyanopropyl)-1*H*-benzo[d]imidazol-2-yl)-methyl)-2'-oxo-1',2'-dihydrospiro[piperidine-4,3'-pyrrolo-[2,3-c]pyridine]-1-sulfonamide 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.80 - 2.04 (m, 4 H), 2.10 (quin, J=7.43 Hz, 2 H), 2.63 (t, J=7.37 Hz, 2 H), 3.26 - 3.30 (m, 2 H), 3.38 - 3.50 (m, 2 H), 4.40 (t, J=7.48 Hz, 2 H), 5.30 (s, 2 H), 6.88 (br. s, 2 H), 7.30 (dd, J=8.58, 1.98 Hz, 1 H), 7.58 (d, J=4.84 Hz, 1 H), 7.64 (d, J=1.76 Hz, 1 H), 7.66 (d, J=8.58 Hz, 1 H), 8.36 (d, J=4.84 Hz, 1 H), 8.48 (s, 1 H): m/z = 514 (M+H) + Cl pattern
90		1'-({5-Chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl}methyl)-1-(cyclopropylcarbonyl)spiro[piperidine-4,3'-pyrrolo[2,3-*c*]pyridin]-2'(1'*H*)-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.60 - 0.88 (m, 4 H) 1.67 - 1.96 (m, 4 H) 1.98 - 2.11 (m, 1 H) 2.14 - 2.25 (m, 2 H) 3.02 (s, 3 H) 3.22 - 3.28 (m, 2 H) 3.71 - 4.12 (m, 4 H) 4.48 (t, *J*=7.26 Hz, 2 H) 5.31 (s, 2 H) 7.31 (dd, *J*=8.58, 1.98 Hz, 1 H) 7.61 - 7.73 (m, 3 H) 8.34 (d, *J*=4.84 Hz, 1 H) 8.49 (s, 1 H); m/z = 556 (M+H)+; MP = 208.64 °C

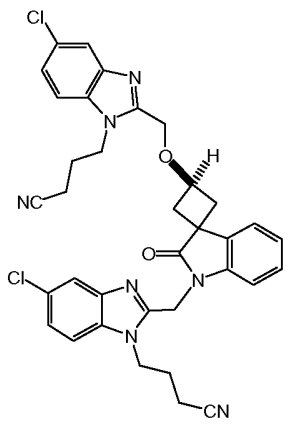
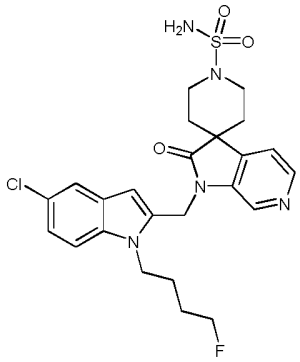
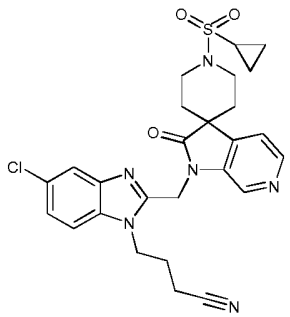
N°	structure	Name / analytical details
91		4-(5-Chloro-2-{[2'-oxo-1-(thiophen-2-ylsulfonyl)spiro-[azetidine-3,3'-indol]-1'(2'*H*)-yl]methyl}-1*H*-benzimidazol-1-yl)butanenitrile 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.03 (quin, J=7.48 Hz, 2 H) 2.59 (t, J=7.37 Hz, 2 H) 3.91 - 4.20 (m, 4 H) 4.35 (t, J=7.59 Hz, 2 H) 5.15 (s, 2 H) 6.78 - 6.84 (m, 1 H) 7.03 (td, J=7.54, 0.77 Hz, 1 H) 7.12 - 7.19 (m, 1 H) 7.23 - 7.32 (m, 2 H) 7.48 (dd, J=4.95, 3.85 Hz, 1 H) 7.59 - 7.67 (m, 2 H) 7.92 (dd, J=3.74, 1.10 Hz, 1 H) 8.27 (dd, J=5.06, 1.32 Hz, 1 H); m/z = 552.04 (M+H)+
92		Oxetan-3-yl 1'-{[5-chloro-1-(3-cyanopropyl)-1*H*-benzimidazol-2-yl]methyl}-2'-oxo-1',2'-dihydro-1*H*-spiro[azetidine-3,3'-indole]-1-carboxylate 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.08 (quin, J=7.48 Hz, 2 H) 2.62 (t, J=7.37 Hz, 2 H) 4.09 - 4.35 (m, 4 H) 4.36 - 4.43 (m, 2 H) 4.50 - 4.57 (m, 2 H) 4.76 - 4.84 (m, 2 H) 5.23 (s, 2 H) 5.34 - 5.42 (m, 1 H) 7.11 - 7.23 (m, 2 H) 7.27 - 7.35 (m, 2 H) 7.63 - 7.69 (m, 2 H) 7.72 - 7.78 (m, 1 H); m/z = 506.09 (M+H)+
93		4-[5-Chloro-2-({1-[(4-fluorophenyl)sulfonyl]-2'-oxospiro-[azetidine-3,3'-indol]-1'(2'*H*)-yl}methyl)-1*H*-benzimidazol-1-yl]butanenitrile 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.02 (quin, J=7.48 Hz, 2 H) 2.57 (t, J=7.37 Hz, 2 H) 3.92 - 4.09 (m, 4 H) 4.32 (t, J=7.59 Hz, 2 H) 5.13 (s, 2 H) 6.95 - 7.01 (m, 1 H) 7.02 - 7.09 (m, 1 H) 7.11 - 7.16 (m, 1 H) 7.23 - 7.33 (m, 2 H) 7.58 - 7.67 (m, 4 H) 7.99 - 8.07 (m, 2 H); m/z = 564.06 (M+H)+
94		4-(5-Chloro-2-{[1-(methylsulfonyl)-2'-oxospiro[azetidine-3,3'-indol]-1'(2'*H*)-yl]methyl}-1*H*-benzimidazol-1-yl)-butanenitrile 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.01 - 2.14 (m, 2 H) 2.63 (t, J=7.37 Hz, 2 H) 3.21 (s, 3 H) 4.12 - 4.27 (m, 4 H) 4.40 (t, J=7.59 Hz, 2 H) 5.23 (s, 2 H) 7.12 - 7.23 (m, 2 H) 7.27 - 7.37 (m, 2 H) 7.62 - 7.71 (m, 3 H); m/z = 484.04 (M+H)+; MP = 214.11 °C

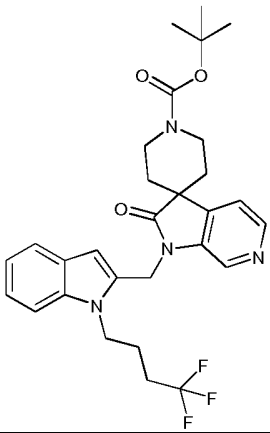
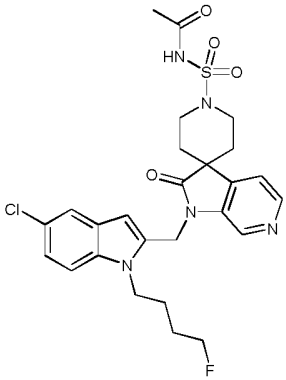
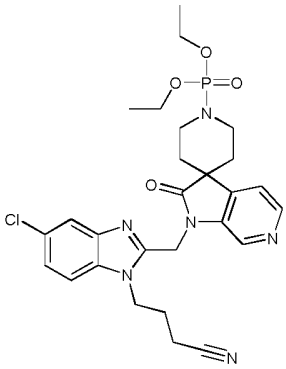
N°	structure	Name / analytical details
95		N-[(1'-{[5-Chloro-1-(3-cyanopropyl)-1*H*-benzimidazol-2-yl]methyl}-2'-oxo-1',2'-dihydro-1*H*-spiro[piperidine-4,3'-pyrrolo[2,3-*c*]pyridin]-1-yl)sulfonyl]acetamide 1H NMR (400 MHz, CHLOROFORM-d) δppm 1.92 - 2.01 (m, 4 H), 2.09 - 2.17 (m, 2 H), 2.18 (s, 3 H), 2.38 (s, 6 H), 2.49 (s, 2 H), 2.55 (br. s., 8 H), 3.66 - 3.75 (m, 2 H), 3.75 - 3.81 (m, 8 H), 3.81 - 3.90 (m, 2 H), 4.38 - 4.47 (m, 2 H), 4.61 - 4.80 (m, 1 H), 5.21 (s, 2 H), 7.27 (s, 1 H), 7.28 - 7.32 (m, 2 H), 7.72 (d, J=1.32 Hz, 1 H), 8.44 (d, J=4.84 Hz, 1 H), 8.81 (s, 1 H); m/z = 556 (M+H)+
96		4-(5-Chloro-2-{[2'-oxo-1-(thiophen-2-ylsulfonyl)spiro-[piperidine-4,3'-pyrrolo[2,3-*c*]pyridin]-1'(2'*H*)-yl]methyl}-1*H*-indol-1-yl)butanenitrile ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.86 - 2.00 (m, 4 H) 2.10 - 2.21 (m, 2 H) 2.52 - 2.57 (m, 2 H) 3.20 - 3.29 (m, 2 H) 3.47 - 3.58 (m, 2 H) 4.13 - 4.31 (m, 2 H) 5.11 (s, 2 H) 6.28 (s, 1 H) 7.14 (dd, *J*=8.69, 2.09 Hz, 1 H) 7.33 (dd, *J*=5.06, 3.74 Hz, 1 H) 7.44 - 7.55 (m, 3 H) 7.71 (dd, *J*=3.74, 1.32 Hz, 1 H) 8.09 (dd, *J*=5.06, 1.32 Hz, 1 H) 8.31 - 8.36 (m, 2 H); m/z = 580 (M+H)+
97		tert-Butyl 1'-{[1-(3-methylbutyl)-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl]methyl}-2'-oxo-1',2'-dihydro-1*H*-spiro[piperidine-4,3'-pyrrolo[2,3-*c*]pyridine]-1-carboxylate ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.05 (d, *J*=6.38 Hz, 6 H), 1.51 (s, 9 H), 1.63 - 1.84 (m, 3 H), 1.93 (t, *J*=5.39 Hz, 4 H), 3.72 - 3.86 (m, 2 H), 3.86 - 3.99 (m, 2 H), 4.27 - 4.42 (m, 2 H), 5.20 - 5.38 (m, 2 H), 6.90 (s, 1 H), 7.63 (d, *J*=6.60 Hz, 1 H), 7.69 (d, *J*=4.84 Hz, 1 H), 8.38 (d, *J*=6.60 Hz, 1 H), 8.54 (br. s., 1 H), 8.67 (br. s., 1 H), 9.01 (br. s., 1 H); m/z = 504 (M+H)+

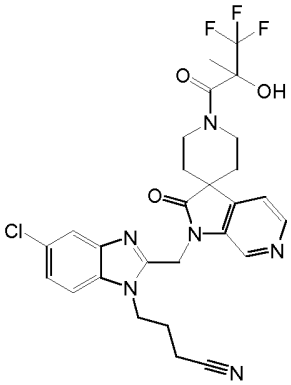
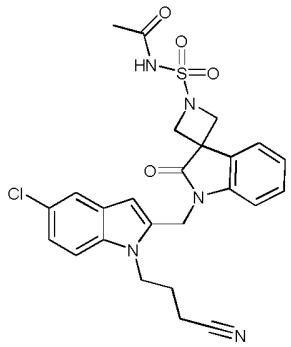
N°	structure	Name / analytical details
98		Methyl 1'-{[5-chloro-1-(3-cyanopropyl)-1*H*-benzimidazol-2-yl]methyl}-2'-oxo-1',2'-dihydro-1*H*-spiro[piperidine-4,3'-pyrrolo[2,3-*c*]pyridine]-1-carboxylate 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.66 - 1.93 (m, 4 H), 2.09 (quin, J=7.5 Hz, 2 H), 2.63 (t, J=7.4 Hz, 2 H), 3.65 (s, 3 H), 3.71 - 3.84 (m, 4 H), 4.39 (t, J=7.6 Hz, 2 H), 5.30 (s, 2 H), 7.30 (dd, J=8.6, 2.0 Hz, 1 H), 7.56 - 7.75 (m, 2 H), 8.33 (d, J=4.8 Hz, 1 H), 8.47 (s, 1 H); m/z = 493 (M+H)+
99		1-Methylethyl 1'-{[5-chloro-1-(3-cyanopropyl)-1*H*-benzimidazol-2-yl]methyl}-2'-oxo-1',2'-dihydro-1*H*-spiro[piperidine-4,3'-pyrrolo[2,3-*c*]pyridine]-1-carboxylate 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.18 - 1.27 (m, 6 H), 1.72 - 1.89 (m, 4 H), 2.09 (quin, J=7.4 Hz, 2 H), 2.63 (t, J=7.4 Hz, 2 H), 3.65 - 3.83 (m, 4 H), 4.39 (t, J=7.5 Hz, 2 H), 4.84 (dt, J=12.5, 6.2 Hz, 1 H), 5.30 (s, 2 H), 7.30 (dd, J=8.6, 2.0 Hz, 1 H), 7.62 - 7.72 (m, 3 H), 8.33 (d, J=4.6 Hz, 1 H), 8.48 (s, 1 H); m/z = 521 (M+H)+
100		4-{5-Chloro-2-[(2'-oxospiro[azetidine-3,3'-indol]-1'(2'*H*)-yl)methyl]-1*H*-benzimidazol-1-yl}butanamide 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.86 - 2.00 (m, 2 H) 2.34 (t, J=7.26 Hz, 2 H) 4.15 - 4.32 (m, 4 H) 4.32 - 4.44 (m, 2 H) 5.21 (s, 2 H) 7.16 - 7.25 (m, 2 H) 7.27 - 7.32 (m, 1 H) 7.32 - 7.39 (m, 1 H) 7.61 - 7.69 (m, 2 H) 7.81 - 7.88 (m, 1 H); m/z = 425.02 (M+H)+
101		4-{5-Chloro-2-[(2'-oxospiro[azetidine-3,3'-indol]-1'(2'*H*)-yl)methyl]-1*H*-benzimidazol-1-yl}butanenitrile 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.00 (quin, J=7.54 Hz, 2 H) 2.57 - 2.67 (m, 2 H) 3.56 (d, J=7.26 Hz, 2 H) 4.00 (d, J=7.48 Hz, 2 H) 4.38 (t, J=7.59 Hz, 2 H) 5.21 (s, 2 H) 7.08 - 7.18 (m, 2 H) 7.21 - 7.32 (m, 2 H) 7.62 - 7.68 (m, 2 H) 7.73 - 7.82 (m, 1 H); m/z = 405.96 (M+H)+

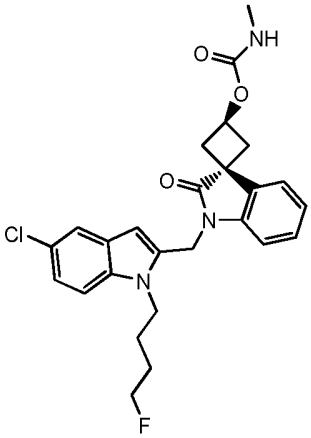
N°	structure	Name / analytical details
102		1-({5-Chloro-1-[3-(methylsulfonyl)propyl]-1*H*-benzimidazol-2-yl}methyl)-1'-(thiophen-2-ylsulfonyl)spiro[indole-3,4'-piperidin]-2(1*H*)-one 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.79 - 1.94 (m, 2 H) 2.00 - 2.26 (m, 4 H) 2.98 (s, 3 H) 3.07 - 3.25 (m, 4 H) 3.42 - 3.78 (m, 2 H) 4.41 (t, J=6.60 Hz, 2 H) 5.17 (s, 2 H) 6.98 - 7.09 (m, 1 H) 7.14 (d, J=7.48 Hz, 1 H) 7.20 - 7.42 (m, 4 H) 7.54 - 7.78 (m, 3 H) 8.03 - 8.15 (m, 1 H); m/z = 632.94 (M+H)+; MP = 233.06 °C
103		Cyclobutyl 1'-{[5-chloro-1-(3-cyanopropyl)-1*H*-indol-2-yl]-methyl}-2'-oxo-1',2'-dihydro-1*H*-spiro[piperidine-4,3'-pyrrolo[2,3-*c*]pyridine]-1-carboxylate ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.50 - 1.65 (m, 1 H) 1.66 - 1.90 (m, 5 H) 1.91 - 2.09 (m, 4 H) 2.20 - 2.36 (m, 2 H) 2.58 (t, *J*=7.37 Hz, 2 H) 3.56 - 3.90 (m, 4 H) 4.16 - 4.38 (m, 2 H) 4.79 - 4.96 (m, 1 H) 5.20 (s, 2 H) 6.36 (s, 1 H) 7.15 (dd, *J*=8.80, 1.98 Hz, 1 H) 7.48 - 7.57 (m, 2 H) 7.70 (d, *J*=4.84 Hz, 1 H) 8.33 (d, *J*=4.84 Hz, 1 H) 8.39 (s, 1 H); m/z = 532 (M+H)+
104		(1R,3R)-1'-((5-chloro-1-(3-(methylsulfonyl)propyl)-1*H*-benzo[*d*]imidazol-2-yl)methyl)-2'-oxospiro[cyclobutane-1,3'-indoline]-3-yl methylcarbamate 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.16 (quin, J=7.59 Hz, 2 H) 2.45 - 2.52 (m, 2 H) 2.59 (d, J=4.62 Hz, 3 H) 2.73 - 2.82 (m, 2 H) 3.00 (s, 3 H) 3.20 - 3.27 (m, 2 H) 4.47 (t, J=7.37 Hz, 2 H) 5.22 (s, 2 H) 5.25 - 5.35 (m, 1 H) 7.07 - 7.16 (m, 3 H) 7.22 - 7.28 (m, 1 H) 7.28 - 7.33 (m, 1 H) 7.48 - 7.54 (m, 1 H) 7.64 - 7.70 (m, 2 H); m/z = 531.15 (M+H)+; MP = 204.17°C
105		4-(5-Chloro-2-{[1-(methylsulfonyl)-2'-oxospiro[piperidine-4,3'-pyrrolo[2,3-*c*]pyridin]-1'(2'*H*)-yl]methyl}-1*H*-indol-1-yl)butanenitrile 1H NMR (360 MHz, DMSO-d_6) δ ppm 1.85 - 2.12 (m, 6 H), 2.60 (t, J=7.3 Hz, 2 H), 3.01 (s, 3 H), 3.40 - 3.51 (m, 2 H), 3.51 - 3.64 (m, 2 H), 4.30 (t, J=7.7 Hz, 2 H), 5.20 (s, 2 H), 6.38 (s, 1 H), 7.09 - 7.21 (m, 1 H), 7.47 - 7.59 (m, 2 H), 7.71 (d, J=4.8 Hz, 1 H), 8.36 (d, J=4.8 Hz, 1 H), 8.41 (s, 1 H); m/z = 512 (M+H)+; MP = 145.30°C

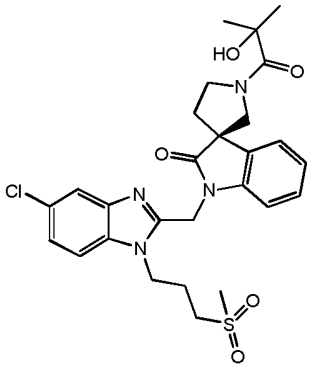
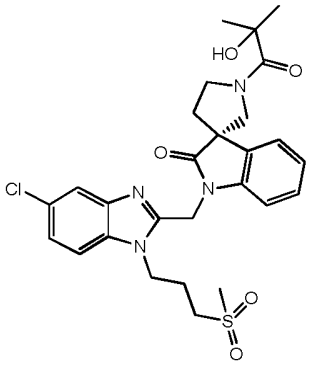
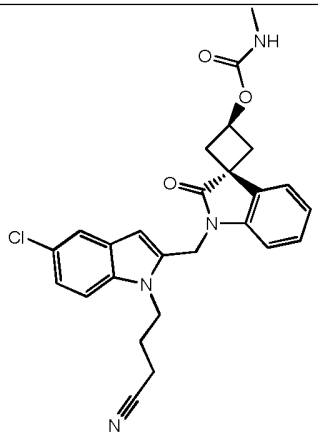
N°	structure	Name / analytical details
106		1'-{[5-Chloro-1-(4-fluorobutyl)-1*H*-indol-2-yl]methyl}-1-(2-hydroxy-2-methylpropanoyl)spiro[piperidine-4,3'-pyrrolo-[2,3-c]pyridin]-2'(1'*H*)-one ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.40 (s, 6 H) 1.58 - 1.98 (m, 8 H) 3.99 - 4.16 (m, 4 H) 4.20 - 4.31 (m, 2 H) 4.33 - 4.42 (m, 1 H) 4.46 - 4.54 (m, 1 H) 5.07 (s, 1 H) 5.16 (s, 2 H) 6.37 (s, 1 H) 7.02 - 7.15 (m, 1 H) 7.41 - 7.47 (m, 1 H) 7.47 - 7.50 (m, 1 H) 7.53 - 7.57 (m, 1 H) 8.29 - 8.35 (m, 2 H); m/z = 527 (M+H)+
107		4-(5-Chloro-2-{[1-(2-hydroxy-2-methylpropanoyl)-2'-oxo-spiro[piperidine-4,3'-pyrrolo[2,3-*c*]pyridin]-1'(2'*H*)-yl]-methyl}-1*H*-benzimidazol-1-yl)butanenitrile 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.37 (s, 6 H), 1.83 (br. s., 4 H), 2.04 - 2.15 (m, 2 H), 2.64 (t, J=7.4 Hz, 2 H), 3.69 - 4.01 (m, 2 H), 4.12 - 4.34 (m, 2 H), 4.39 (t, J=7.5 Hz, 2 H), 5.31 (s, 2 H), 7.30 (dd, J=8.8, 2.0 Hz, 1 H), 7.63 - 7.69 (m, 3 H), 8.34 (d, J=4.6 Hz, 1 H), 8.49 (s, 1 H); m/z = 521 (M+H)+
108		4-{5-Chloro-2-[(1',1'-dioxido-2-oxo-2',3',5',6'-tetrahydro-spiro[pyrrolo[2,3-*c*]pyridine-3,4'-thiopyran]-1(2*H*)-yl)-methyl]-1*H*-benzimidazol-1-yl}butanenitrile 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.12 (quin, J=7.26 Hz, 2 H) 2.25 (m, J=15.19 Hz, 2 H) 2.41 - 2.48 (m, 2 H) 2.65 (t, J=7.37 Hz, 2 H) 3.16 - 3.28 (m, 2 H) 3.56 - 3.76 (m, 2 H) 4.40 (t, J=7.37 Hz, 2 H) 5.32 (s, 2 H) 7.30 (dd, J=8.69, 1.65 Hz, 1 H) 7.56 - 7.72 (m, 3 H) 8.37 (d, J=4.84 Hz, 1 H) 8.50 (s, 1 H); m/z = 484.07 (M+H)+
109		4-{5-Chloro-2-[(3-hydroxy-2'-oxospiro[cyclobutane-1,3'-indol]-1'(2'*H*)-yl)methyl]-1*H*-benzimidazol-1-yl}butanenitrile 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.96 (quin, J=7.65 Hz, 2 H) 2.38 - 2.48 (m, 4 H) 2.59 (t, J=7.48 Hz, 2 H) 4.30 - 4.43 (m, 2 H) 4.65 - 4.79 (m, 1 H) 5.22 (s, 2 H) 5.58 (d, J=6.60 Hz, 1 H) 7.07 (td, J=7.48, 0.88 Hz, 1 H) 7.10 - 7.14 (m, 1 H) 7.22 (td, J=7.70, 1.10 Hz, 1 H) 7.29 (dd, J=8.58, 1.98 Hz, 1 H) 7.48 - 7.53 (m, 1 H) 7.65 (d, J=8.58 Hz, 1 H) 7.66 (d, J=1.98 Hz, 1 H); m/z = 421 (M+H)+

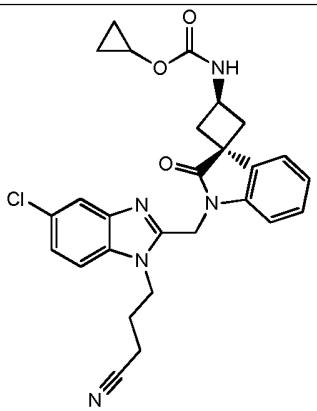
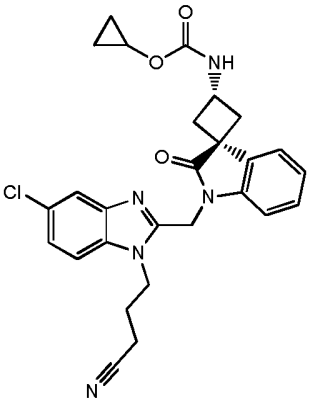
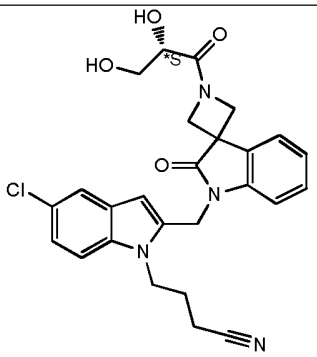
N°	structure	Name / analytical details
110		4-(5-chloro-2-(((1S,3S)-1'-((5-chloro-1-(3-cyanopropyl)-1*H*-benzo[*d*]imidazol-2-yl)methyl)-2'-oxospiro[cyclobutane-1,3'-indoline]-3-yloxy)methyl)-1*H*-benzo[*d*]imidazol-1-yl)butanenitrile 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.97 (quin, J=7.54 Hz, 2 H) 2.15 (quin, J=7.37 Hz, 2 H) 2.44 - 2.56 (m, 4 H) 2.59 (t, J=7.48 Hz, 2 H) 2.66 (t, J=7.15 Hz, 2 H) 4.29 - 4.46 (m, 4 H) 4.75 - 4.87 (m, 3 H) 5.22 (s, 2 H) 7.06 - 7.15 (m, 2 H) 7.20 - 7.26 (m, 1 H) 7.29 (dd, J=8.58, 1.98 Hz, 1 H) 7.33 (dd, J=8.58, 1.98 Hz, 1 H) 7.48 - 7.53 (m, 1 H) 7.62 - 7.66 (m, 2 H) 7.69 (d, J=8.80 Hz, 1 H) 7.72 (d, J=1.76 Hz, 1 H); m/z = 652 (M+H)+
111		1'-{[5-Chloro-1-(4-fluorobutyl)-1*H*-indol-2-yl]methyl}-2'-oxo-1',2'-dihydro-1*H*-spiro[piperidine-4,3'-pyrrolo[2,3-*c*]-pyridine]-1-sulfonamide ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.60 - 1.81 (m, 4 H), 1.84 - 2.09 (m, 4 H), 3.31 (s, 2 H), 3.41 - 3.53 (m, 2 H), 4.27 (t, *J*=7.04 Hz, 2 H), 4.40 (t, *J*=5.83 Hz, 1 H), 4.47 - 4.57 (m, 1 H), 5.18 (s, 2 H), 6.38 - 6.47 (m, 1 H), 6.89 (s, 2 H), 7.13 (dd, *J*=8.69, 2.09 Hz, 1 H), 7.51 (d, *J*=8.80 Hz, 1 H), 7.53 (d, *J*=1.98 Hz, 1 H), 7.59 (d, *J*=5.28 Hz, 1 H), 8.35 (d, *J*=4.62 Hz, 1 H), 8.38 (s, 1 H); m/z = 520 $(M+H)^+$;
112		4-(5-Chloro-2-{[1-(cyclopropylsulfonyl)-2'-oxospiro-[piperidine-4,3'-pyrrolo[2,3-c]pyridin]-1'(2'*H*)-yl]methyl}-1*H*-benzimidazol-1-yl)butanenitrile 1H NMR (400 MHz, DMSO-d_6) δ ppm 0.94 - 1.11 (m, 4 H), 1.86 - 1.97 (m, 2 H), 1.98 - 2.15 (m, 4 H), 2.64 (t, J=7.3 Hz, 2 H), 2.68 - 2.78 (m, 1 H), 3.49 - 3.59 (m, 2 H), 3.60 - 3.72 (m, 2 H), 4.40 (t, J=7.5 Hz, 2 H), 5.31 (s, 2 H), 7.30 (dd, J=8.7, 1.9 Hz, 1 H), 7.61 - 7.71 (m, 3 H), 8.37 (d, J=4.8 Hz, 1 H), 8.49 (s, 1 H); m/z = 539 $(M+H)^+$;

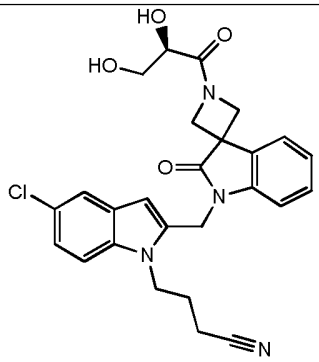
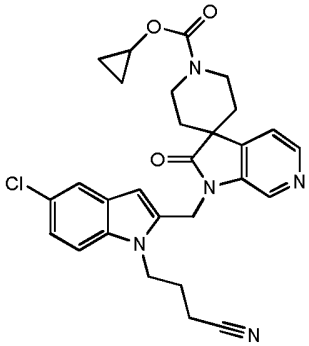
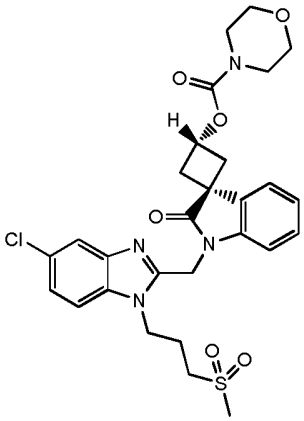
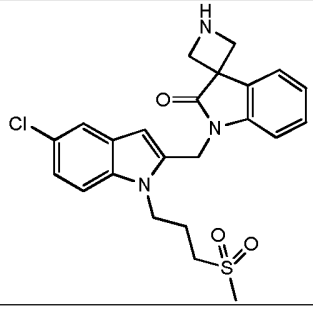
N°	structure	Name / analytical details
113		tert-Butyl 2'-oxo-1'-{[1-(4,4,4-trifluorobutyl)-1*H*-indol-2-yl]methyl}-1',2'-dihydro-1*H*-spiro[piperidine-4,3'-pyrrolo[2,3-*c*]pyridine]-1-carboxylate ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.51 (s, 9 H), 1.71 - 1.82 (m, 2 H), 1.83 - 1.92 (m, 2 H), 1.93 - 2.04 (m, 2 H), 2.11 - 2.27 (m, 2 H), 3.70 - 3.81 (m, 2 H), 3.84 - 3.96 (m, 2 H), 4.23 - 4.32 (m, 2 H), 5.10 (s, 2 H), 6.62 (s, 1 H), 7.12 (ddd, *J*=7.81, 6.60, 1.43 Hz, 1 H), 7.19 - 7.30 (m, 3 H), 7.58 (d, *J*=7.92 Hz, 1 H), 8.38 (d, *J*=4.62 Hz, 1 H), 8.48 (s, 1 H); m/z = 543 $(M+H)^+$;
114		*N*-[(1'-{[5-Chloro-1-(4-fluorobutyl)-1*H*-indol-2-yl]methyl}-2'-oxo-1',2'-dihydro-1*H*-spiro[piperidine-4,3'-pyrrolo[2,3-*c*]-pyridin]-1-yl)sulfonyl]acetamide ^{1}H NMR (400 MHz, DMSO-d_6) *d* ppm 1.60 - 1.78 (m, 4 H), 1.85 - 2.02 (m, 4 H), 2.04 (s, 3 H), 3.50 - 3.61 (m, 2 H), 3.68 (ddd, J=12.71, 8.97, 3.63 Hz, 2 H), 4.27 (t, J=7.04 Hz, 2 H), 4.40 (t, J=5.72 Hz, 1 H), 4.52 (s, 1 H), 5.17 (s, 2 H), 6.41 (s, 1 H), 7.13 (dd, J=8.69, 2.09 Hz, 1 H), 7.49 - 7.54 (m, 2 H), 7.56 (d, J=4.84 Hz, 1 H), 8.35 (d, J=4.84 Hz, 1 H), 8.38 (s, 1 H), 11.54 (s, 1 H); m/z = 562 $(M+H)^+$; MP = 236.92°C
115		Diethyl (1'-{[5-chloro-1-(3-cyanopropyl)-1*H*-benzimidazol-2-yl]methyl}-2'-oxo-1',2'-dihydro-1*H*-spiro[piperidine-4,3'-pyrrolo[2,3-*c*]pyridin]-1-yl)phosphonate ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.28 (t, *J*=7.70 Hz, 6 H) 1.66 - 1.89 (m, 4 H) 1.99 - 2.16 (m, 2 H) 2.63 (t, *J*=7.30 Hz, 2 H) 3.26 - 3.38 (m, 2 H) 3.41 - 3.58 (m, 2 H) 3.89 - 4.07 (m, 4 H) 4.37 (t, *J*=7.50 Hz, 2 H) 5.27 (s, 2 H) 7.30 (dd, *J*=8.80, 1.98 Hz, 1 H) 7.54 - 7.71 (m, 3 H) 8.34 (d, *J*=6.16 Hz, 1 H) 8.47 (s, 1 H); m/z = 571 $(M+H)^+$

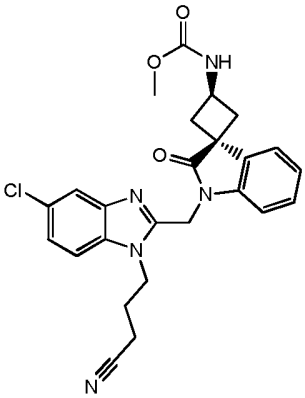
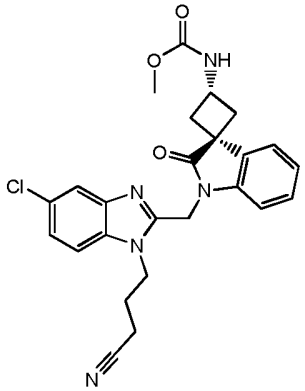
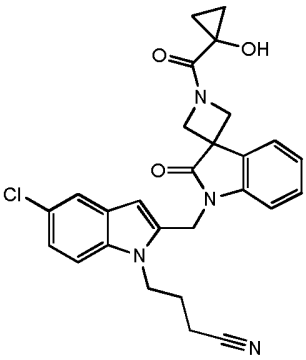
N°	structure	Name / analytical details
116		4-(5-Chloro-2-{[2'-oxo-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropanoyl)spiro[piperidine-4,3'-pyrrolo[2,3-*c*]pyridin]-1'(2'*H*)-yl]methyl}-1*H*-benzimidazol-1-yl)butanenitrile ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.55 (s, 3 H) 1.70 - 1.99 (m, 4 H) 2.02 - 2.17 (m, 2 H) 2.63 (t, *J*=7.50 Hz, 2 H) 3.73 - 3.99 (m, 2 H) 4.15 - 4.29 (m, 2 H) 4.40 (t, *J*=7.90 Hz, 2 H) 5.26 (s, 2 H) 7.17 (br. s, 1 H) 7.29 (dd, *J*=8.58, 1.98 Hz, 1 H) 7.56 - 7.74 (m, 3 H) 8.32 (d, *J*=5.06 Hz, 1 H) 8.47 (s, 1 H); m/z = 575 $(M+H)^+$
117		*N*-[(1'-{[5-Chloro-1-(3-cyanopropyl)-1*H*-indol-2-yl]methyl}-2'-oxo-1',2'-dihydro-1*H*-spiro[azetidine-3,3'-indol]-1-yl)sulfonyl]acetamide ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.93 - 2.04 (m, 1 H), 2.16 (s, 3 H), 2.58 (t, J=7.4 Hz, 2 H), 4.25 (d, J=8.1 Hz, 2 H), 4.27 - 4.35 (m, 2 H), 4.40 (d, J=8.4 Hz, 2 H), 5.12 (s, 2 H), 6.38 (s, 1 H), 7.08 (d, J=7.9 Hz, 1 H), 7.11 - 7.21 (m, 2 H), 7.26 - 7.35 (m, 1 H), 7.48 - 7.55 (m, 2 H), 7.58 (d, J=7.0 Hz, 1 H), 10.84 - 10.85 (m, 0 H), 11.75 (br. s., 2 H); m/z = 524 $(M-H)^-$; MP = 182.85°C

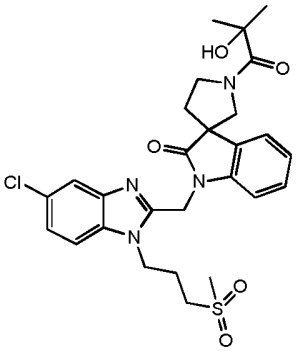
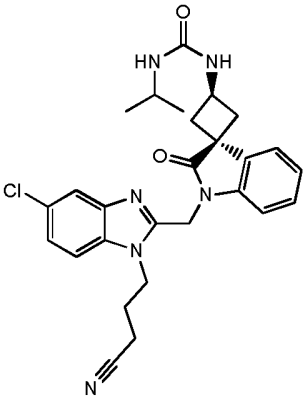
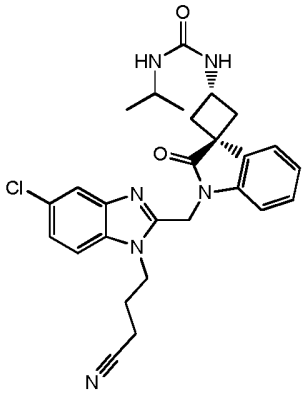
N°	structure	Name / analytical details
120		(1r,3r)-1'-((5-chloro-1-(4-fluorobutyl)-1H-indol-2-yl)methyl)-2'-oxospiro[cyclobutane-1,3'-indolin]-3-yl methylcarbamate ^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 1.58 - 1.76 (m, 4 H) 2.59 (d, J=4.62 Hz, 3 H) 2.78 (ddd, J=9.96, 7.32, 2.53 Hz, 2 H) 4.28 (t, J=6.82 Hz, 2 H) 4.38 (t, J=5.61 Hz, 1 H) 4.50 (t, J=5.39 Hz, 1 H) 5.08 - 5.14 (m, 2 H) 5.31 (quin, J=7.32 Hz, 1 H) 6.33 - 6.37 (m, 1 H) 7.02 (d, J=7.92 Hz, 1 H) 7.07 - 7.16 (m, 3 H) 7.19 - 7.26 (m, 1 H) 7.46 - 7.55 (m, 3 H); m/z = 484 (M+H)+

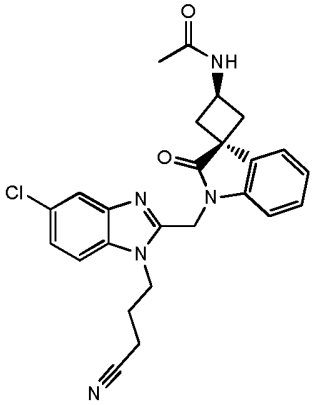
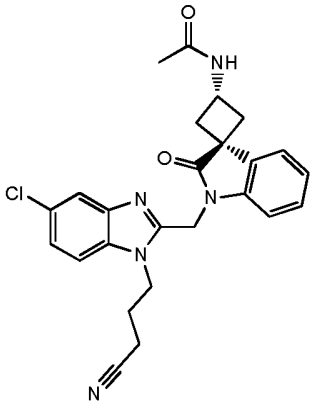
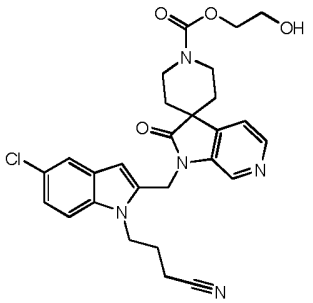
N°	structure	Name / analytical details
121		(R)-1-({5-Chloro-1-[3-(methylsulfonyl)propyl]-1H-benzimidazol-2-yl}methyl)-1'-(2-hydroxy-2-methylpropanoyl)spiro[indole-3,3'-pyrrolidin]-2(1H)-one --- ^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 1.27 (d, J=7.0 Hz, 3 H), 1.36 (d, J=9.5 Hz, 3 H), 2.05 - 2.39 (m, 4 H), 3.01 (s, 3 H), 3.24 (t, J=7.7 Hz, 2 H), 3.59 - 3.85 (m, 2 H), 4.04 (s, 1 H), 4.20 (br. s., 1 H), 4.47 (t, J=7.5 Hz, 2 H), 5.17 - 5.35 (m, 3 H), 7.04 - 7.12 (m, 1 H), 7.17 - 7.41 (m, 4 H), 7.61 - 7.74 (m, 2 H); m/z = 559 (M+H)+
122		(S)-1-((5-chloro-1-(3-(methylsulfonyl)propyl)-1H-benzo[d]imidazol-2-yl)methyl)-1'-(2-hydroxy-2-methylpropanoyl)spiro[indoline-3,3'-pyrrolidin]-2-one --- ^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 1.27 (d, J=7.3 Hz, 3 H), 1.37 (d, J=9.5 Hz, 3 H), 2.05 - 2.39 (m, 4 H), 3.01 (s, 3 H), 3.24 (t, J=7.8 Hz, 2 H), 3.59 - 3.86 (m, 2 H), 4.05 (s, 1 H), 4.20 (br. s., 1 H), 4.48 (t, J=7.5 Hz, 2 H), 5.18 - 5.35 (m, 3 H), 7.04 - 7.12 (m, 1 H), 7.17 - 7.42 (m, 4 H), 7.63 - 7.71 (m, 2 H); m/z = 559 (M+H)+
123		(1r,3r)-1'-((5-chloro-1-(3-cyanopropyl)-1H-indol-2-yl)methyl)-2'-oxospiro[cyclobutane-1,3'-indolin]-3-yl methylcarbamate --- ^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 1.92 - 2.02 (m, 2 H) 2.54 - 2.61 (m, 5 H) 2.79 (ddd, J=9.96, 7.32, 2.75 Hz, 2 H) 4.31 (t, J=7.48 Hz, 2 H) 5.13 (s, 2 H) 5.31 (quin, J=7.37 Hz, 1 H) 6.27 (s, 1 H) 7.03 (d, J=7.70 Hz, 1 H) 7.08 - 7.17 (m, 3 H) 7.20 - 7.28 (m, 1 H) 7.49 - 7.56 (m, 3 H); m/z = 478 (M+H)+

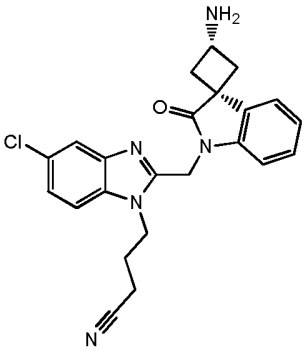
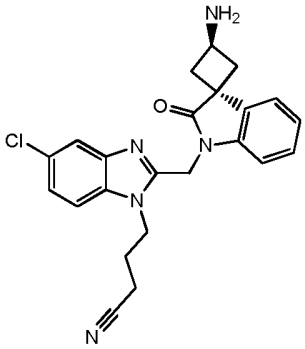
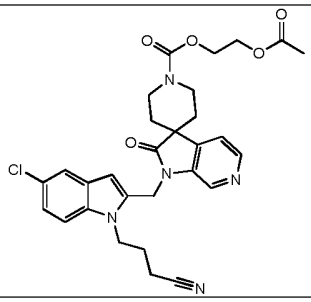
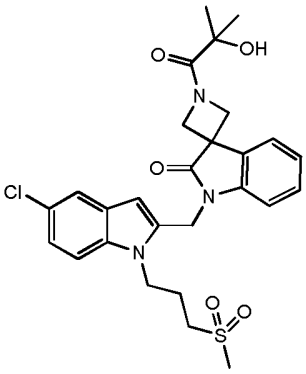
N°	structure	Name / analytical details
125		cyclopropyl ((1s,3s)-1'-((5-chloro-1-(3-cyanopropyl)-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxospiro[cyclobutane-1,3'-indolin]-3-yl)carbamate --- ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.46 - 0.73 (m, 4 H) 1.86 - 2.05 (m, 2 H) 2.52 - 2.63 (m, 6 H) 3.79 - 4.07 (m, 1 H) 4.34 (t, *J*=7.70 Hz, 2 H) 4.49 - 4.65 (m, 1 H) 5.20 (s, 2 H) 7.07 - 7.15 (m, 2 H) 7.24 (td, *J*=8.80, 1.10 Hz, 1 H) 7.29 (dd, *J*=8.80, 2.20 Hz, 1 H) 7.59 (d, *J*=7.26 Hz, 1 H) 7.62 - 7.67 (m, 2 H) 7.79 (d, *J*=6.82 Hz, 1 H); m/z = 504 (M+H)+
126		cyclopropyl ((1r,3r)-1'-((5-chloro-1-(3-cyanopropyl)-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxospiro[cyclobutane-1,3'-indolin]-3-yl)carbamate --- ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.50 - 0.69 (m, 4 H) 1.97 - 2.11 (m, 2 H) 2.51 - 2.56 (m, 2 H) 2.57 - 2.71 (m, 4 H) 3.89 - 4.02 (m, 1 H) 4.39 (t, *J*=7.30 Hz, 2 H) 4.43 - 4.53 (m, 1 H) 5.21 (s, 2 H) 7.04 - 7.15 (m, 2 H) 7.23 (td, *J*=7.70, 1.32 Hz, 1 H) 7.29 (dd, *J*=8.69, 1.87 Hz, 1 H) 7.53 (d, *J*=7.04 Hz, 1 H) 7.65 (dd, *J*=5.28, 3.30 Hz, 2 H) 7.69 (br. d, *J*=8.60 Hz, 1 H); m/z = 504 (M+H)+
129		(S)-4-(5-chloro-2-((1-(2,3-dihydroxypropanoyl)-2'-oxospiro[azetidine-3,3'-indolin]-1'-yl)methyl)-1H-indol-1-yl)butanenitrile --- m/z = 493 (M+H)+

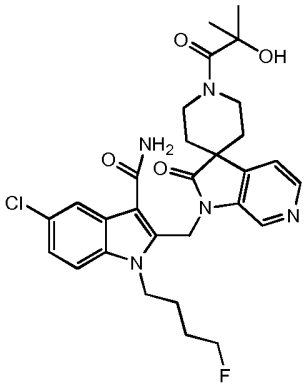
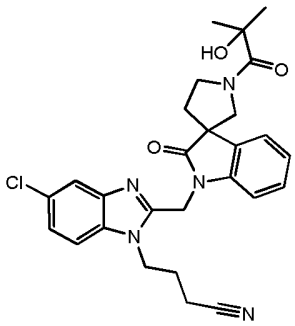
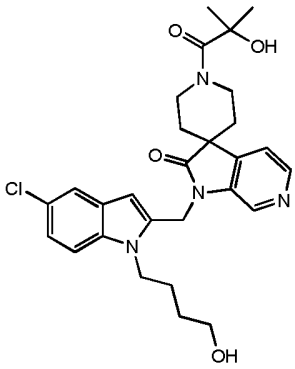
N°	structure	Name / analytical details
131		(R)-4-(5-chloro-2-((1-(2,3-dihydroxypropanoyl)-2'-oxospiro[azetidine-3,3'-indolin]-1'-yl)methyl)-1H-indol-1-yl)butanenitrile m/z = 493 (M+H)+
132		Cyclopropyl 1'-{[5-chloro-1-(3-cyanopropyl)-1H-indol-2-yl]methyl}-2'-oxo-1',2'-dihydro-1H-spiro[piperidine-4,3'-pyrrolo[2,3-c]pyridine]-1-carboxylate ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.49 - 0.74 (m, 4 H) 1.60 - 1.90 (m, 4 H) 1.92 - 2.05 (m, 2 H) 2.58 (t, *J*=7.50 Hz, 2 H) 3.61 - 3.84 (m, 4 H) 3.99 - 4.11 (m, 1 H) 4.30 (t, *J*=7.30 Hz, 2 H) 5.19 (s, 2 H) 6.36 (s, 1 H) 7.13 (dd, *J*=8.80, 1.98 Hz, 1 H) 7.46 - 7.57 (m, 2 H) 7.70 (d, *J*=4.84 Hz, 1 H) 8.33 (d, *J*=4.84 Hz, 1 H) 8.39 (s, 1 H); m/z = 518 (M+H)+
133		(1r,3r)-1'-((5-chloro-1-(3-(methylsulfonyl)propyl)-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxospiro[cyclobutane-1,3'-indolin]-3-yl morpholine-4-carboxylate ^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 2.16 (dt, J=15.24, 7.67 Hz, 2 H) 2.53 - 2.62 (m, 2 H) 2.72 - 2.84 (m, 2 H) 3.00 (s, 3 H) 3.19 - 3.27 (m, 2 H) 3.33 - 3.55 (m, 4 H) 3.55 - 3.66 (m, 4 H) 4.47 (t, J=7.37 Hz, 2 H) 5.22 (s, 2 H) 5.33 (quin, J=7.43 Hz, 1 H) 7.06 - 7.17 (m, 2 H) 7.22 - 7.28 (m, 1 H) 7.30 (dd, J=8.58, 1.98 Hz, 1 H) 7.56 (d, J=7.48 Hz, 1 H) 7.64 - 7.72 (m, 2 H); m/z = 587.17 (M+H)+
134		1'-({5-Chloro-1-[3-(methylsulfonyl)propyl]-1H-indol-2-yl}methyl)spiro[azetidine-3,3'-indol]-2'(1'H)-one m/z = 458 (M+H)+

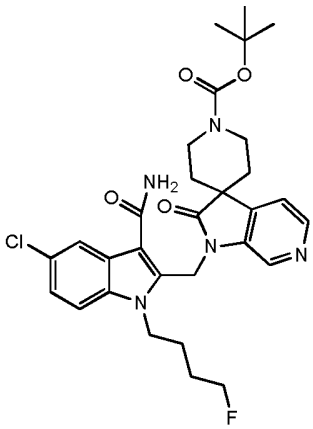
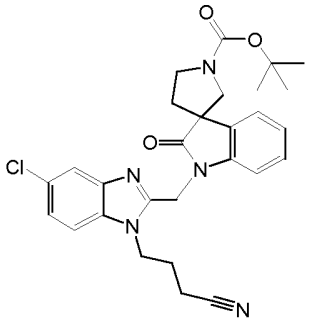
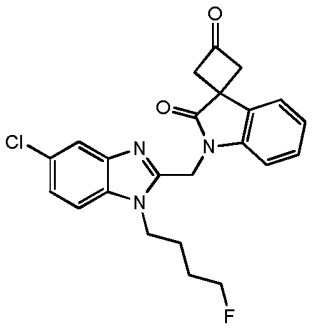
N°	structure	Name / analytical details
135		methyl ((1s,3s)-1'-((5-chloro-1-(3-cyanopropyl)-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxospiro[cyclobutane-1,3'-indolin]-3-yl)carbamate --- ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.90 - 2.07 (m, 2 H) 2.36 - 2.49 (m, 2 H) 2.54 - 2.66 (m, 4 H) 3.55 (s, 3 H) 4.33 (t, *J*=7.70 Hz, 2 H) 4.48 - 4.66 (m, 1 H) 5.22 (s, 2 H) 7.06 - 7.15 (m, 2 H) 7.20 - 7.27 (m, 1 H) 7.30 (dd, *J*=8.58, 2.20 Hz, 1 H) 7.59 (d, *J*=7.48 Hz, 1 H) 7.64 (d, *J*=8.80 Hz, 1 H) 7.65 (d, *J*=1.98 Hz, 1 H) 7.74 - 7.83 (m, 1 H); m/z = 478 (M+H)+
136		methyl ((1r,3r)-1'-((5-chloro-1-(3-cyanopropyl)-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxospiro[cyclobutane-1,3'-indolin]-3-yl)carbamate --- ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.94 - 2.12 (m, 2 H) 2.51 - 2.57 (m, 2 H) 2.58 - 2.69 (m, 4 H) 3.58 (s, 3 H) 4.35 (t, *J*=7.50 Hz, 2 H) 4.43 - 4.54 (m, 1 H) 5.17 (s, 2 H) 7.06 - 7.16 (m, 2 H) 7.19 - 7.26 (m, 1 H) 7.19 (td, *J*=7.70, 1.32 Hz, 1 H) 7.29 (dd, *J*=8.80, 1.98 Hz, 1 H) 7.54 (d, *J*=7.26 Hz, 1 H) 7.62 - 7.68 (m, 3 H); m/z = 478 (M+H)+
137		4-[5-Chloro-2-({1-[(1-hydroxycyclopropyl)carbonyl]-2'-oxospiro[azetidine-3,3'-indol]-1'(2'H)-yl}methyl)-1H-indol-1-yl]butanenitrile --- ^{1}H-NMR (360 MHz, DMSO-d6) δ ppm 0.87 (d, J=3.7 Hz, 2 H), 1.04 (d, J=6.2 Hz, 6 H), 1.12 (d, J=5.5 Hz, 1 H), 1.98 (s, 1 H), 2.58 (t, J=7.5 Hz, 1 H), 3.60 (t, J=6.0 Hz, 1 H), 4.18 (s, 1 H), 4.31 (br. s., 1 H), 4.79 (s, 1 H), 5.15 (s, 1 H), 6.21 (br. s., 1 H), 6.35 (s, 1 H), 7.06 - 7.19 (m, 2 H), 7.29 (d, J=1.1 Hz, 1 H), 7.49 - 7.56 (m, 1 H), 7.69 (d, J=6.6 Hz, 1 H); m/z = 489 (M+H)+

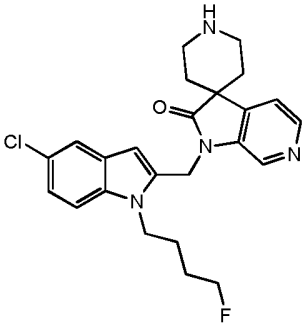
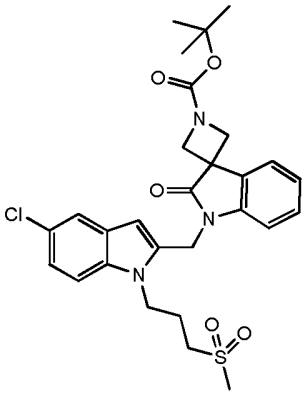
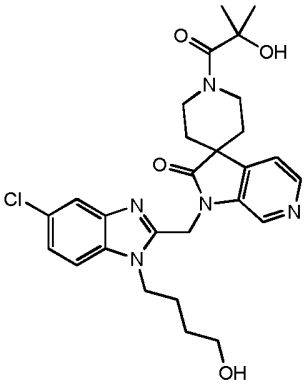
N°	structure	Name / analytical details
138		1-((5-chloro-1-(3-(methylsulfonyl)propyl)-1H-benzo[d]imidazol-2-yl)methyl)-1'-(2-hydroxy-2-methylpropanoyl)spiro[indoline-3,3'-pyrrolidin]-2-one --- ^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 1.27 (d, J=7.3 Hz, 6 H), 2.06 - 2.28 (m, 4 H), 3.01 (s, 3 H), 3.24 (t, J=7.7 Hz, 2 H), 3.59 - 3.86 (m, 2 H), 4.05 (s, 1 H), 4.20 (br. s., 1 H), 4.48 (t, J=7.5 Hz, 2 H), 5.18 - 5.36 (m, 2 H), 7.04 - 7.12 (m, 1 H), 7.17 - 7.23 (m, 1 H), 7.25 - 7.33 (m, 2 H), 7.63 - 7.72 (m, 2 H); m/z = 559 (M+H)+
143		1-((1s,3s)-1'-((5-chloro-1-(3-cyanopropyl)-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxospiro[cyclobutane-1,3'-indolin]-3-yl)-3-isopropylurea --- ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.04 (d, *J*=6.60 Hz, 6 H) 1.90 - 2.06 (m, 2 H) 2.32 - 2.46 (m, 2 H) 2.60 (t, *J*=7.48 Hz, 2 H) 3.50 - 3.81 (m, 1 H) 4.24 - 4.48 (m, 2 H) 4.54 - 4.75 (m, 1 H) 5.23 (s, 2 H) 5.65 (d, *J*=8.80 Hz, 1 H) 6.32 (d, *J*=9.02 Hz, 1 H) 7.05 - 7.15 (m, 2 H) 7.23 (dd, *J*=8.14, 1.32 Hz, 1 H) 7.29 (dd, *J*=8.58, 1.98 Hz, 1 H) 7.58 (d, *J*=8.36 Hz, 1 H) 7.62 - 7.68 (m, 2 H); m/z = 505 (M+H)+; MP = 242.49 °C
144		1-((1r,3r)-1'-((5-chloro-1-(3-cyanopropyl)-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxospiro[cyclobutane-1,3'-indolin]-3-yl)-3-isopropylurea --- ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.04 (d, *J*=6.60 Hz, 6 H) 1.92 - 2.12 (m, 2 H) 2.37 - 2.48 (m, 2 H) 2.55 - 2.69 (m, 4 H) 3.52 - 3.79 (m, 1 H) 4.24 - 4.46 (m, 2 H) 4.48 - 4.65 (m, 1 H) 5.21 (s, 2 H) 5.75 (d, *J*=7.70 Hz, 1 H) 6.26 (d, *J*=8.58 Hz, 1 H) 7.09 (dd, *J*=15.19, 7.92 Hz, 2 H) 7.22 (s, 1 H) 7.29 (dd, *J*=8.80, 1.98 Hz, 1 H) 7.57 (d, *J*=6.60 Hz, 1 H) 7.65 (dd, *J*=5.17, 3.19 Hz, 2 H); m/z = 505 (M+H)+; MP = 219.90 °C

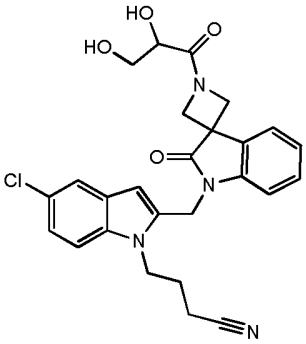
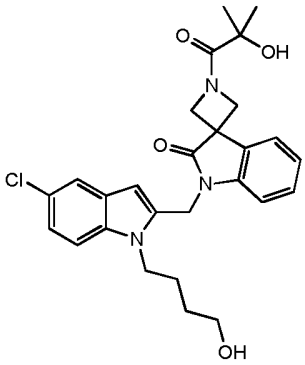
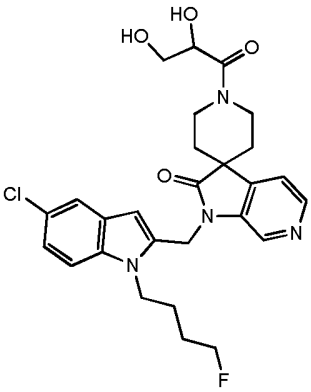
N°	structure	Name / analytical details
145		N-((1s,3s)-1'-((5-chloro-1-(3-cyanopropyl)-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxospiro[cyclobutane-1,3'-indolin]-3-yl)acetamide --- ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.85 (s, 3 H) 1.93 - 2.07 (m, 2 H) 2.52 - 2.65 (m, 6 H) 4.17 - 4.48 (m, 2 H) 4.66 - 4.87 (m, 1 H) 5.24 (s, 2 H) 7.07 - 7.16 (m, 2 H) 7.20 - 7.27 (m, 1 H) 7.30 (dd, *J*=8.80, 2.20 Hz, 1 H) 7.58 - 7.69 (m, 3 H) 8.45 (d, *J*=7.92 Hz, 1 H); m/z = 462 (M+H)+; MP = 250.91 °C
146		N-((1r,3r)-1'-((5-chloro-1-(3-cyanopropyl)-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxospiro[cyclobutane-1,3'-indolin]-3-yl)acetamide --- ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.84 (s, 3 H) 1.96 - 2.10 (m, 2 H) 2.41 - 2.47 (m, 1 H) 2.57 - 2.67 (m, 5 H) 4.37 (t, *J*=7.30 Hz, 2 H) 4.61 - 4.75 (m, 1 H) 5.12 (s, 2 H) 7.04 - 7.15 (m, 2 H) 7.22 (td, *J*=7.70, 1.10 Hz, 1 H) 7.28 (dd, *J*=8.58, 1.76 Hz, 1 H) 7.53 (dd, *J*=8.80, 0.88 Hz, 1 H) 7.61 - 7.68 (m, 2 H) 8.26 (d, *J*=9.68 Hz, 1 H); m/z = 462 (M+H)+; MP = 194.77 °C
147		2-Hydroxyethyl 1'-{[5-chloro-1-(3-cyanopropyl)-1H-indol-2-yl]methyl}-2'-oxo-1',2'-dihydro-1H-spiro[piperidine-4,3'-pyrrolo[2,3-c]pyridine]-1-carboxylate --- ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.75 - 1.91 (m, 4 H), 1.95 - 2.08 (m, 2 H), 2.56 (t, *J*=7.4 Hz, 2 H), 3.61 (t, *J*=5.1 Hz, 2 H), 3.69 - 3.89 (m, 4 H), 4.03 - 4.13 (m, 2 H), 4.25 - 4.35 (m, 2 H), 4.61 (br. s., 1 H), 5.18 (s, 2 H), 6.35 (s, 1 H), 7.13 (dd, *J*=8.8, 2.0 Hz, 1 H), 7.50 (dd, *J*=5.5, 3.3 Hz, 2 H), 7.63 (dd, *J*=4.8, 0.7 Hz, 1 H), 8.33 (d, *J*=4.8 Hz, 1 H), 8.36 (s, 1 H); m/z = 522 (M+H)+ MP = 144.55 °C;

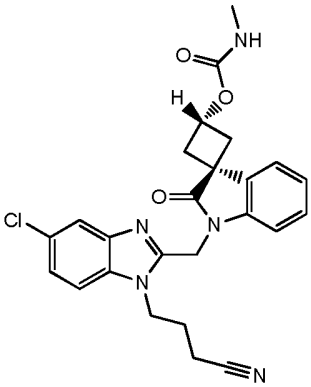
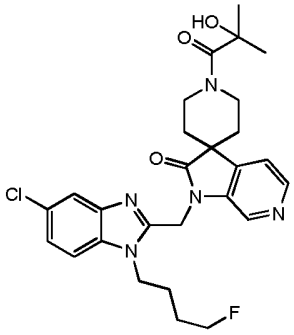
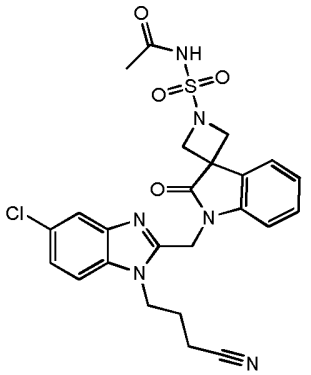
N°	structure	Name / analytical details
148		4-(2-(((1r,3r)-3-amino-2'-oxospiro[cyclobutane-1,3'-indolin]-1'-yl)methyl)-5-chloro-1H-benzo[d]imidazol-1-yl)butanenitrile --- ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.91 - 2.10 (m, 2 H) 2.13 - 2.27 (m, 2 H) 2.55 - 2.71 (m, 4 H) 3.78 (quin, *J*=8.03 Hz, 1 H) 4.38 (t, *J*=7.59 Hz, 2 H) 5.20 (s, 2 H) 7.08 (td, *J*=8.10, 1.54 Hz, 2 H) 7.20 (td, *J*=7.70, 1.32 Hz, 1 H) 7.29 (dd, *J*=8.58, 1.98 Hz, 1 H) 7.53 - 7.70 (m, 3 H); m/z = 420 (M+H)+
149		4-(2-(((1s,3s)-3-amino-2'-oxospiro[cyclobutane-1,3'-indolin]-1'-yl)methyl)-5-chloro-1H-benzo[d]imidazol-1-yl)butanenitrile --- ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.80 - 2.20 (m, 4 H) 2.20 - 2.34 (m, 2 H) 2.36 - 2.47 (m, 2 H) 2.59 (t, *J*=7.48 Hz, 2 H) 3.77 - 3.95 (m, 1 H) 4.36 (t, *J*=7.50 Hz, 2 H) 5.21 (s, 2 H) 7.00 - 7.14 (m, 2 H) 7.16 - 7.25 (m, 1 H) 7.29 (dd, *J*=8.58, 1.98 Hz, 1 H) 7.55 (d, *J*=6.82 Hz, 1 H) 7.64 (d, *J*=8.80 Hz, 1 H) 7.66 (d, *J*=1.76 Hz, 1 H); m/z = 420 (M+H)+
150		2-(Acetyloxy)ethyl 1'-{[5-chloro-1-(3-cyanopropyl)-1H-indol-2-yl]methyl}-2'-oxo-1',2'-dihydro-1H-spiro[piperidine-4,3'-pyrrolo[2,3-c]pyridine]-1-carboxylate --- m/z = 564 (M+H)+
152		1'-({5-Chloro-1-[3-(methylsulfonyl)propyl]-1H-indol-2-yl}methyl)-1-(2-hydroxy-2-methylpropanoyl)spiro[azetidine-3,3'-indol]-2'(1'H)-one --- ^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 1.32 (s, 3 H) 1.34 (s, 3 H) 2.02 - 2.14 (m, 2 H) 2.99 (s, 3 H) 3.14 - 3.23 (m, 2 H) 4.03 - 4.23 (m, 2 H) 4.39 (t, J=7.48 Hz, 2 H) 4.55 - 4.78 (m, 2 H) 5.14 (s, 2 H) 5.26 (s, 1 H) 6.38 (s, 1 H) 7.08 (d, J=7.70 Hz, 1 H) 7.12 - 7.19 (m, 2 H) 7.25 - 7.32 (m, 1 H) 7.52 (d, J=1.98 Hz, 1 H) 7.55 (d, J=8.80 Hz, 1 H) 7.64 (dd, J=7.37, 0.77 Hz, 1 H); m/z = 544.08 (M+H)+

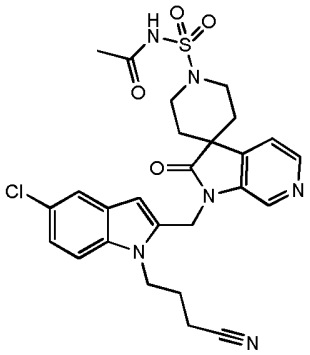
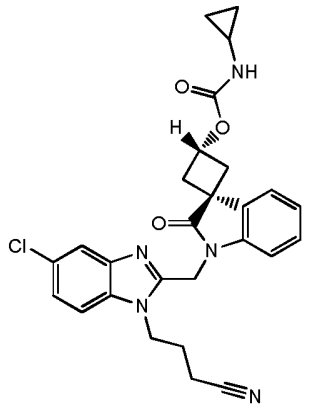
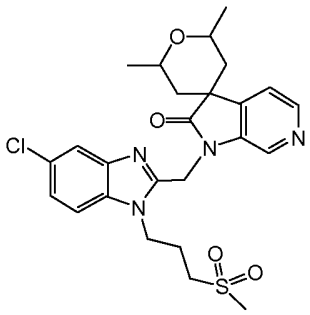
N°	structure	Name / analytical details
153		5-Chloro-1-(4-fluorobutyl)-2-{[1-(2-hydroxy-2-methylpropanoyl)-2'-oxospiro[piperidine-4,3'-pyrrolo[2,3-c]pyridin]-1'(2'H)-yl]methyl}-1H-indole-3-carboxamide ——— ^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 1.37 (s, 6 H), 1.54 - 1.69 (m, 4 H), 1.71 - 1.91 (m, 4 H), 3.63 - 4.06 (m, 2 H), 4.13 - 4.31 (m, 2 H), 4.14 - 4.23 (m, 2 H), 4.36 (br. s., 1 H), 4.47 (t, J=5.6 Hz, 1 H), 5.48 (s, 1 H), 5.53 (s, 2 H), 7.26 (dd, J=8.9, 2.1 Hz, 1 H), 7.58 (d, J=9.0 Hz, 1 H), 7.61 (d, J=4.8 Hz, 1 H), 7.63 - 7.73 (m, 2 H), 7.84 (d, J=2.0 Hz, 1 H), 8.29 (d, J=4.8 Hz, 1 H), 8.44 (s, 1 H); m/z = 570 (M+H)+
154		4-(5-Chloro-2-{[1'-(2-hydroxy-2-methylpropanoyl)-2-oxospiro[indole-3,3'-pyrrolidin]-1(2H)-yl]methyl}-1H-benzimidazol-1-yl)butanenitrile ——— ^{1}H-NMR (400 MHz, DMSO-d6) δ□ppm 1.22 - 1.43 (m, 6 H), 2.00 - 2.15 (m, 2 H), 2.15 - 2.38 (m, 2 H), 2.62 (t, J=7.4 Hz, 2 H), 3.59 - 3.86 (m, 2 H), 4.04 (s, 1 H), 4.20 (br. s., 1 H), 4.39 (t, J=7.9 Hz, 2 H), 5.16 - 5.35 (m, 3 H), 7.04 - 7.12 (m, 1 H), 7.15 - 7.21 (m, 1 H), 7.22 - 7.40 (m, 3 H), 7.61 - 7.69 (m, 2 H); m/z = 506 (M+H)+
155		1'-{[5-Chloro-1-(4-hydroxybutyl)-1H-indol-2-yl]methyl}-1-(2-hydroxy-2-methylpropanoyl)spiro[piperidine-4,3'-pyrrolo[2,3-c]pyridin]-2'(1'H)-one ——— ^{1}H-NMR (360 MHz, DMSO-d6) δ ppm 1.37 (s, 6 H), 1.41 - 1.51 (m, 2 H), 1.65 (m, J=6.6 Hz, 2 H), 1.83 (br. s., 4 H), 3.37 - 3.46 (m, 2 H), 3.73 - 4.41 (m, 4 H), 4.24 (t, J=7.5 Hz, 2 H), 4.48 (t, J=5.1 Hz, 1 H), 5.19 (s, 2 H), 5.52 (s, 1 H), 6.42 (s, 1 H), 7.13 (dd, J=8.8, 1.8 Hz, 1 H), 7.43 - 7.57 (m, 2 H), 7.68 (d, J=4.8 Hz, 1 H), 8.33 (d, J=4.8 Hz, 1 H), 8.38 (s, 1 H); m/z = 525 (M+H)+

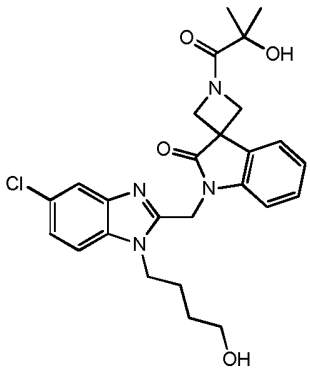
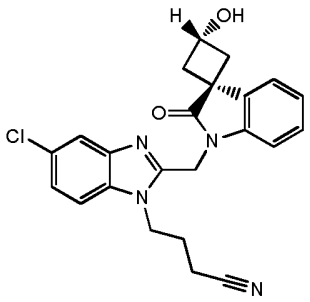
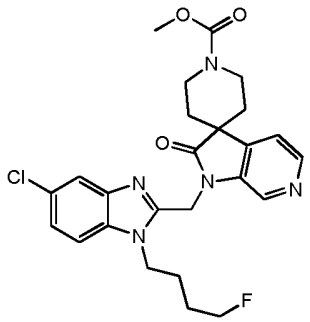
N°	structure	Name / analytical details
156		*tert*-Butyl 1'-{[3-carbamoyl-5-chloro-1-(4-fluorobutyl)-1H-indol-2-yl]methyl}-2'-oxo-1',2'-dihydro-1H-spiro[piperidine-4,3'-pyrrolo[2,3-c]pyridine]-1-carboxylate ^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 1.45 (s, 9 H), 1.54 - 1.70 (m, 4 H), 1.77 (t, J=5.6 Hz, 4 H), 3.59 - 3.69 (m, 2 H), 3.70 - 3.80 (m, 2 H), 4.18 (t, J=7.0 Hz, 2 H), 4.33 - 4.39 (m, 1 H), 4.48 (t, J=5.6 Hz, 1 H), 5.52 (s, 2 H), 7.26 (dd, J=8.8, 2.0 Hz, 1 H), 7.57 (d, J=8.8 Hz, 1 H), 7.63 (d, J=4.6 Hz, 1 H), 7.64 - 7.71 (m, 2 H), 7.84 (d, J=2.0 Hz, 1 H), 8.27 (d, J=4.6 Hz, 1 H), 8.43 (s, 1 H); m/z = 584 (M+H)+
157		*tert*-Butyl 1-{[5-chloro-1-(3-cyanopropyl)-1H-benzimidazol-2-yl]methyl}-2-oxo-1,2-dihydro-1'H-spiro[indole-3,3'-pyrrolidine]-1'-carboxylate ^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 1.35 - 1.52 (m, 9 H), 2.02 - 2.14 (m, 2 H), 2.18 - 2.30 (m, 2 H), 2.62 (t, J=7.4 Hz, 2 H), 3.50 - 3.62 (m, 2 H), 3.62 - 3.77 (m, 2 H), 4.39 (t, J=7.6 Hz, 2 H), 5.17 - 5.33 (m, 2 H), 7.08 (td, J=7.5, 0.9 Hz, 1 H), 7.16 - 7.21 (m, 1 H), 7.24 - 7.32 (m, 2 H), 7.35 (d, J=7.3 Hz, 1 H), 7.62 - 7.69 (m, 2 H); m/z = 521 (M+H)+
158		1'-{[5-Chloro-1-(4-fluorobutyl)-1H-benzimidazol-2-yl]methyl}-3H-spiro[cyclobutane-1,3'-indole]-2',3(1'H)-dione ^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 1.52 - 1.86 (m, 4 H) 3.39 - 3.50 (m, 2 H) 3.60 - 3.74 (m, 2 H) 4.32 - 4.42 (m, 3 H) 4.50 (t, J=5.50 Hz, 1 H) 5.26 (s, 2 H) 7.11 (dd, J=7.48, 0.88 Hz, 1 H) 7.19 (d, J=7.92 Hz, 1 H) 7.24 - 7.30 (m, 2 H) 7.60 - 7.69 (m, 3 H); m/z = 426 (M+H)+

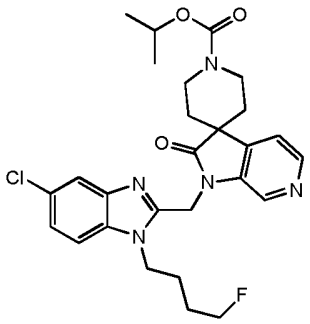
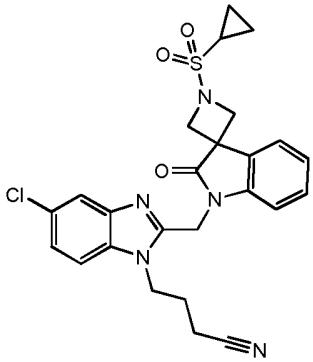
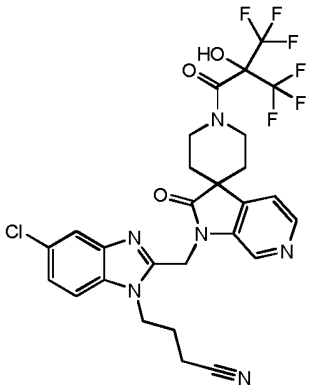
N°	structure	Name / analytical details
162		1'-{[5-Chloro-1-(4-fluorobutyl)-1H-indol-2-yl]methyl}spiro[piperidine-4,3'-pyrrolo[2,3-c]pyridin]-2'(1'H)-one --- ^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 1.53 - 1.85 (m, 8 H) 2.77 - 3.00 (m, 2 H) 3.03 - 3.16 (m, 2 H) 4.26 (t, J=6.93 Hz, 2 H) 4.40 (t, J=5.72 Hz, 1 H) 4.47 - 4.56 (m, 1 H) 5.17 (s, 2 H) 6.40 (s, 1 H) 7.13 (dd, J=8.80, 2.20 Hz, 1 H) 7.50 (d, J=8.58 Hz, 1 H) 7.53 (d, J=1.98 Hz, 1 H) 7.64 (d, J=4.62 Hz, 1 H) 8.32 (d, J=4.84 Hz, 1 H) 8.35 (s, 1 H); m/z = 441 (M+H)+
163		*tert*-Butyl 1'-({5-chloro-1-[3-(methylsulfonyl)propyl]-1H-indol-2-yl}methyl)-2'-oxo-1',2'-dihydro-1H-spiro[azetidine-3,3'-indole]-1-carboxylate --- ^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 1.45 (s, 9 H) 1.98 - 2.13 (m, 2 H) 2.99 (s, 3 H) 3.13 - 3.22 (m, 2 H) 4.01 - 4.24 (m, 4 H) 4.38 (t, J=7.59 Hz, 2 H) 5.13 (s, 2 H) 6.39 (s, 1 H) 7.05 - 7.19 (m, 3 H) 7.24 - 7.33 (m, 1 H) 7.52 (d, J=1.98 Hz, 1 H) 7.54 (d, J=8.80 Hz, 1 H) 7.65 - 7.71 (m, 1 H); m/z = 558.23 (M+H)+
164		1'-{[5-Chloro-1-(4-hydroxybutyl)-1H-benzimidazol-2-yl]methyl}-1-(2-hydroxy-2-methylpropanoyl)spiro[piperidine-4,3'-pyrrolo[2,3-c]pyridin]-2'(1'H)-one --- ^{1}H-NMR (360 MHz, DMSO-d6) δ ppm 1.37 (s, 6 H), 1.40 - 1.57 (m, 2 H), 1.63 - 1.79 (m, 2 H), 1.82 (br. s., 4 H), 3.42 (q, J=6.1 Hz, 2 H), 3.85 (br. s., 2 H), 4.34 (m, J=7.5, 7.5 Hz, 4 H), 4.50 (t, J=5.1 Hz, 1 H), 5.29 (s, 2 H), 5.51 (s, 1 H), 7.28 (dd, J=8.8, 1.8 Hz, 1 H), 7.55 - 7.75 (m, 3 H), 8.34 (d, J=4.8 Hz, 1 H), 8.48 (s, 1 H); m/z = 526 (M+H)+; MP = 191.87 °C

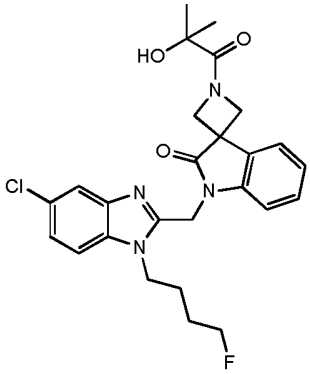
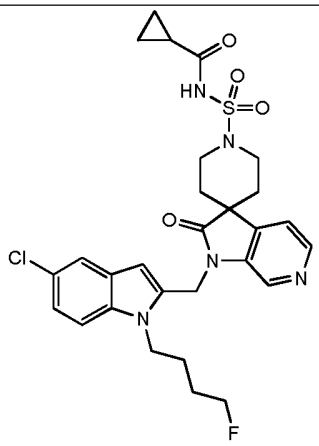
N°	structure	Name / analytical details
165		4-(5-chloro-2-((1-(2,3-dihydroxypropanoyl)-2'-oxospiro[azetidine-3,3'-indolin]-1'-yl)methyl)-1H-indol-1-yl)butanenitrile --- ^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 1.83 - 2.05 (m, 2 H) 2.56 (t, J=7.30 Hz, 2 H) 3.44 - 3.66 (m, 2 H) 4.01 - 4.24 (m, 3 H) 4.25 - 4.34 (m, 2 H) 4.43 - 4.67 (m, 2 H) 4.76 - 4.92 (m, 1 H) 5.13 (s, 2 H) 5.30 (dd, J=49.08, 5.50 Hz, 1 H) 6.32 (d, J=2.86 Hz, 1 H) 7.05 (br. d, J=9.00 Hz, 1 H) 7.10 - 7.16 (m, 2 H) 7.22 - 7.31 (m, 1 H) 7.47 - 7.54 (m, 2 H) 7.59 - 7.69 (m, 1 H); m/z = 493 (M+H)+
166		1'-{[5-Chloro-1-(4-hydroxybutyl)-1H-indol-2-yl]methyl}-1-(2-hydroxy-2-methylpropanoyl)spiro[azetidine-3,3'-indol]-2'(1'H)-one --- ^{1}H-NMR (360 MHz, DMSO-d6) δ ppm 1.33 (d, J=5.9 Hz, 6 H), 1.37 - 1.50 (m, 2 H), 1.61 (m, J=7.0 Hz, 2 H), 3.39 (q, J=6.2 Hz, 2 H), 4.06 (d, J=9.5 Hz, 1 H), 4.17 (d, J=9.5 Hz, 1 H), 4.24 (t, J=7.7 Hz, 2 H), 4.46 (t, J=5.1 Hz, 1 H), 4.59 (d, J=9.9 Hz, 1 H), 4.72 (d, J=9.5 Hz, 1 H), 5.12 (s, 2 H), 5.29 (s, 1 H), 6.42 (s, 1 H), 7.02 - 7.18 (m, 3 H), 7.27 (m, J=7.0 Hz, 1 H), 7.47 (d, J=8.8 Hz, 1 H), 7.52 (d, J=2.2 Hz, 1 H), 7.63 (d, J=7.0 Hz, 1 H); m/z = 496 (M+H)+; MP = 157.11 °C
167		1'-{[5-Chloro-1-(4-fluorobutyl)-1H-indol-2-yl]methyl}-1-(2,3-dihydroxypropanoyl)spiro[piperidine-4,3'-pyrrolo[2,3-c]pyridin]-2'(1'H)-one --- ^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 1.55 - 1.95 (m, 8 H) 3.42 - 3.52 (m, 1 H) 3.53 - 3.65 (m, 1 H) 3.74 - 4.02 (m, 4 H) 4.17 - 4.31 (m, 2 H) 4.38 (t, J=6.40 Hz, 2 H) 4.46 - 4.55 (m, 1 H) 4.71 (t, J=5.90 Hz, 1 H) 4.95 (dd, J=21.13, 6.82 Hz, 1 H) 5.18 (s, 2 H) 6.40 (s, 1 H) 7.11 (dd, J=8.80, 2.20 Hz, 1 H) 7.50 (d, J=8.80 Hz, 1 H) 7.52 (d, J=2.20 Hz, 1 H) 7.59 - 7.70 (m, 1 H) 8.32 (d, J=4.62 Hz, 1 H) 8.37 (s, 1 H); m/z = 530 (M+H)+

N°	structure	Name / analytical details
168		(1r,3r)-1'-((5-chloro-1-(3-cyanopropyl)-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxospiro[cyclobutane-1,3'-indolin]-3-yl methylcarbamate --- ^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 2.07 (quin, J=7.48 Hz, 2 H) 2.44 - 2.53 (m, 2 H) 2.56 - 2.67 (m, 5 H) 2.72 - 2.83 (m, 2 H) 4.40 (t, J=7.50 Hz, 2 H) 5.23 (s, 2 H) 5.30 (quin, J=7.37 Hz, 1 H) 7.06 - 7.19 (m, 3 H) 7.22 - 7.27 (m, 1 H) 7.29 (dd, J=8.80, 1.98 Hz, 1 H) 7.48 - 7.55 (m, 1 H) 7.62 - 7.68 (m, 2 H); m/z = 478.10 (M+H)+
169		1'-{[5-Chloro-1-(4-fluorobutyl)-1H-benzimidazol-2-yl]methyl}-1-(2-hydroxy-2-methylpropanoyl)spiro[piperidine-4,3'-pyrrolo[2,3-c]pyridin]-2'(1'H)-one --- ^{1}H-NMR (400 MHz, DMSO-d6) δ□ppm 1.40 (s, 6 H), 1.69 - 1.93 (m, 8 H), 4.05 (t, J=5.6 Hz, 4 H), 4.35 (t, J=7.5 Hz, 2 H), 4.40 (t, J=6.1 Hz, 1 H), 4.52 (t, J=5.8 Hz, 1 H), 5.06 (s, 1 H), 5.25 (s, 2 H), 7.24 (dd, J=8.6, 2.0 Hz, 1 H), 7.53 (dd, J=4.6, 0.7 Hz, 1 H), 7.55 - 7.61 (m, 1 H), 8.32 (d, J=4.8 Hz, 1 H), 8.45 (s, 1 H); m/z = 528 (M+H)+; MP = 222.72 °C
170		N-[(1'-{[5-Chloro-1-(3-cyanopropyl)-1H-benzimidazol-2-yl]methyl}-2'-oxo-1',2'-dihydro-1H-spiro[azetidine-3,3'-indol]-1-yl)sulfonyl]acetamide --- ^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 2.00 - 2.13 (m, 2 H) 2.16 (s, 3 H) 2.62 (t, J=7.37 Hz, 2 H) 4.24 (d, J=8.36 Hz, 2 H) 4.33 - 4.44 (m, 4 H) 5.21 (s, 2 H) 7.07 - 7.23 (m, 2 H) 7.25 - 7.35 (m, 2 H) 7.56 (d, J=6.82 Hz, 1 H) 7.62 - 7.68 (m, 2 H) 11.73 (s, 1 H); m/z = 527 (M+H)+

N°	structure	Name / analytical details
172		N-[(1'-{[5-Chloro-1-(3-cyanopropyl)-1H-indol-2-yl]methyl}-2'-oxo-1',2'-dihydro-1H-spiro[piperidine-4,3'-pyrrolo[2,3-c]pyridin]-1-yl)sulfonyl]acetamide --- ^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 1.84 - 2.08 (m, 9 H) 2.58 (t, J=7.37 Hz, 2 H) 3.49 - 3.74 (m, 4 H) 4.24 - 4.37 (m, 2 H) 5.19 (s, 2 H) 6.34 (s, 1 H) 7.15 (dd, J=8.69, 2.09 Hz, 1 H) 7.50 - 7.61 (m, 3 H) 8.36 (d, J=4.84 Hz, 1 H) 8.39 (s, 1 H) 11.54 (s, 1 H); m/z = 555.06 (M+H)+; MP = 230.52 °C
173		(1r,3r)-1'-((5-chloro-1-(3-cyanopropyl)-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxospiro[cyclobutane-1,3'-indolin]-3-yl cyclopropylcarbamate --- ^{1}H-NMR (400 MHz, DMSO-d6) δppm 0.36 - 0.50 (m, 2 H) 0.53 - 0.67 (m, 2 H) 2.06 (quin, J=7.43 Hz, 2 H) 2.42 - 2.52 (m, 3 H) 2.62 (t, J=7.37 Hz, 2 H) 2.70 - 2.83 (m, 2 H) 4.40 (t, J=7.48 Hz, 2 H) 5.23 (s, 2 H) 5.31 (quin, J=7.37 Hz, 1 H) 7.07 - 7.14 (m, 2 H) 7.22 - 7.27 (m, 1 H) 7.29 (dd, J=8.58, 1.98 Hz, 1 H) 7.41 - 7.55 (m, 2 H) 7.62 - 7.69 (m, 2 H); m/z = 504.15 (M+H)+
174		1'-({5-Chloro-1-[3-(methylsulfonyl)propyl]-1H-benzimidazol-2-yl}methyl)-2,6-dimethyl-2,3,5,6-tetrahydrospiro[pyran-4,3'-pyrrolo[2,3-c]pyridin]-2'(1'H)-one --- ^{1}H-NMR (400 MHz, CHLOROFORM-d) δ ppm 1.23 (d, J=6.16 Hz, 6 H) 1.59 - 1.74 (m, 4 H) 2.30 - 2.41 (m, 2 H) 2.98 (s, 3 H) 3.12 (t, J=7.04 Hz, 2 H) 4.33 - 4.43 (m, 2 H) 4.48 - 4.56 (m, 2 H) 5.18 (s, 2 H) 7.10 - 7.14 (m, 1 H) 7.27 - 7.35 (m, 2 H) 7.73 (d, J=1.54 Hz, 1 H) 8.43 (d, J=4.84 Hz, 1 H) 8.69 - 8.74 (m, 1 H); m/z = 517.05 (M+H)+

N°	structure	Name / analytical details
175		1'-{[5-Chloro-1-(4-hydroxybutyl)-1H-benzimidazol-2-yl]methyl}-1-(2-hydroxy-2-methylpropanoyl)spiro[azetidine-3,3'-indol]-2'(1'H)-one --- ^{1}H-NMR (360 MHz, DMSO-d6): δ ppm 1.31 (s, 3 H), 1.33 (s, 3 H), 1.39 - 1.51 (m, 2 H), 1.61 - 1.75 (m, 2 H), 3.36 - 3.44 (m, 2 H), 4.02 - 4.18 (m, 2 H), 4.33 (t, J=7.5 Hz, 2 H), 4.48 (t, J=5.1 Hz, 1 H), 4.54 - 4.74 (m, 2 H), 5.21 (s, 2 H), 5.29 (s, 1 H), 7.10 - 7.21 (m, 2 H), 7.25 - 7.33 (m, 2 H), 7.59 - 7.65 (m, 2 H), 7.67 (d, J=1.8 Hz, 1 H); m/z = 497 (M+H)+
176		4-(5-chloro-2-(((1r,3r)-3-hydroxy-2'-oxospiro[cyclobutane-1,3'-indolin]-1'-yl)methyl)-1H-benzo[d]imidazol-1-yl)butanenitrile --- ^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 2.03 (quin, J=7.54 Hz, 2 H) 2.27 - 2.40 (m, 2 H) 2.57 - 2.73 (m, 4 H) 4.38 (t, J=7.48 Hz, 2 H) 4.56 (sxt, J=7.35 Hz, 1 H) 5.20 (s, 2 H) 5.45 (d, J=7.26 Hz, 1 H) 7.05 - 7.14 (m, 2 H) 7.22 (td, J=7.70, 1.10 Hz, 1 H) 7.29 (dd, J=8.58, 1.76 Hz, 1 H) 7.48 - 7.54 (m, 1 H) 7.61 - 7.68 (m, 2 H); m/z = 421.01 (M+H)+; MP = 217.25 °C
178		Methyl 1'-{[5-chloro-1-(4-fluorobutyl)-1H-benzimidazol-2-yl]methyl}-2'-oxo-1',2'-dihydro-1H-spiro[piperidine-4,3'-pyrrolo[2,3-c]pyridine]-1-carboxylate --- ^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 1.65 - 1.91 (m, 8 H), 3.66 (s, 3 H), 3.71 - 3.81 (m, 4 H), 4.37 (t, J=7.3 Hz, 2 H), 4.43 (t, J=5.9 Hz, 1 H), 4.55 (t, J=5.6 Hz, 1 H), 5.29 (s, 2 H), 7.29 (dd, J=8.7, 1.9 Hz, 1 H), 7.62 - 7.70 (m, 3 H), 8.33 (d, J=4.8 Hz, 1 H), 8.49 (s, 1 H); m/z = 500 (M+H)+; MP = 182.68 °C

N°	structure	Name / analytical details
179		1-Methylethyl 1'-{[5-chloro-1-(4-fluorobutyl)-1H-benzimidazol-2-yl]methyl}-2'-oxo-1',2'-dihydro-1H-spiro[piperidine-4,3'-pyrrolo[2,3-c]pyridine]-1-carboxylate --- ^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 1.23 (d, J=6.2 Hz, 6 H), 1.65 - 1.91 (m, 8 H), 3.65 - 3.81 (m, 4 H), 4.37 (t, J=7.3 Hz, 2 H), 4.43 (t, J=5.9 Hz, 1 H), 4.54 (t, J=5.6 Hz, 1 H), 4.78 - 4.90 (m, 1 H), 5.29 (s, 2 H), 7.28 (dd, J=8.7, 1.9 Hz, 1 H), 7.65 (dd, J=5.4, 3.2 Hz, 2 H), 7.68 (dd, J=4.7, 0.6 Hz, 1 H), 8.33 (d, J=4.8 Hz, 1 H), 8.48 (s, 1 H); m/z = 528 (M+H)+; MP = 198.92 °C
180		4-(5-Chloro-2-{[1-(cyclopropylsulfonyl)-2'-oxospiro[azetidine-3,3'-indol]-1'(2'H)-yl]methyl}-1H-benzimidazol-1-yl)butanenitrile --- ^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 1.01 - 1.19 (m, 4 H) 2.01 - 2.14 (m, 2 H) 2.63 (t, J=7.26 Hz, 2 H) 2.93 - 3.03 (m, 1 H) 4.12 - 4.34 (m, 4 H) 4.40 (t, J=7.59 Hz, 2 H) 5.23 (s, 2 H) 7.12 - 7.24 (m, 2 H) 7.27 - 7.37 (m, 2 H) 7.61 - 7.72 (m, 3 H); m/z = 510.10 (M+H)+; MP = 190.42 °C
181		4-[5-Chloro-2-({2'-oxo-1-[3,3,3-trifluoro-2-hydroxy-2-(trifluoromethyl)propanoyl]spiro[piperidine-4,3'-pyrrolo[2,3-c]pyridin]-1'(2'H)-yl}methyl)-1H-benzimidazol-1-yl]butanenitrile --- ^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 1.72 - 2.01 (m, 4 H) 2.03 - 2.16 (m, 2 H) 2.64 (t, J=7.50 Hz, 2 H) 3.81 - 4.03 (m, 2 H) 4.22 - 4.35 (m, 2 H) 4.35 - 4.45 (m, 2 H) 5.32 (s, 2 H) 7.29 (dd, J=8.58, 1.98 Hz, 1 H) 7.57 - 7.73 (m, 3 H) 8.35 (d, J=4.62 Hz, 1 H) 8.49 (s, 1 H) 9.41 (s, 1 H); m/z = 629 (M+H)+; MP = 240.41 °C

N°	structure	Name / analytical details
183		1'-{[5-Chloro-1-(4-fluorobutyl)-1H-benzimidazol-2-yl]methyl}-1-(2-hydroxy-2-methylpropanoyl)spiro[azetidine-3,3'-indol]-2'(1'H)-one --- ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (d, *J*=7.70 Hz, 6 H) 1.60 - 1.83 (m, 4 H) 4.06 (d, *J*=9.68 Hz, 1 H) 4.16 (d, *J*=9.68 Hz, 1 H) 4.27 - 4.45 (m, 3 H) 4.52 (t, *J*=5.39 Hz, 1 H) 4.59 (d, *J*=9.68 Hz, 1 H) 4.71 (d, *J*=9.68 Hz, 1 H) 5.22 (s, 2 H) 7.10 - 7.23 (m, 2 H) 7.25 - 7.33 (m, 2 H) 7.59 - 7.66 (m, 2 H) 7.67 (d, *J*=1.76 Hz, 1 H); m/z = 499 (M+H)+; MP = 219.71 °C
184		N-[(1'-{[5-Chloro-1-(4-fluorobutyl)-1H-indol-2-yl]methyl}-2'-oxo-1',2'-dihydro-1H-spiro[piperidine-4,3'-pyrrolo[2,3-c]pyridin]-1-yl)sulfonyl]cyclopropanecarboxamide --- m/z = 588 (M+H)+

Antiviral activity

Black 96-well clear-bottom microtiter plates (Corning, Amsterdam, The Netherlands) were filled in duplicate using a customized robot system with serial 4-fold dilutions of compound in a final volume of 50 µl culture medium [RPMI medium without phenol red, 10% FBS, 0.04% gentamycin (50 mg/ml) and 0.5% DMSO]. Then, 100 µl of a HeLa cell suspension (5 x 10^4 cells/ml) in culture medium was added to each well followed by the addition of 50 µl rgRSV224 (MOI = 0.02) virus in culture medium using a multidrop dispenser (Thermo Scientific, Erembodegem, Belgium). rgRSV224 virus is an engineered virus that includes an additional GFP gene (Hallak et al, 2000) and was in-licensed from the NIH (Bethesda, MD, USA). Medium, virus- and mock-infected controls were included in each test. Cells were incubated at 37°C in a 5% CO_2 atmosphere. Three days post-virus exposure, viral replication was quantified by measuring GFP expression in the cells by a MSM laser microscope (Tibotec, Beerse, Belgium). The EC_{50} was defined as the 50% inhibitory concentration for GFP expression. In parallel, compounds were incubated for three days in a set of white 96-

well microtitier plates (Corning) and the cytotoxicity of compounds in HeLa cells was determined by measuring the ATP content of the cells using the ATPlite kit (PerkinElmer, Zaventem, Belgium) according to the manufacturer's instructions. The CC_{50} was defined as the 50% concentration for cytotoxicity. SI is calculated as CC_{50} /EC_{50}.

References

Hallak LK, Spillmann D, Collins PL, Peeples ME. Glycosaminoglycan sulfation requirements for respiratory syncytial virus infection. J. Virol.*740*, 10508-10513 (2000).

N°	pEC_{50}	SI
1	9.2	19370
2	7.3	>2193.76
3	10.5	>3.23668e+006
4	10.1	654998
5	8.3	>20325
6	9.3	>220491
7	10.6	>3.59137e+006
8	9.1	>127462
9	9.4	>234634
10	8.7	49544
11	9.4	>249735
12	9.3	>194729
13	10.3	>2.13334e+006
14	>9.8	>655360
15	>9.8	>655360
16	>9.8	>643591
17	9.5	79869
18	8.9	>84288.8
19	8.4	>21417.6
20	8.4	1880
21	8.3	>21256.9
22	8.1	3515
23	8.1	606
24	8.1	>13913.6
25	7.5	1386
26	6.5	164
27		-
28	>9.8	>660861

N°	pEC_{50}	SI
29	>9.8	>660861
30	9.6	>405070
31	8.5	>34055.7
32	9.2	>147839
33	9.8	>563300
34	8.9	>79744.4
35	9.1	65535
36	9.6	353419
37	10.0	>935083
38	9.8	>571387
39	9.2	59894
40	8.6	>43461
41	7.34	>2230.95
42	>9.8	>655360
43	9.6	>419527
44	9.6	>384096
45	9.4	>227520
46	9.2	>155253
47	8.8	>61850
48	8.6	>43054.6
49	8.3	2615
50	8.0	>8995.8
51	7.2	595
52	8.6	22757
53	>9.8	>305014
54	8.8	20155
55	10.3	1382102
56	9.5	>298202
57	7.08	842.91
58	>9.7	>386305
59	8.3	14980
60	9.6	>390292
61	9.4	>241324
62	9.0	46732
63	9.8	100580
64	9.6	>379778
65	9.2	158245
66	8.5	>29357.6
67	10.3	1260115
68	9.3	>204235

N°	pEC_{50}	SI
69	8.3	4891
70	>9.8	>325484
70	>9.8	>313148
71	8.5	12968
72	9.6	>405070
73	9.3	51488
74	9.7	342437
75	8.3	>21707.5
76	>9.8	>263057
77	>9.8	>96511.7
78	9.2	24938
80	>9.8	>319161
81	>9.8	>655360
82	>9.8	>655360
83	>9.8	>655360
84	9.2	>176673
85	>9.8	>655360
86	>9.8	>349849
88	9.4	>253700
89	10.1	>124385

Compound Number	RSV-wt_pEC50	SI_TOX-HELA_wt
90	10.33	>2.13954e+006
91	9.63	>428924
92	10.16	>1.43463e+006
93	8.79	>62290.2
94	9.89	>770442
95	10.10	>1.25505e+006
96	9.37	>233222
97	8.84	31764
98	10.17	>1.46504e+006
99	10.62	2437755
100	6.58	>380.041
101	9.05	>111491
102	8.84	>68433.7
103	9.58	76392
104	10.64	3927534

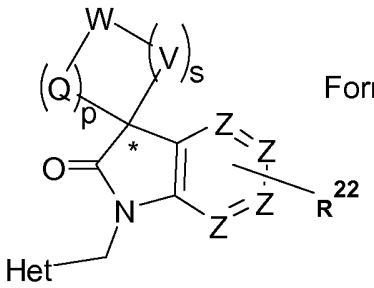
Compound Number	RSV-wt_pEC50	SI_TOX-HELA_wt
105	10.08	895262
106	9.62	80390
107	10.10	>1.25219e+006
108	9.06	>57149.2
109	9.72	>523866
110	8.84	>69368.1
111	9.91	274530
112	10.60	>3.96908e+006
113	7.18	>1507.51
114	9.37	120036
115	10.16	>1.45522e+006
116	10.15	>1.42033e+006
117	8.0	6595

Compound Number	RSV-wt_pEC50	SI_TOX-HELA_wt
120	8.62	4817
121	8.07	>11676.2
122	8.08	>12032.3
123	9.47	33180
124	8.23	>16849.6
125	9.54	>342949
126	9.59	199719
129	9.45	144016
131	9.37	107026
132	10.19	281041
133	9.85	>714628
134	8.70	21330
135	10.02	>1.05419e+006
136	9.61	251299
137	9.97	232965
138	8.67	>46631.6
143	8.48	>30292.8
144	9.64	>435994
145	9.52	>330255
146	9.30	>198577
147	10.26	872087
148	8.33	10550
149	8.92	43155

Compound Number	RSV-wt_pEC50	SI_TOX-HELA_wt
150	10.31	862700
152	8.80	31147
153	10.24	388687
154	8.93	>85767
155	9.77	291340
156	10.17	178008
157	8.40	6934
158	9.24	78873
162	8.34	2405
163	9.70	95825
164	9.90	>800424
165	9.84	288416
166	9.27	64805
167	9.91	>408517
168	10.46	2134519
169	10.56	-
170	9.57	>370143
172	10.18	>1.51471e+006
173	10.65	2178763
174	7.75	>5597.19
175	10.13	>1.34645e+006
176	9.44	>278272
178	10.54	3132492
179	10.36	1045996
180	9.93	>847754
181	9.60	271188
183	10.12	1295538
184	9.66	215909

Claims

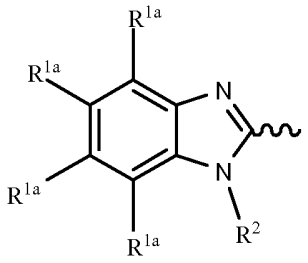
1. A compound of Formula (RI),



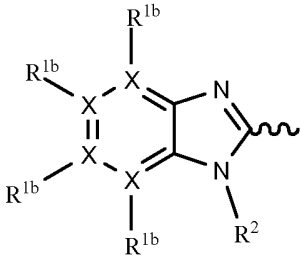
Formula (RI)

or any stereoisomeric form thereof, wherein:

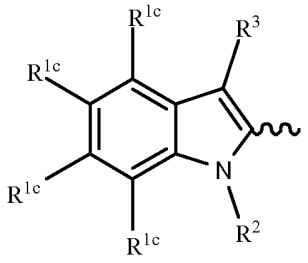
Het is a heterocycle of either of the following formula (a), (b), (c), (d):



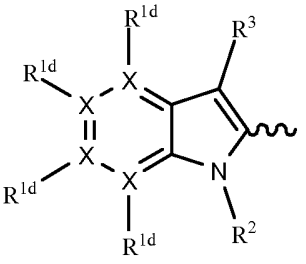
(a)



(b)



(c)



(d)

each X independently is C or N; provided that at least two X is C;

each of R^{1a}, R^{1b}, R^{1c} or R^{1d} is independently selected from the group consisting of H, halogen, C_1-C_6alkyl, C_3-C_7cycloalkyl, C_1-C_6alkyloxy, $N(R^6)_2$, $CO(R^7)$, CH_2NH_2, CH_2OH, CN, $C(=NOH)NH_2$, $C(=NOCH_3)NH_2$, $C(=NH)NH_2$, CF_3 and OCF_3;

R^{1b} or R^{1d} is absent when the X to which it is bound is N;

each R^2 is $-(CR^8R^9)_m-R^{10}$;

m is an integer from 0 to 6;

each R^3 is independently selected from the group consisting of H, halogen, aryl, heteroaryl, C_1-C_6alkyl, C_3-C_7cycloalkyl, C_1-C_6alkyloxy and $CO(R^7)$;

each R^6 is independently selected from the group consisting of H, C_1-C_6alkyl, $COOCH_3$ and $CONHSO_2CH_3$;

each R^7 is independently selected from the group consisting of H, C_1-C_6alkyl, OH, C_1-C_6alkyloxy, NH_2, $NHSO_2N(C_1\text{-}C_6\text{alkyl})_2$, $NHSO_2NHCH_3$, $NHSO_2(C_1\text{-}C_6\text{alkyl})$, $NHSO_2(C_3\text{-}C_7\text{cycloalkyl})$ and $N(C_1\text{-}C_6\text{-alkyl})_2$ NR^8R^9 and NR^9R^{10};

each R^8 and R^9 are independently selected from the group consisting of H, C_1-C_{10}alkyl and C_3-C_7cycloalkyl; or R^8 and R^9 taken together form a 4 to 6 membered saturated ring that optionally contains one or more heteroatoms selected from the group consisting of N, S and O;

each R^{10} is independently selected from the group consisting of H, halogen, OH, CN, CF_2H, CF_3, C_1-C_6 alkyl, C_3-C_7cycloalkyl, $C(=O)C_1$-C_6alkyl, $C(=O)C_3$-C_7cycloalkyl, $C(=O)NR^8R^9$, $C(=O)OR^8$, SO_2R^8, $C(=O)N(R^8)SO_2R^9$, $C(=O)N(R^8)SO_2N(R^8R^9)$, NR^8R^9, $NR^8C(=O)OR^9$, $OC(=O)R^8$, O-benzyl, $NR^8SO_2R^9$, $SO_2NR^8R^9$, SO_2R^8, $OC(=O)NR^8R^9$, $OC(=O)NR^8R^{12}$, $N(R^8)C(=O)N(R^8R^9)$, R^{11}, $N(R^8)C(=O)OR^{12}$, OR^{11}, $C(=O)R^{11}$ and a 4 to 6 membered saturated ring containing one oxygen atom;

R^{11} is phenyl, pyridinyl or pyrazolyl; each of which can be optionally substituted with one or more substituents each independently selected from the group consisting of CF_3, CH_3, OCH_3, OCF_3 and halogen;

R^{12} is C_1-C_6 alkyl or C_3-C_7cycloalkyl; each substituted with one or more substituents each independently selected from the group consisting of CF_3, CH_3, OCH_3, OCF_3 and halogen;

each Z independently is C or N, provided that at least two Z is C;

Q and V each independently represent C=O, SO_2 or $CR^{20}R^{21}$;

p and s independently represent an integer from 0 to 3, wherein the sum of p and s minimally should be 2, and when p = 0 or s = 0 then the carbon atom marked with * is directly bound to W;

R^{20} and R^{21} are independently selected from the group consisting of hydrogen, hydroxyl, C_1-C_3alkyl, C_3-C_7cycloalkyl, CF_3, OCH_3, OCF_3 and halogen;

R^{22} is selected from the group consisting of hydrogen, hydroxyl, C_1-C_6alkyl, C_3-C_7cycloalkyl, CF_3, OCH_3, OCF_3 and halogen;

W is selected from the group consisting of SO, SO_2, S, C, O and N, wherein such C or N is optionally substituted with one or more R^{23};

R^{23} is selected from the group consisting of hydrogen, hydroxyl, C_1-C_6alkyl, C_3-C_7cycloalkyl, C_1-C_6alkyl-R^{24}, SO_2R^{24}, $SO_2N(R^{24})_2$, aryl, heteroaryl, $C(=O)OR^{24}$, OR^{24}, $C(=O)R^{24}$, $C(=O)N(R^{24})_2$, $OC(=O)N(R^{24})_2$, $P(=O)$-$(O$-C_1-C_6-alkyl$)_2$, $N(R^{24})_2$, $NR^{25}C(=O)OR^{24}$, $NR^{25}C(=O)N(R^{24})_2$, $NR^{25}SO_2R^{24}$ and a 4 to 6 membered saturated ring containing one oxygen atom, wherein any of such C_1-C_6alkyl, C_3-C_7cycloalkyl, aryl or heteroaryl is optionally substituted with one or more of the substituents selected from the group consisting of halogen, OH, CN, OCH_3;

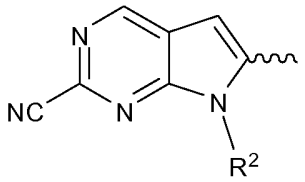
R^{24} is selected from the group of hydrogen, OH, halogen, C_1-C_6alkyl, C_3-C_7cycloalkyl, C(=O) C_1-C_6alkyl, C(=O) C_3-C_7cycloalkyl, aryl, heteroaryl, benzyl, and a 4 to 6 membered saturated ring containing one oxygen atom wherein any of such C_1-C_6alkyl, C_3-C_7cycloalkyl, C(=O) C_1-C_6alkyl, C(=O) C_3-C_7cycloalkyl, aryl, heteroaryl, benzyl is optionally substituted with one or more substituents selected from the group consisting of halogen, CF_3, OH, CN, OCH_3,$OC(=O)CH_3$) and C_1-C_3alkyl substituted with at least one CN;

R^{25} is selected from the group consisting of hydrogen and C_1-C_3 alkyl;

aryl represents phenyl or naphthalenyl;

heteroaryl represents a monocyclic 5 to 6 membered aromatic heterocycle containing one or more heteroatoms each independently selected from the group consisting of O, S and N; or a bicyclic 8 to 12 membered aromatic heterocycle containing one or more heteroatoms each independently selected from the group consisting of O, S and N;

provided that Het does not satisfy a formula d(x)



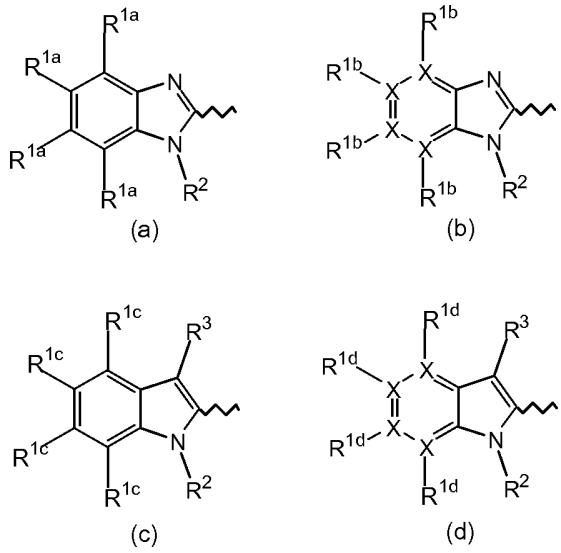
d(x)

or a pharmaceutically acceptable addition salt or a solvate thereof.

2. The compound of formula (RI) as claimed in claim 1, or any stereoisomeric form

thereof, wherein

Het is a heterocycle of either of the following formula (a), (b), (c), (d):



each X independently is C or N; provided that at least two X is C;

each of R^{1a}, R^{1b}, R^{1c} or R^{1d} is independently selected from the group consisting of H, halogen, C_1-C_6alkyl, C_1-C_6alkyloxy, CF_3 and OCF_3;

R^{1b} or R^{1d} is absent when the X to which it is bound is N;

each R^2 is $-(CR^8R^9)_m-R^{10}$;

m is an integer from 2 to 6;

each R^3 is H, halogen or C_1-C_6alkyl;

each R^8 and R^9 are independently selected from the group consisting of H and C_1-C_{10}alkyl;

each R^{10} is independently selected from the group consisting of H, halogen, OH, CN, CF_2H, CF_3, C_1-C_6 alkyl, C_3-C_7cycloalkyl, $C(=O)NR^8R^9$, $C(=O)OR^8$, and SO_2R^8;

each Z independently is C or N, provided that at least two Z is C;

Q and V each independently represent $CR^{20}R^{21}$;

p and s independently represent an integer from 0 to 3, wherein the sum of p and s minimally should be 2, and when p = 0 or s = 0 then the carbon atom marked with * is directly bound to W;

R^{20} and R^{21} are hydrogen;

R^{22} is selected from the group consisting of hydrogen, hydroxyl, C_1-C_6alkyl, CF_3, OCH_3, OCF_3 and halogen;

W is selected from the group consisting of SO_2, C, O and N, wherein such C or N is optionally substituted with one or more R^{23};

R^{23} is selected from the group consisting of hydrogen, hydroxyl, C_1-C_6alkyl, C_3-C_7cycloalkyl, C_1-C_6alkyl-R^{24}, SO_2R^{24}, $SO_2N(R^{24})_2$, aryl, heteroaryl, $C(=O)OR^{24}$, OR^{24}, $C(=O)R^{24}$, $C(=O)N(R^{24})_2$, $OC(=O)N(R^{24})_2$, $P(=O)$-$(O$-C_1-C_6-alkyl$)_2$, $N(R^{24})_2$, $NR^{25}C(=O)OR^{24}$, $NR^{25}C(=O)N(R^{24})_2$ $NR^{25}SO_2R^{24}$ and a 4 to 6 membered saturated ring containing one oxygen atom, wherein any of such C_1-C_6alkyl, C_3-C_7cycloalkyl, aryl or heteroaryl is optionally substituted with one or more of the substituents selected from the group consisting of halogen, OH, CN, OCH_3;

R^{24} is selected from the group of hydrogen, OH, halogen, C_1-C_6alkyl, C_3-C_7cycloalkyl, C(=O) C_1-C_6alkyl, C(=O) C_3-C_7cycloalkyl, aryl, heteroaryl, benzyl, and a 4 to 6 membered saturated ring containing one oxygen atom wherein any of such C_1-C_6alkyl, C_3-C_7cycloalkyl, C(=O) C_1-C_6alkyl, C(=O) C_3-C_7cycloalkyl, aryl, heteroaryl, benzyl is optionally substituted with one or more substituents selected from the group consisting of halogen, CF_3, OH, CN, OCH_3,$OC(=O)CH_3$) and C_1-C_3alkyl substituted with at least one CN;

R^{25} is selected from the group consisting of hydrogen and C_1-C_3 alkyl;

aryl represents phenyl or naphthalenyl;

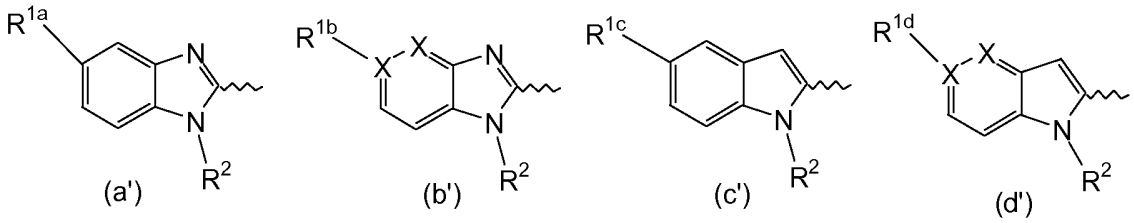
heteroaryl is furanyl, thiophenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinoxalinyl, or benzimidazolyl;

or a pharmaceutically acceptable addition salt or a solvate thereof.

3. The compound according to claim 2, wherein R^{23} is selected from the group consisting of hydrogen, hydroxyl, C_1-C_6alkyl, C_3-C_7cycloalkyl, C_1-C_6alkyl-R^{24}, SO_2R^{24}, $SO_2N(R^{24})_2$, aryl, heteroaryl, $C(=O)OR^{24}$, OR^{24}, $C(=O)R^{24}$, $C(=O)N(R^{24})_2$, $OC(=O)N(R^{24})_2$ and a 4 to 6 membered saturated ring containing one oxygen atom, wherein any of such C_1-C_6alkyl, C_3-C_7cycloalkyl, aryl or heteroaryl is optionally substituted with one or more of the substituents selected from the group consisting of halogen, OH, CN, OCH_3;

R^{24} is selected from the group of hydrogen, OH, halogen, C_1-C_6alkyl, C_3-C_7cycloalkyl, C(=O) C_1-C_6alkyl, C(=O) C_3-C_7cycloalkyl, aryl, heteroaryl, benzyl, and a 4 to 6 membered saturated ring containing one oxygen atom wherein any of such C_1-C_6alkyl, C_3-C_7cycloalkyl, C(=O) C_1-C_6alkyl, C(=O) C_3-C_7cycloalkyl, aryl, heteroaryl, benzyl is optionally substituted with one or more substituents selected from the group consisting of halogen, CF_3, OH, CN, OCH_3,and $OC(=O)CH_3$).

4. The compound according to formula (RI) as claimed in claim 1, wherein Het is represented by formula (a'), (b'), (c') or (d'):



wherein at least one X is N;
and R^{1a}, R^{1b} R^{1c}, R^{1d} and R^2 are defined as in claim 1.

5. The compound according to any one of the previous claims, wherein for Formula (b') and (d') one X is N.

6. A compound according to any one of the previous claims, wherein each of R^{1a}, R^{1b} R^{1c} or R^{1d} is independently selected from the group consisting of H and halogen.

7. A compound according to any one of the previous claims, wherein each of R^{1a},R^{1b} R^{1c} or R^{1d} is independently selected from the group consisting of chloro, bromo and fluoro.

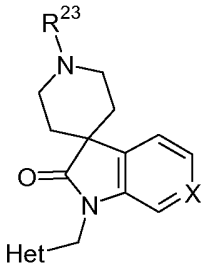
8. A compound according to claim 4, wherein each of R^{1a},R^{1b} R^{1c} or R^{1d} is chloro.

9. A compound according to any one of the previous claims wherein R^2 is $-(CR^8R^9)_m-R^{10}$ and wherein m is an integer from 1 to 4 and each R^8 and R^9 are independently chosen H or C_1-C_6alkyl.

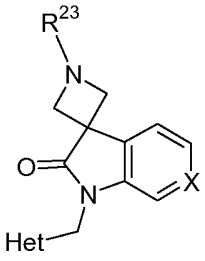
10. A compound according to any one of the previous claims wherein R^2 is C_1-C_6 alkyl-R^{10}.

11. A compound according to any one of the previous claims wherein R^{10} is selected from the group consisting of C_1-C_3 alkyl, H, OH, CN, F, CF_2H, CF_3, SO_2-C_1-C_3alkyl and SO_2C_3-C_6cycloalkyl.

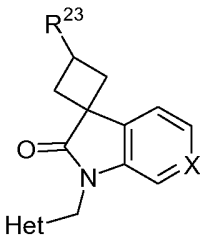
12. A compound according to any one of the previous claims, wherein the compound has Formula RII, $_{RIII}$, RIV, RV, RVI or RVII;



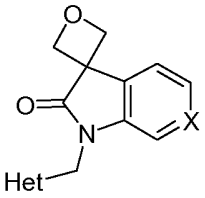
Formula RII



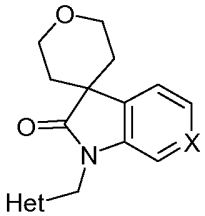
Formula RIII



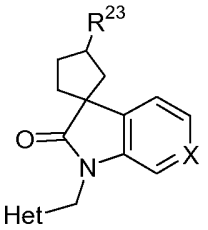
Formula RIV



Formula RV



Formula RVI

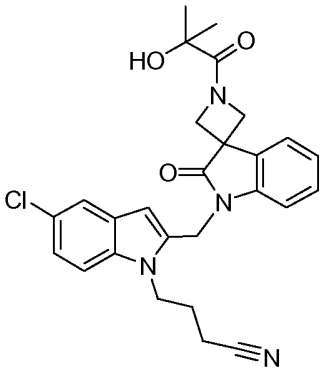


Formula RVII

or any stereoisomeric form thereof, wherein Het, X and R^{23} are defined as in any one of the previous claims.

13. The compound as claimed in claim 12 wherein R^{23} is selected from the group consisting of hydrogen, hydroxyl, C_1-C_6alkyl, C_1-C_3alkyl-R^{24}, SO_2R^{24}, O-R^{24}, phenyl, pyridinyl pyrimidyl, pyrazolyl, C(=O)OR^{24}, C(=O)R^{24}, wherein any of such C_1-C_6alkyl, phenyl, pyridinyl, pyrimidyl, pyrazolyl is optionally substituted with one or more of the following substituents; OCH_3, halogen, OH or CN.

14. The compound as claimed in claim 1 wherein the compound is



or a pharmaceutically acceptable addition salt or a solvate thereof.

15. A compound as defined in any one of claims 1 to 14 for use as a medicine.

16. A pharmaceutical composition comprising a pharmaceutically acceptable carrier, and as active ingredient a therapeutically effective amount of a compound as defined in any one of claims 1 to 14.

17. A compound as claimed in any of claims 1 to 14, or a pharmaceutical composition as claimed in claim 15 for use in the treatment of a respiratory syncytial virus infection.

18. A method for treating viral RSV infections in a subject in need thereof, comprising administering to said subject an effective amount of a compound as defined in any one of claims 1 to 14.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/071525

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D403/06 C07D403/14 C07D471/04 C07D471/10 C07D471/20
C07D487/10 C07D491/107 C07D491/20 C07D495/20 C07D519/00
A61P31/00 A61K31/435 A61K31/4184 A61K31/498 A61K31/501

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.
A	WO 2012/080449 A1 (JANSSEN R & D IRELAND [IE]; COOYMANS LUDWIG PAUL [BE]; DEMIN SAMUEL DO) 21 June 2012 (2012-06-21) cited in the application page 1, column 1; claims 1,13-18; tables 1-3	1-18

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[X] Further documents are listed in the continuation of Box C.

[X] 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
26 November 2013	13/12/2013

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	Guspanová, Jana

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/071525

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	COMBRINK ET AL: "Respiratory syncytial virus fusion inhibitors. Part 6: An examination of the effect of structural variation of the benzimidazol-2-one heterocycle moiety", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB, vol. 17, no. 17, 4 August 2007 (2007-08-04), pages 4784-4790, XP022184908, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2007.06.065 page 4784, column 1, paragraph 1 - page 4785, column 1, paragraph 1; table 1 -----	1-18

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2013/071525

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2012080449 A1	21-06-2012	AR 084336 A1	08-05-2013
		AU 2011343258 A1	18-04-2013
		CA 2822001 A1	21-06-2012
		CN 103347881 A	09-10-2013
		EP 2651933 A1	23-10-2013
		US 2013261151 A1	03-10-2013
		WO 2012080449 A1	21-06-2012