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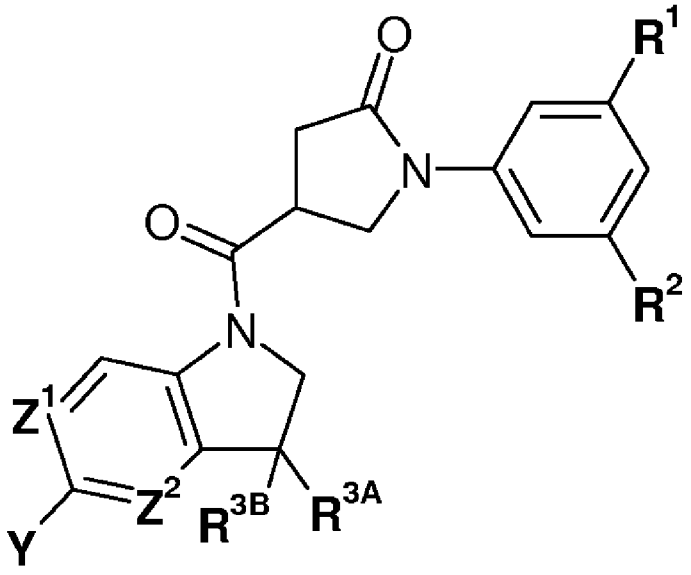
[Continued on next page]

(54) Title: INHIBITORS OF CYTOMEGALOVIRUS

(57) Abstract: Compounds of Formula (I) wherein R^1, R^2, R^{3A}, R^{3B}, Y, Z^1 and Z^2 are defined herein, are useful for the treatment of cytomegalovirus disease and/or infection.



(I)

WO 2014/070976 A1

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INHIBITORS OF CYTOMEGALOVIRUS

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on October 15, 2013, is named 13-0180_SL.txt and is 728 bytes in size.

FIELD OF THE INVENTION

The present invention relates to γ-lactam analogs and their use as inhibitors of cytomegalovirus (CMV) DNA polymerase, pharmaceutical compositions containing such analogs, and methods of using these analogs in the treatment and prevention of CMV disease and/or infection.

BACKGROUND OF THE INVENTION

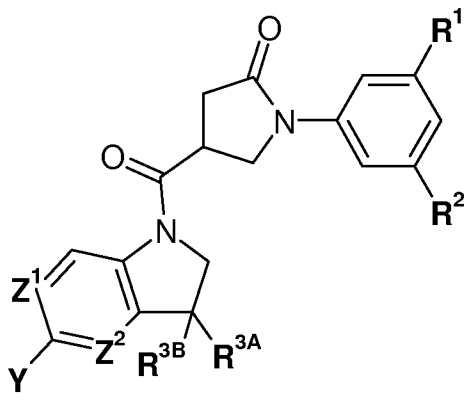
CMV, a β-herpes virus, is a frequent and ubiquitous virus that affects all populations, worldwide, including adults and children with normal or compromised immune systems. The current therapies approved for the treatment of CMV include Valganciclovir, Ganciclovir, Cidofovir and Foscarnet. Each of these therapies inhibit CMV DNA polymerase, a protein encoded by the UL54 gene, which is an enzyme essential for viral replication (*PNAS* **2003**, 100(24), 14223-14228 and WO 2005/012545).

SUMMARY OF THE INVENTION

The present invention provides a novel series of compounds having inhibitory activity against CMV DNA polymerase.

Further objects of this invention arise for the one skilled in the art from the following description and the examples.

An embodiment of the invention provides a compound of Formula (I) or a racemate, enantiomer, diastereomer or tautomer thereof:



(I)

wherein

R^1 and R^2 are each independently selected from the group consisting of H, halo and -CN;

R^{3A} and R^{3B} are each independently selected from the group consisting of H, (C_{1-6})alkyl and (C_{3-7})cycloalkyl, wherein each said alkyl and cycloalkyl are optionally mono-, di-, or tri-substituted with R^{32};

or R^{3A} and R^{3B}, together with the C to which they are attached, are linked to form a (C_{3-7})heterocyclyl or (C_{3-7})cycloalkyl; wherein each said heterocyclyl and cycloalkyl are optionally mono-, di-, or tri-substituted with R^{32};

R^{32} is each independently selected from the group consisting of halo, -CN, OH, -O-(C_{1-6})alkyl, -C(=O)-(C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})haloalkyl and (C_{1-6})alkyl optionally mono- or di-substituted with OH, CN, -O-(C_{1-6})alkyl, $-NH_2$, -NH(C_{1-6})alkyl or -N$((C_{1-6})\text{alkyl})_2$;

Z^1 is C(R^4) or N;

R^4 is H, halo, -CN, (C_{1-6})alkyl, OH, -O-(C_{1-6})alkyl or (C_{1-6})haloalkyl;

Y is -(C_{1-6})alkyl-R^5, -(C_{1-6})alkyl-O-R^5, -(C_{1-6})alkyl-N(R^{51})-(C_{1-6})alkyl-R^5 or -(C_{1-6})alkyl-N(R^{51})-R^5;

R^{51} is H or (C_{1-6})alkyl;

R^5 is aryl, heterocyclyl or heteroaryl; wherein each said aryl, heterocyclyl and heteroaryl are optionally mono-, di-, or tri-substituted with R^{52};

R^{52} is each independently selected from the group consisting of (C_{1-6})alkyl, (C_{2-6})alkenyl, -CN, -OH, -O(C_{1-6})alkyl, halo, -C(=O)OH, -O-(C_{1-6})alkyl, (C_{3-7})cycloalkyl, -O-(C_{3-7})cycloalkyl, (C_{1-6})haloalkyl, $-NH_2$, -NH(C_{1-6})alkyl, -N$((C_{1-6})\text{alkyl})_2$, -$(C_{1-6})$alkyl-C(=O)OH, -$(C_{2-6})$alkenyl-

C(=O)OH, -C(=O)-O-(C_{1-6})alkyl and -C(=O)-NH_2;

Z^2 is C(R^6) or N;

R^6 is H, halo, -CN, (C_{1-6})alkyl, OH, -O-(C_{1-6})alkyl or (C_{1-6})haloalkyl;

or a salt thereof.

Another embodiment of this invention provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as a medicament.

Also within the scope of this invention is the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prevention of CMV disease and/or infection in a human being.

Included within the scope of this invention is a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

According to a further aspect of this embodiment the pharmaceutical composition according to this invention further comprises a therapeutically effective amount of at least one other antiviral agent.

The invention also provides the use of a pharmaceutical composition as described hereinabove for the treatment of a CMV infection in a human being having or at risk of having the infection.

The invention also provides the use of a pharmaceutical composition as described hereinabove for the treatment of CMV disease in a human being having or at risk of having the disease.

Another aspect of the invention involves a method of treating or preventing CMV disease and/or infection in a human being by administering to the human being an anti-CMV virally effective amount of a compound of the invention, a pharmaceutically acceptable salt thereof, or a composition as described above, alone or in combination with at least one other antiviral agent, administered together or separately.

An additional aspect of this invention refers to an article of manufacture comprising a composition effective to treat CMV disease and/or infection; and packaging material comprising a label which indicates that the composition can be used to treat disease and/or infection by CMV; wherein the composition comprises a compound of formula (I) according to this invention

or a pharmaceutically acceptable salt thereof.

Still another aspect of this invention relates to a method of inhibiting the replication of CMV comprising exposing the virus to an effective amount of the compound of Formula (I), or a salt thereof, under conditions where replication of CMV is inhibited.

Further included in the scope of the invention is the use of a compound of Formula (I), or a salt thereof, to inhibit the replication of CMV.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

DEFINITIONS

Terms not specifically defined herein should be given the meanings that would be given to them by one of skill in the art in light of the disclosure and the context. As used in the specification, however, unless specified to the contrary, the following terms have the meaning indicated and the following conventions are adhered to. In the groups, radicals, or moieties defined below, the number of carbon atoms is often specified preceding the group, for example, C_{1-6}-alkyl means an alkyl group or radical having 1 to 6 carbon atoms. In general, for groups comprising two or more subgroups, the first named subgroup is the radical attachment point, for example, the substituent "-C_{1-3}-alkyl-aryl" means an aryl group which is bound to a C_{1-3}-alkyl-group, with the C_{1-3}-alkyl group bound to the core. Unless specifically stated otherwise, for groups comprising two or more subgroups, the substituent may be attached to either subgroup.

In case a compound of the present invention is depicted in the form of a chemical name and as a formula in case of any discrepancy the formula shall prevail. An asterisk or the designation, ---- , may be used in sub-formulas to indicate the bond which is connected to the core molecule as defined.

Unless specifically indicated, throughout the specification and the appended claims, a given chemical formula or name shall encompass tautomers and all stereo, optical and geometrical isomers (e.g. enantiomers, diastereomers, E/Z isomers, atropisomers) and racemates thereof as well as mixtures in different proportions of the separate enantiomers, mixtures of diastereomers, or mixtures of any of the foregoing forms where such isomers and enantiomers exist, as well as salts, including pharmaceutically acceptable salts thereof and solvates thereof such as for instance hydrates including solvates of the free compounds or solvates of a salt of the compound.

One skilled in the art would know how to separate, enrich, or selectively prepare the enantiomers of the compounds of the present invention. Preparation of pure stereoisomers, e.g. enantiomers and diastereomers, or mixtures of desired enantiomeric excess (ee) or enantiomeric purity, are accomplished by one or more of the many methods of (a) separation or resolution of enantiomers, or (b) enantioselective synthesis known to those of skill in the art, or a combination thereof. These resolution methods generally rely on chiral recognition and include but not limited to chromatography using chiral stationary phases, enantioselective host-guest complexation, resolution or synthesis using chiral auxiliaries, enantioselective synthesis, enzymatic and nonenzymatic kinetic resolution, or spontaneous enantioselective crystallization. Such methods are disclosed generally in Chiral Separation Techniques: A Practical Approach (2nd Ed.), G. Subramanian (ed.), Wiley-VCH, 2000; T.E. Beesley and R.P.W. Scott, Chiral Chromatography, John Wiley & Sons, 1999; and Satinder Ahuja, Chiral Separations by Chromatography, Am. Chem. Soc., 2000. Furthermore, there are equally well-known methods for the quantitation of enantiomeric excess or purity, including but not limited to GC, HPLC, CE, or NMR, and assignment of absolute configuration and conformation, including but not limited to CD, ORD, X-ray crystallography, or NMR.

The term “halo” generally denotes fluorine, chlorine, bromine and iodine.

The term “C_{1-n}-alkyl”, wherein n is an integer from 2 to n, either alone or in combination with another radical denotes an acyclic, saturated, branched or linear hydrocarbon radical with 1 to n C atoms. For example the term C_{1-3}-alkyl embraces the radicals H_3C-, H_3C-CH_2-, H_3C-CH_2-CH_2- and H_3C-$CH(CH_3)$-.

The term “C_{2-n}-alkenyl”, is used for a group as defined in the definition for "C_{1-n}-alkyl" with at least two carbon atoms, if at least two of those carbon atoms of said group are bonded to each other by a double bond.

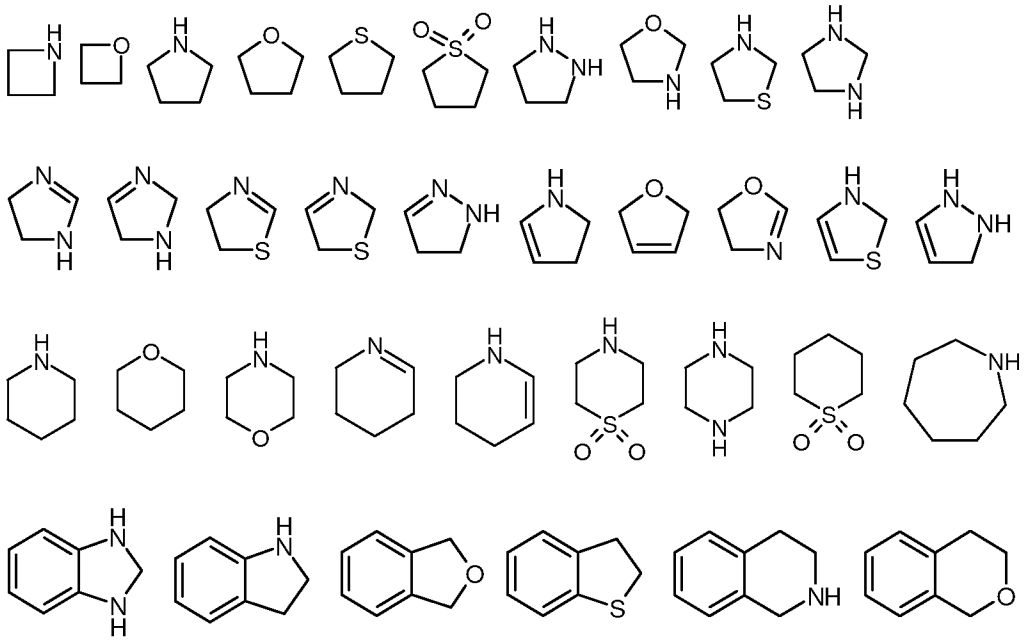
The term “carbocyclyl” or "carbocycle" as used herein, either alone or in combination with another radical, means a mono-, bi- or tricyclic ring structure consisting of 3 to 14 carbon atoms. The term “carbocyclyl” or "carbocycle" refers to fully saturated and aromatic ring systems and partially saturated ring systems. The term “carbocyclyl” or "carbocycle" encompasses fused, bridged and spirocyclic systems.

The term “C_{3-n}-cycloalkyl”, wherein n is an integer 4 to n, either alone or in combination with another radical, denotes a cyclic, saturated, unbranched hydrocarbon radical with 3 to n C

atoms. For example the term C_{3-7}-cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

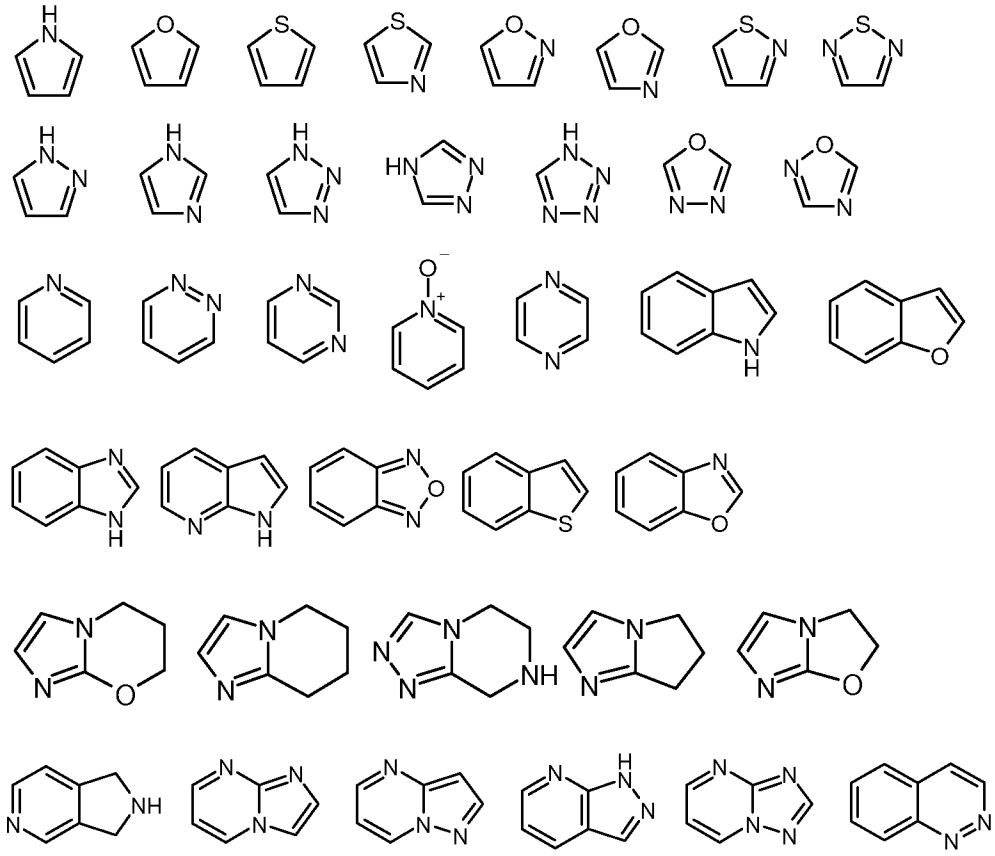
The term “aryl” as used herein, either alone or in combination with another radical, denotes a carbocyclic aromatic monocyclic group containing 6 carbon atoms which may be further fused to at least one other 5- or 6-membered carbocyclic group which may be aromatic, saturated or unsaturated. Aryl includes, but is not limited to, phenyl, indanyl, indenyl, naphthyl, anthracenyl, phenanthrenyl, tetrahydronaphthyl and dihydronaphthyl.

The term "heterocyclyl" or “heterocycle” means a saturated or unsaturated mono- or polycyclic-ring system including aromatic ring systems containing one or more heteroatoms selected from N, O or $S(O)_r$,wherein r=0, 1 or 2, consisting of 3 to 14 ring atoms wherein none of the heteroatoms is part of the aromatic ring. The term "heterocyclyl" or “heterocycle” is intended to include all the possible isomeric forms and all spiro, bridged and fused systems. Thus, the term "heterocyclyl" or “heterocyclyl” includes the following exemplary structures which are not depicted as radicals as each form may be attached through a covalent bond to any atom so long as appropriate valences are maintained:



The term "heteroaryl" means a mono- or polycyclic-ring system containing one or more heteroatoms selected from N, O or $S(O)_r$, wherein r=0, 1 or 2, consisting of 5 to 14 ring atoms wherein at least one of the heteroatoms is part of an aromatic ring. The term “heteroaryl” is intended to include all the possible isomeric forms and all spiro, bridged and fused systems.

Thus, the term “heteroaryl” includes the following exemplary structures which are not depicted as radicals as each form may be attached through a covalent bond to any atom so long as appropriate valences are maintained:



Many of the terms given above may be used repeatedly in the definition of a formula or group and in each case have one of the meanings given above, independently of one another.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, and commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. For example, such salts include acetates, ascorbates,

benzenesulfonates, benzoates, besylates, bicarbonates, bitartrates, bromides/hydrobromides, Ca-edetates/edetates, camsylates, carbonates, chlorides/hydrochlorides, citrates, edisylates, ethane disulfonates, estolates esylates, fumarates, gluceptates, gluconates, glutamates, glycolates, glycollylarsnilates, hexylresorcinates, hydrabamines, hydroxymaleates, hydroxynaphthoates, iodides, isothionates, lactates, lactobionates, malates, maleates, mandelates, methanesulfonates, mesylates, methylbromides, methylnitrates, methylsulfates, mucates, napsylates, nitrates, oxalates, pamoates, pantothenates, phenylacetates, phosphates/diphosphates, polygalacturonates, propionates, salicylates, stearates subacetates, succinates, sulfamides, sulfates, tannates, tartrates, teoclates, toluenesulfonates, triethiodides, ammonium, benzathines, chloroprocaines, cholines, diethanolamines, ethylenediamines, meglumines and procaines. Further pharmaceutically acceptable salts can be formed with cations from metals like aluminium, calcium, lithium, magnesium, potassium, sodium, zinc and the like. (also see Pharmaceutical salts, Birge, S.M. et al., J. Pharm. Sci., (1977), 66, 1-19).

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a sufficient amount of the appropriate base or acid in water or in an organic diluent like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile, or a mixture thereof.

Salts of other acids than those mentioned above which for example are useful for purifying or isolating the compounds of the present invention also comprise a part of the invention.

As used herein, the term “treatment” means the administration of a compound or composition according to the present invention to alleviate or eliminate symptoms of CMV disease and/or to reduce viral load in a patient.

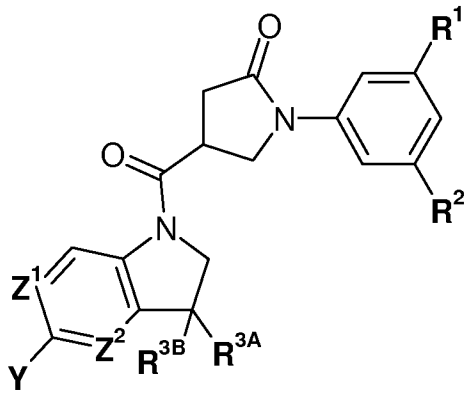
As used herein, the term “prevention” means the administration of a compound or composition according to the present invention post-exposure of the individual to the virus but before the appearance of symptoms of the disease, and/or prior to the detection of the virus in the blood, to prevent the appearance of symptoms of the disease.

The term “therapeutically effective amount” means an amount of a compound according to the invention, which when administered to a patient in need thereof, is sufficient to effect treatment for disease-states, conditions, or disorders for which the compounds have utility. Such an amount would be sufficient to elicit the biological or medical response of a tissue system, or

patient that is sought by a researcher or clinician. The amount of a compound according to the invention which constitutes a therapeutically effective amount will vary depending on such factors as the compound and its biological activity, the composition used for administration, the time of administration, the route of administration, the rate of excretion of the compound, the duration of the treatment, the type of disease-state or disorder being treated and its severity, drugs used in combination with or coincidentally with the compounds of the invention, and the age, body weight, general health, sex and diet of the patient. Such a therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to their own knowledge, the state of the art, and this disclosure.

Further embodiments

In the following preferred embodiments, groups and substituents of the compounds of Formula (I) according to this invention are described in detail.



(I)

Any and each of the definitions below may be combined with each other.

R^1/R^2:

R^1/R^2-A: R^1 and R^2 are each independently selected from the group consisting of H, halo and -CN.

R^1/R^2-B: One of R^1 and R^2 is halo or –CN and the other of R^1 and R^2 is H.

R^1/R^2-C: One of R^1 and R^2 is Cl or –CN and the other of R^1 and R^2 is H.

R^{3A} and R^{3B}:

R^{3A} and R^{3B}-A: R^{3A} and R^{3B} are each independently selected from the group consisting of H, (C_{1-6})alkyl and (C_{3-7})cycloalkyl, wherein each said alkyl and cycloalkyl are optionally mono-, di-,

or tri-substituted with $\mathbf{R^{32}}$;

or $\mathbf{R^{3A}}$ and $\mathbf{R^{3B}}$, together with the C to which they are attached, are linked to form a (C_{3-7})heterocyclyl or (C_{3-7})cycloalkyl; wherein each said heterocyclyl and cycloalkyl are optionally mono-, di-, or tri-substituted with $\mathbf{R^{32}}$;

$\mathbf{R^{32}}$ is each independently selected from the group consisting of halo, -CN, OH, -O-(C_{1-6})alkyl, -C(=O)-(C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})haloalkyl and (C_{1-6})alkyl optionally mono- or di-substituted with OH, CN, -O-(C_{1-6})alkyl, $-NH_2$, -NH(C_{1-6})alkyl or -N$((C_{1-6})\text{alkyl})_2$.

$\mathbf{R^{3A}}$ and $\mathbf{R^{3B}}$-B: $\mathbf{R^{3A}}$ and $\mathbf{R^{3B}}$ are each independently selected from the group consisting of H or (C_{1-6})alkyl, optionally mono- or di-substituted with OH or –O-(C_{1-6})alkyl;

or $\mathbf{R^{3A}}$ and $\mathbf{R^{3B}}$, together with the C to which they are attached, are linked to form a (C_{3-7})cycloalkyl; optionally mono- or di-substituted with halo, -CN, OH, -O-(C_{1-6})alkyl, -C(=O)-(C_{1-6})alkyl, (C_{1-6})haloalkyl and (C_{1-6})alkyl.

$\mathbf{R^{3A}}$ and $\mathbf{R^{3B}}$-C: $\mathbf{R^{3A}}$ and $\mathbf{R^{3B}}$ are each independently selected from the group consisting of H and (C_{1-6})alkyl.

$\mathbf{Z^1}$:

$\mathbf{Z^1}$-A: $\mathbf{Z^1}$ is C($\mathbf{R^4}$) or N;

$\mathbf{R^4}$ is H, halo, -CN, (C_{1-6})alkyl, OH, -O-(C_{1-6})alkyl or (C_{1-6})haloalkyl.

$\mathbf{Z^1}$-B: $\mathbf{Z^1}$ is C($\mathbf{R^4}$);

$\mathbf{R^4}$ is H, halo, -CN, (C_{1-6})alkyl, OH, -O-(C_{1-6})alkyl or (C_{1-6})haloalkyl.

$\mathbf{Z^1}$-C: $\mathbf{Z^1}$ is CH.

Y:

Y-A: Y is -(C_{1-6})alkyl-$\mathbf{R^5}$, -(C_{1-6})alkyl-O-$\mathbf{R^5}$, -(C_{1-6})alkyl-N($\mathbf{R^{51}}$)-(C_{1-6})alkyl-$\mathbf{R^5}$ or -(C_{1-6})alkyl-N($\mathbf{R^{51}}$)-$\mathbf{R^5}$ and $\mathbf{R^{51}}$ is H or (C_{1-6})alkyl.

Y-B: Y is -(C_{1-6})alkyl-$\mathbf{R^5}$ or -(C_{1-6})alkyl-N($\mathbf{R^{51}}$)-$\mathbf{R^5}$ and $\mathbf{R^{51}}$ is H or (C_{1-6})alkyl.

Y-C: Y is (C_{1-6})alkyl-$\mathbf{R^5}$.

$\mathbf{R^5}$:

R^5-A: R^5 is aryl, heterocyclyl or heteroaryl; wherein each said aryl, heterocyclyl and heteroaryl are optionally mono-, di-, or tri-substituted with R^{52};

R^{52} is each independently selected from the group consisting of (C_{1-6})alkyl, (C_{2-6})alkenyl, -CN, -OH, -O(C_{1-6})alkyl, halo, -C(=O)OH, -O-(C_{1-6})alkyl, (C_{3-7})cycloalkyl, -O-(C_{3-7})cycloalkyl, (C_{1-6})haloalkyl, $-NH_2$, -NH(C_{1-6})alkyl, -N$((C_{1-6})\text{alkyl})_2$, -$(C_{1-6})$alkyl-C(=O)OH, -$(C_{2-6})$alkenyl-C(=O)OH, -C(=O)-O-(C_{1-6})alkyl and $-C(=O)-NH_2$.

R^5-B: R^5 is a heterocyclyl or heteroaryl, wherein each said heterocyclyl and heteroaryl are optionally mono-, di-, or tri-substituted with R^{52};

R^{52} is each independently selected from the group consisting of (C_{1-6})alkyl, -CN, -OH, -O(C_{1-6})alkyl, halo, -C(=O)OH, -O-(C_{1-6})alkyl, (C_{1-6})haloalkyl, $-NH_2$, -NH(C_{1-6})alkyl, -N$((C_{1-6})\text{alkyl})_2$, -$(C_{1-6})$alkyl-C(=O)OH, (C_{2-6})alkenyl and -(C_{2-6})alkenyl-C(=O)OH.

R^5-C: R^5 is a 5- or 6-membered heteroaryl, optionally mono-, di-, or tri-substituted with R^{52};

R^{52} is each independently selected from the group consisting of (C_{1-6})alkyl, -CN, -OH, -O(C_{1-6})alkyl, halo, -C(=O)OH, -O-(C_{1-6})alkyl, (C_{1-6})haloalkyl, $-NH_2$, -NH(C_{1-6})alkyl and -N$((C_{1-6})\text{alkyl})_2$.

Z^2:

Z^2-A: Z^2 is C(R^6) or N;

R^6 is H, halo, -CN, (C_{1-6})alkyl, OH, -O-(C_{1-6})alkyl or (C_{1-6})haloalkyl.

Z^2-B: Z^2 is C(R^6);

R^6 is H, halo, -CN, (C_{1-6})alkyl, OH, -O-(C_{1-6})alkyl or (C_{1-6})haloalkyl.

Z^2-C: Z^2 is CH.

Further subgeneric embodiments of the present invention are set forth in the following table, wherein each substituent group of each embodiment is defined according to the definitions set forth above:

Embodiment	R^1/R^2	R^{3A}/R^{3B}	Z^1	Y	R^5	Z^2
E-1	R^1/R^2-C	R^{3A}/R^{3B}-C	Z^1-C	Y-C	R^5-C	Z^2-C
E-2	R^1/R^2-B	R^{3A}/R^{3B}-C	Z^1-C	Y-B	R^5-B	Z^2-C
E-3	R^1/R^2-A	R^{3A}/R^{3B}-B	Z^1-C	Y-C	R^5-C	Z^2-C
E-4	R^1/R^2-A	R^{3A}/R^{3B}-C	Z^1-C	Y-B	R^5-B	Z^2-C
E-5	R^1/R^2-A	R^{3A}/R^{3B}-B	Z^1-B	Y-B	R^5-B	Z^2-B

Examples of most preferred compounds according to this invention are each single compound of the invention namely, compounds 11a1, 11aa1, 11aaa1, 11bb1, 11bbb1, 11bbb2, 11c1, 11cc1, 11ccc1, 11dd1, 11ddd1, 11e1, 11ee1, 11eee1, 11f1, 11ff1, 11fff1, 11g1, 11gg1, 11ggg1, 11h1, 11hh1, 11hhh1, 11i1, 11iii1, 11jjj1, 11m1, 11n1, 11oo1, 11pp1, 11q1, 11qq1, 11r1, 11rr1, 11s1, 11ss1, 11t1, 11tt1, 11u1, 11uu1, 11v1, 11vv1, 11w1, 11ww1, 11x1, 11xx1, 11y1, 11yy1, 11z1, 11zz1, 13a1, 13b1, 13c1, 13d1, 13e1, 13f1, 13g1, 13k1, 13l1, 13n1, 13o1, 13p1, 13q1, 13r1, 13s1, 13t1, 13u1, 13v1, 13w1, 13w2, 13x1, 13y1, 16a3, 16b3, 16c3, 16d3, 17b1, 17f1, 17g1, 17l1, 17m1, 17n1, 17o1, 19a2, 19b2, 19c2, 22a1, 22a2, 22aa1, 22b1, 22bb1, 22c1, 22d1, 22dd1, 22e1, 22f1, 22g1, 22h1, 22i1, 22j1, 22k1, 22l1.1, 22l1.2, 22m1, 22n1, 22o1, 22p1, 22q1, 22r1, 22s1, 22t1, 22u1, 22v1, 22w1, 22x1, 22y1, 22z1, 24a1, 24d1, 24e1, 24f1, 31a1 and 8l1.

PHARMACEUTICAL COMPOSITION

Suitable preparations for administering the compounds of the invention will be apparent to those with ordinary skill in the art and include for example tablets, pills, capsules, suppositories, lozenges, troches, solutions, syrups, elixirs, sachets, injectables, inhalatives and powders. The content of the pharmaceutically active compound(s) should be in the range from 0.05 to 90 wt.-%, preferably 0.1 to 50 wt.-% of the composition as a whole.

Suitable tablets may be obtained, for example, by mixing one or more compounds according to the invention with known excipients, for example inert diluents, carriers, disintegrants, adjuvants, surfactants, binders and/or lubricants. The tablets may also consist of several layers.

Suitable injectables may be obtained, for example, by mixing one or more compounds according to the invention with known excipients, for example inert diluents, carriers, co-solvent,

adjuvants, surfactants and/or cyclodextrin complex. The injectable formulation may be an emulsion or suspension.

COMBINATION THERAPY

Combination therapy is contemplated wherein a compound of the invention, or a pharmaceutically acceptable salt thereof, is co-administered with at least one additional agent selected from: a CMV entry inhibitor, a CMV early transcription event inhibitor, a CMV helicase-primase inhibitor, an other CMV DNA polymerase inhibitor, an inhibitor of UL97 kinase, a CMV protease inhibitor, a CMV terminase inhibitor, a CMV maturation inhibitor, an inhibitor of another target in the CMV life cycle, a CMV vaccine and a CMV biological agent.

These additional agents may be combined with the compounds of this invention to create a single pharmaceutical dosage form. Alternatively these additional agents may be separately administered to the patient as part of a multiple dosage form, for example, using a kit. Such additional agents may be administered to the patient prior to, concurrently with, or following the administration of a compound of the invention, or a pharmaceutically acceptable salt thereof.

The dose range of the compounds of the invention applicable per day is usually from 0.01 to 100 mg/kg of body weight, preferably from 0.1 to 50 mg/kg of body weight. Each dosage unit may conveniently contain from 5% to 95% active compound (w/w). Preferably such preparations contain from 20% to 80% active compound.

The actual pharmaceutically effective amount or therapeutic dosage will of course depend on factors known by those skilled in the art such as age and weight of the patient, route of administration and severity of disease. In any case the combination will be administered at dosages and in a manner which allows a pharmaceutically effective amount to be delivered based upon patient's unique condition.

When the composition of this invention comprises a combination of a compound of the invention and one or more additional therapeutic or prophylactic agent, both the compound and the additional agent should be present at dosage levels of between about 10 to 100%, and more preferably between about 10 and 80% of the dosage normally administered in a monotherapy regimen.

Antiviral agents contemplated for use in such combination therapy include agents (compounds or biologicals) that are effective to inhibit the production and/or replication of a virus in a human

being, including but not limited to agents that interfere with either host or viral mechanisms necessary for the production and/or replication of a virus in a human being. Such agents can be selected from: a CMV entry inhibitor; a CMV early transcription event inhibitor; a CMV helicase-primase inhibitor; a CMV DNA polymerase inhibitor such as Ganciclovir (Cytovene), Valganciclovir (Valcyte; Cymeval), Cidofovir (Vistide), Foscarnet (Foscavir), CMX001, cyclopropavir (MBX-400) and Valaciclovir (Valtrex; Zelitrex); an inhibitor of UL97 kinase such as Maribavir; a CMV protease inhibitor; a CMV terminase inhibitor such as AIC246 (Letermovir); a CMV maturation inhibitor; other inhibitors such as Artesunate; a CMV vaccine such as TransVax and a CMV biological agent such as Cytogam (Cytotect), TCN-202 and CMV IgG.

EXAMPLES

Other features and advantages of the present invention will become apparent from the following more detailed Examples which illustrate, by way of example, the principles of the invention. As is well known to a person skilled in the art, reactions are performed in an inert atmosphere (including but not limited to nitrogen or argon) where necessary to protect reaction components from air or moisture. Temperatures are given in degrees Celsius (°C). Solution percentages and ratios express a volume to volume relationship, unless stated otherwise. Flash chromatography is performed on Teledyne Isco CombiFlash® Rf system or Teledyne Torrent using RediSep® Normal-phase Silica Flash Columns or RediSep Rf Gold® Normal-Phase Silica Columns or SiliaSep™ Universal Closed-Top Flash Cartridges or InnoFlash™ Silica Flash Column.

All of the compounds of the invention are synthesized analogously to the specific Examples described below. Retention times (t_R) for each compound are measured using the standard analytical HPLC or UPLC conditions described below. As is well known to one skilled in the art, retention time values are sensitive to the specific measurement conditions. Therefore, even if identical conditions of solvent, flow rate, linear gradient, and the like are used, the retention time values may vary when measured, for example, on different HPLC or UPLC instruments. Even when measured on the same instrument, the values may vary when measured, for example, using different individual HPLC or UPLC columns, or, when measured on the same instrument and the same individual column, the values may vary, for example, between individual measurements taken on different occasions. A person skilled in the art will recognize that obvious modifications to the synthetic methods, including the amount of time indicated to perform the various steps, may be required to generate each of the specific compounds listed in the Examples section.

Preparative RP-HPLC is performed under standard conditions using one of the following specific measuring conditions:

Compounds are purified by preparative RP-HPLC under standard conditions using a Waters SunFire Prep OBD™ C18 column (5µm, 19 x 50 mm) eluting with a linear MeOH : water gradient containing 10 mM Ammonium Formate (pH 3.8) over 10 minutes at 30 mL/min. Fractions containing the desired product are pooled and lyophilized.

Compounds are purified by preparative RP-HPLC under standard conditions using a Waters XBridge Prep OBD™ C18 (5µm, 19 x 50 mm) eluting with a linear MeOH : water gradient containing 10 mM Ammonium Bicarbonate (pH 10) over 10 minutes at 30 mL/min. Fractions containing the desired product are pooled and lyophilized.

Compounds are purified by preparative RP-HPLC under standard conditions using a Waters SunFire Prep OBD™ C18 column (5µm, 19 x 50 mm) eluting with a linear acetonitrile : water gradient containing 0.06 % TFA (v/v) 10 minutes at 30 mL/min. Fractions containing the desired product are pooled and lyophilized.

Analytical UPLC is performed under standard conditions using one of the following specific measuring conditions:

Analytical UPLC is carried out under standard conditions using a Waters ACQUITY UPLC® HSS T3 column (1.8µm, 2.1 x 50 mm) eluting with a segmented linear MeCN gradient containing 0.06%TFA (v/v) over 2.6 min at 0.9 mL/min.

Analytical UPLC is also carried out under standard conditions using a Waters ACQUITY UPLC® BEH C18 column (1.8µm, 2.1 x 30 mm) eluting with a linear MeOH gradient containing 10 mM Ammonium Bicarbonate (pH 10) over 2.2 min at 0.75 mL/min or a Waters ACQUITY UPLC® HSS C18 column (1.8µm, 2.1 x 30 mm) eluting with a linear MeOH gradient containing 10 mM Ammonium Formate (pH 3.8) over 2.3 min at 0.8 mL/min.

Mass spectral analyses are recorded using electrospray mass spectrometry.

Enantiomers can be separated by preparative SFC-MS under standard conditions using one condition combination of the following matrix of conditions:

1. SFC (multiple stacked injections): SFC-MS: Waters Prep 100, Column: *type see table 1*: 21.2 x 250 mm at 40ºC, Eluent A: CO_2, Eluent B: *see table 1*, Gradient: Isocratic *X:Y* CO_2:*eluant B* at 50 mL / min, Back Pressure Regulator: 150 Bars, Run Time: 10 min.
2. SFC (multiple stacked injections): SFC-MS: Waters Prep 15, Column: *type see table 1*:10 x 250 mm at 40ºC, Eluent A: CO_2, Eluent B: *see table 1*, Gradient: Isocratic *X:Y* CO_2:*eluant B* at 10 mL / min, Back Pressure Regulator: 150 Bars, Run Time: 10 min.

Table 1: Matrix of SFC conditions (Column type and Eluant B)

Column / Eluant B	ChiralPak IA	ChiralPak IB	ChiralPak IC	ChiralPak IS	Lux Cellulose-2	Lux Cellulose-3	Lux Cellulose-4	Lux Amylose-2
MeOH	•	•	•	•	•	•	•	•
EtOH	•	•	•	•	•	•	•	•
iPrOH	•	•	•	•	•	•	•	•
MeOH + 2mM AmBic	•	•	•	•	•	•	•	•
MeOH + 10 mM AmFor	•	•	•	•	•	•	•	•
EtOH + 2mM AmBic	•	•	•	•	•	•	•	•

Analytical SFC-MS is performed under standard conditions using one condition combination of the following matrix of conditions:

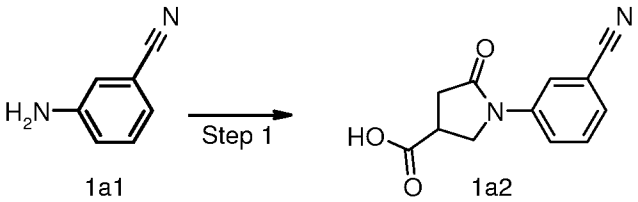
1. SFC (multiple stacked injections): SFC-MS: Waters Prep 15, Column: *type see table 1*: 10 x 250 mm at 40ºC, Eluent A: CO_2, Eluent B: *see table 1*, Gradient: Isocratic *X:Y* CO_2:*eluant B* at 10 mL / min, Back Pressure Regulator: 150 Bars, Run Time: 10 min.

Abbreviations or symbols used herein include:
Ac: acetyl; AcOH: acetic acid; ACCN: 1,1'-azobis(cyclohexanecarbonitrile);AmBic: Ammonium bicarbonate; AmFor: Ammonium formate; BEH: ethylene bridged hybrid; Bn: benzyl (phenylmethyl); BOC or Boc: *tert*-butyloxycarbonyl; Bu: butyl; BBN: 9-borabicyclo[3.3.1]nonane;

DCM: dichloromethane; DIPEA: *N,N*-diisopropylethylamine; DMAP: 4-dimethylaminopyridine; DME: dimethoxyethane; DMF: *N,N*-dimethylformamide; EC_{50}: 50% effective concentration; EDCI:1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; Et: ethyl; Et_3N: triethylamine; Et_2O: diethyl ether; EtOAc: ethyl acetate; EtOH: ethanol; Hex: hexanes; HATU: N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate; HPLC: high performance liquid chromatography; HSS: high strength silica; ^{i}Pr or i-Pr: 1-methylethyl (*iso*-propyl); LC-MS: liquid chromatography-mass spectrometry; m/z: mass-to-charge ratio; $[M+H]^+$: protonated molecular ion; Me: methyl; MeCN: acetonitrile; MeOH: methanol; MS: mass spectrometry; NMP: N-methyl-2-pyrrolidone; OBD: optimum bed density; Ph: phenyl; Pr: propyl; Prep LCMS: preparative liquid chromatography-mass spectrometry; SFC: Supercritical fluid chromatography; SFC-MS: Supercritical fluid chromatography-mass spectrometry; RP-HPLC: reversed-phase high pressure liquid chromatography; RT: room temperature (approximately 18°C to 25°C); *tert*-butyl or t-butyl: 1,1-dimethylethyl; TFA: trifluoroacetic acid; THF: tetrahydrofuran; t_R: retention time; UPLC: ultra performance liquid chromatography.

Example 1

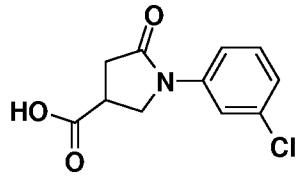
Preparation of intermediate 1a2



Step 1:

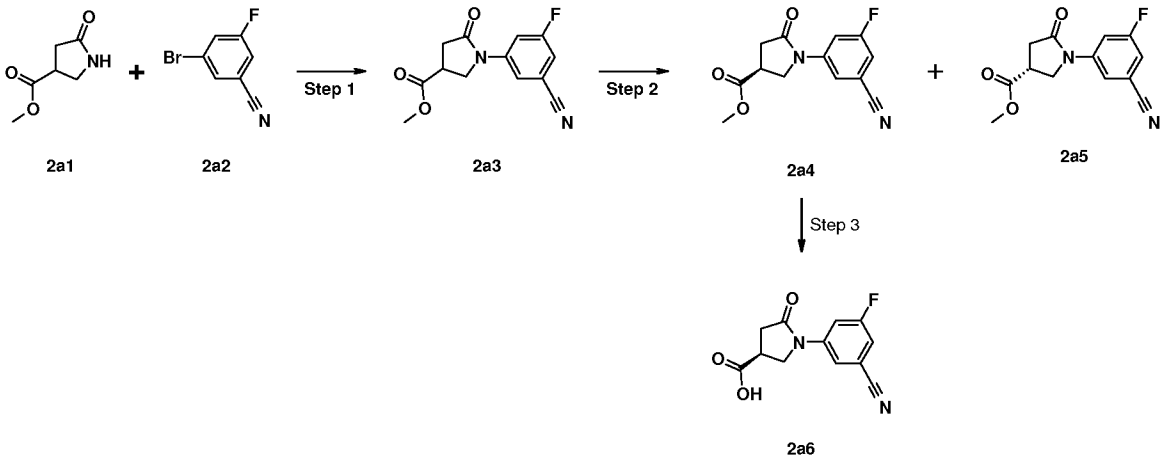
A mixture of the 3-aminobenzonitrile **1a1** (Aldrich) (43.7 g, 0.37 mol) and itaconic acid (Aldrich) (47.6 g, 0.37 mol) is heated at 160 °C for 1 h. The residue is cooled to RT then water is added. The resulting precipitate is dissolved in NaOH 1N. The residue is filtered then the filtrate is acidified with concentrated HCl. The residue is filtered and washed with water. The solids are dried under vacuum, pre-adsorbed on silica gel and purified on Rf Combi-Flash (eluting 0-35% $MeCN/CH_2Cl_2$) to afford **1a2** (t_R = 0.9 min, $(M+H)^+$ 231.1).

The following intermediates are prepared analogously to the procedure described in **Example 1** starting from the appropriate aniline.

1b2	

Example 2

Preparation of intermediate 2a2



Step 1:

2a1 (Synchem-inc, 1.72 g, 12 mmol), **2a2** (Matrix, 2 g, 10 mmol), cesium carbonate (4.9 g, 15 mmol), tris(dibenzylideneacetone)dipalladium(0) (229 mg, 0.25 mmol) and 4,5-bis-diphenylphosphanyl-9,9-dimethyl-9H-xanthene (289 mg, 0.5 mmol) are placed in 1,4-dioxane (20 mL). The mixture is degassed with argon for 20 min and heated at 100ºC for 16 h. The reaction mixture is cooled to RT, EtOAc is added and the organic layer is washed with water and brine. The organic layer is dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product is purified by flash chromatography (10%-80% EtOAc:hexanes) to afford **2a3** (t_R = 1.3 min, $(M+H)^+$ 263.1).

Step 2:

2a3 (1.8 g, 6.7 mmol) is dissolved in a (1:1) mixture of MeOH and DCM (16 mL). The enantiomers are separated by SFC (multiple stacked injections): SFC-MS: Waters Prep 100, Column: IA 21 x 250 mm at 40ºC, Eluent A: CO_2, Eluent B: MeOH, Gradient: Isocratic 90:10 CO_2:MeOH at 50 mL / min, Back Pressure Regulator: 120 Bars, Run Time: 12 min.
Desired fractions are collected and concentrated *in vacuo* affording **2a4** (*S*-enantiomer) and **2a5**

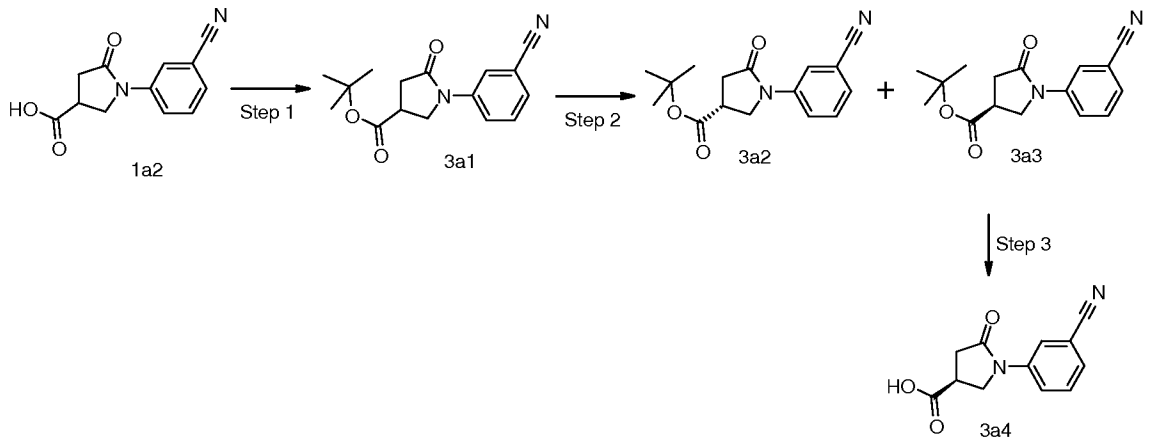
(*R*-enantiomer).

Step 3:

The compound **2a4** (0.52 g; 2 mmol) is dissolved in a 1:1 mixture of MeOH and THF (10 mL) and treated with an aqueous solution of LiOH (840 mg in 3 mL of water, 2 mmol). The mixture is stirred at RT for 10 min, poured into a mixture of EtOAc and saturated aqueous $NaHCO_3$ solution. The layers are separated and the aqueous layer is acidified with 6N HCl and extracted with EtOAc (3X). The organic layer is dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford **2a6** (t_R = 1.05 min, $(M+H)^+$ 249).

Example 3

Preparation of intermediate 3a4



Step 1:

To a mixture of the carboxylic acid **1a2** (5 g, 22 mmol), *tert*-butanol (5.7 mL, 59.5 mmol), triethylamine (6 mL, 43 mmol) and DMAP (250 mg, 2.1 mmol) in DCM (50 mL) at 0 °C is added 2,4,6-trichlorobenzoyl chloride (7 mL, 44.8 mmol). The ice bath is removed and the reaction mixture is stirred overnight at RT. The reaction mixture is poured into a mixture of water and EtOAc. The organic layer is separated and is washed with water and a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by Combi-Flash Rf (eluting 30-70% EtOAc/Hexanes) gives **3a1** (t_R = 1.3 min, $(M+H)^+$ 287.0).

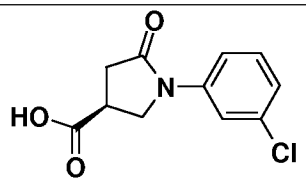
Step 2:

3a1 (4.8 g, 17 mmol) is dissolved in 96 mL of MeOH and the enantiomers are separated by SFC

(multiple stacked injections): SFC-MS: Waters/Thar Prep 15, Column: IA 10 x 250 mm at 40ºC, Eluent A: CO_2, Eluent B: MeOH, Gradient: Isocratic 80:20 CO_2:MeOH at 10 mL / min, Back Pressure Regulator: 150 Bars, Run Time: 7 min.
Desired fractions are collected and concentrated *in vacuo* to afford **3a2** (*R*-enantiomer) (t_R = 1.31 min, $(M+H)^+$ 287.1) and **3a3** (*S*-enantiomer) (t_R = 1.31 min, $(M+H)^+$ 287.1).

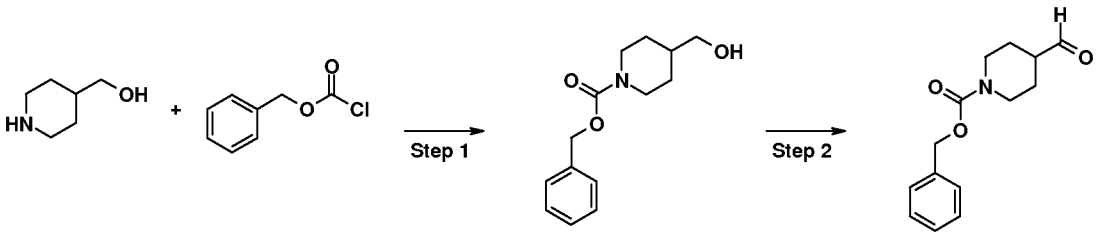
Step 3:
(*S*)-1-(3-cyano-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid tert-butyl ester **3a3** (1.37 g; 4.8 mmol) is dissolved in DCM (25 mL) and treated with trifluoroacetic acid (25 mL, 0.32 mol). The mixture is stirred at RT for 1 h. Toluene (10 mL) is added and the solvent is evaporated. The residue is dried under high vacuum to afford **3a4** (t_R = 0.59 min, $(M+H)^+$ 231.1).

The following intermediates are prepared analogously to the procedure described in **Example 3** starting from the appropriate acid derivative.

3b4	

Example 4

Preparation of intermediate 4a4



4a1 4a2 4a3 4a4

Step 1:
Piperidin-4-yl-methanol **4a1** (Lancaster, 5 g, 43 mmol) is dissolved in DCM (250 mL) and cooled to 0°C. The solution is treated with triethylamine (12 mL; 87 mmol) and dropwise addition of benzyl chloroformate **4a2** (12 mL; 87 mmol). The mixture is stirred overnight at RT. The mixture is diluted with DCM, washed with saturated aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$, filtered and concentrated. Purification by Combiflash (80 g column, 50-100% EtOAc/Hex) gives **4a3**.

Step 2:

Oxalyl chloride (9.4 g; 74 mmol) is dissolved in DCM (55 mL) and cooled to -78°C. DMSO (7.5 mL; 106 mmol) is added dropwise and the mixture is stirred for 15 min at -78°C. In a separate flask, **4a3** (13 g; 53 mmol) is dissolved in DCM (55 mL) and added dropwise to the first flask via cannula. Once the addition is finished, the mixture is stirred at -55°C for 15 min. The reaction mixture is cooled to -78°C and a solution of triethylamine (22 mL; 158 mmol) in DCM (28 mL) is added dropwise to the reation mixture via cannula. The mixture is stirred for 1 h at -78°C then 15 min at 0°C and 30 min at RT. The reaction is neutralized with 11 mL of AcOH and diluted with 100 mL of DCM and 100 mL of water. The layers are separated and the aqueous layer is extracted with DCM (2 x 100 mL). The combined organic layers are washed with brine, dried over $MgSO_4$, filtered and concentrated. Purification by Combiflash (120 g column, 0-50% EtOAc/Hex) gives **4a4**.

Example 5

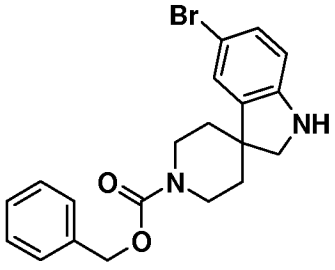
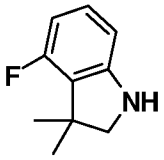
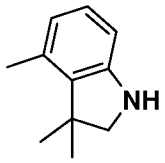
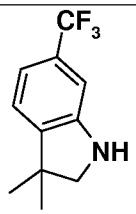
Preparation of intermediate 5a2

5a1 5a2

Step 1:

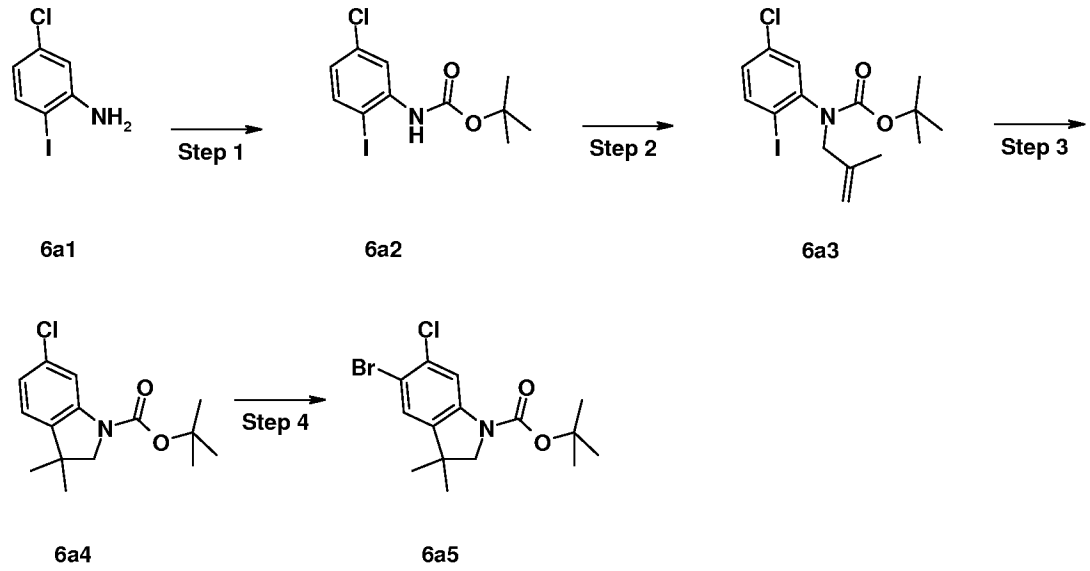
Hydrazine **5a1** (Matrix, 15 g, 67 mmol) is mixed with 2-methyl-propionaldehyde (Aldrich, 5.1g, 70 mmol) and dissolved in DCM (105 mL). TFA (38 g, 340 mmol) is added to the reaction mixture and is refluxed for 1 h. Sodium borohydride (7.6 g, 201 mmol) is added to the mixture and after 10 min, the mixture is placed in an ice bath. Excess ammonium hydroxide (28% in water, 47 g, 1.3 mol) is added portionwise, followed by water (150 mL). The layers are separated and the organic layer is dried with sodium sulfate, filtered and concentrated under reduced pressure.The residue is purified by Combiflash RF (120 g column, 0-20% EtOAc:Hexanes) to give **5a2** (t_R = 1.52 min, $(M+H)^+$ 226; 228).

The following intermediates are prepared analogously to the procedure described in **Example 5** starting from the appropriate hydrazine and aldehyde derivatives.

5b2	
5c2	
5d2	 *(Mixture of 4- and 6-methyl)
5e2	

Example 6

Preparation of intermediate 6a5



Step 1:

5-chloro-2-iodo-phenylamine **6a1** (Combi-Blocks,15 g, 59 mmol) is dissolved in tetrahydrofuran (610 mL, 7.5 mol) and treated with boc anhydride (54 g; 250 mmol) and DMAP (720 mg, 5.9 mmol). The mixture is refluxed overnight. The reaction mixture is cooled to RT and diluted with EtOAc, washed with 1N HCl, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated.

The crude bis-Boc product is taken into MeOH (609 mL, 15 mol), treated with potassium carbonate (25 g; 178 mmol) and refluxed for 2 h. The reaction mixture is cooled to RT and concentrated. The crude product is dissolved in EtOAc and water. The layers are separated and the organic layer is washed with water and brine, dried over $MgSO_4$, filtered and concentrated. Purification by Teledyne Torrent (330 g column, 0-10% EtOAc/Hex) affords **6a2** (t_R = 1.94 min, $(M-H)^+$ 351.8; 353.8).

Step 2:

6a2 (2.5 g, 7 mmol) is dissolved in DMF (30 mL) and cooled to 0°C. NaH (60% in mineral oil, 880 mg; 27 mmol) is added. The mixture is stirred for 15 min at 0°C and then 15 min at RT. 3-chloro-2-methyl-propene (Aldrich, 2.2 mL; 23 mmol) is added and the mixture is stirred at RT for 1.5 h. The reaction mixture is neutralized with the addition of water and EtOAc then diluted with EtOAc and water. The layers are separated and the organic layer is washed with water (4X) and brine, dried over $MgSO_4$, filtered and concentrated to afford **6a3** (t_R = 2.12 min).

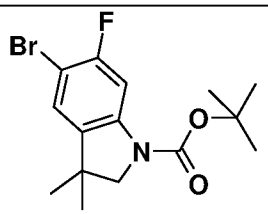
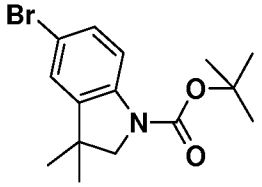
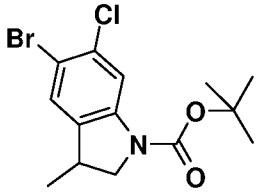
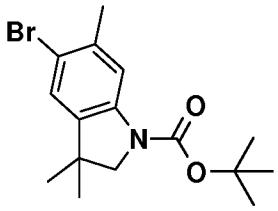
Step 3:

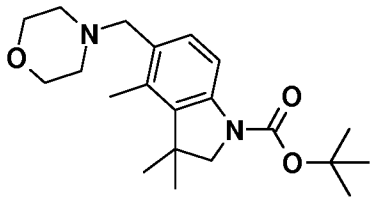
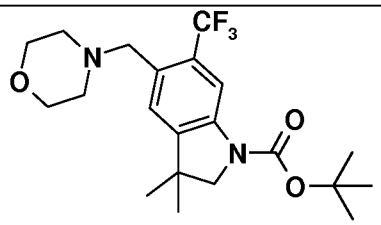
6a3 (2.9 g; 7 mmol) is dissolved in toluene (160 mL). Triphenyltinhydride (3 g; 8.5 mmol) is added followed by ACCN (259 mg; 1.1 mmol) and the mixture is bubbled with nitrogen for 15 min. The mixture is stirred at 80°C for 1 h. Silica is added and the solvent is evaporated. Purification by Combiflash RF (80 g column, 0-100% toluene/Hex) gives **6a4** (t_R = 2.07 min).

Step 4:

6a4 (1 g, 3.7 mmol) is dissolved in acetonitrile (120 mL) and 1-bromo-pyrrolidine-2,5-dione (720 mg; 4.1 mmol) is added. The mixture is stirred at RT for 45 min. The reaction mixture is concentrated to about 20 mL of MeCN, diluted with EtOAc, washed with saturated aqueous $Na_2S_2O_3$, 1N NaOH (3X) and brine, dried over $MgSO_4$, filtered and concentrated to afford **6a5** (t_R = 2.22 min).

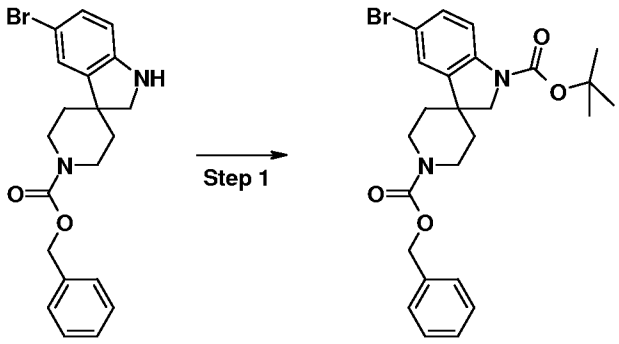
The following intermediates are prepared analogously to the procedure described in **Example 6** starting from the appropriate aniline derivative.

6b5	
6c5	
6d5	
6e5	

6f5	
6g5	

Example 7

Preparation of intermediate 7a1

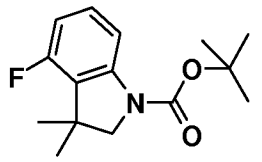
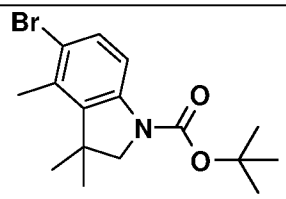
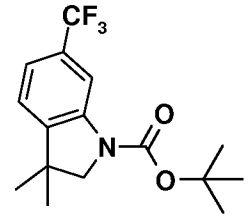
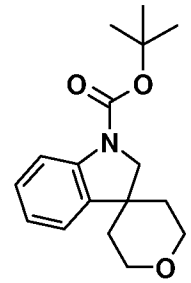


4a4 **7a1**

Step 1:

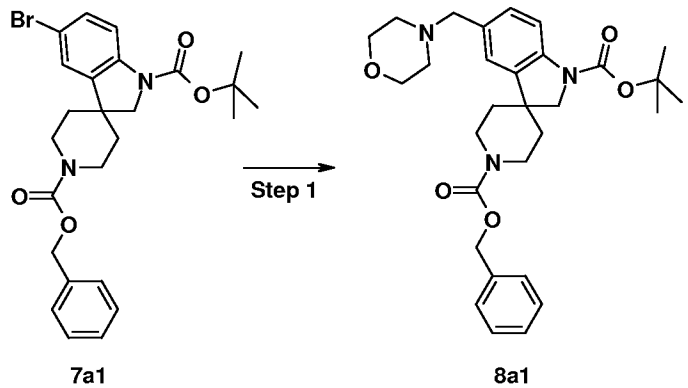
4a4 (1 g, 2.5 mmol) is dissolved in DCM (15 mL) and treated with a solution of boc anhydride (600 mg; 2.7 mmol) in DCM (5 mL) followed by the addition of diisopropylamine (0.9 mL, 5 mmol). The mixture is stirred at RT for 2 days. The reaction mixture is diluted with EtOAc and washed with 1 N HCl. The aqueous layer is extracted with EtOAc (2x). The combined organic layers are washed with water and brine, dried over $MgSO_4$, filtered and concentrated. Purification by Combiflash RF (80 g column, 0-40% toluene/Hex) gives **7a1** (t_R = 2.37 min, $(M+H)^+$ 501.3; 503.3).

The following intermediates are prepared analogously to the procedure described in **Example 7** starting from the appropriate amine derivative.

7b1	
7c1	 (Mixture of regioisomers)
7d1	
7e1	

Example 8

Preparation of intermediate 8a1



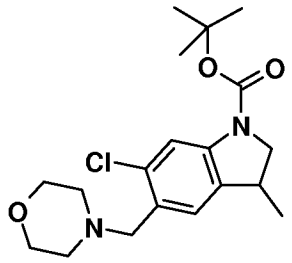
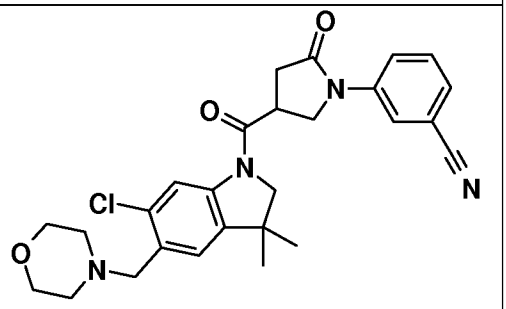
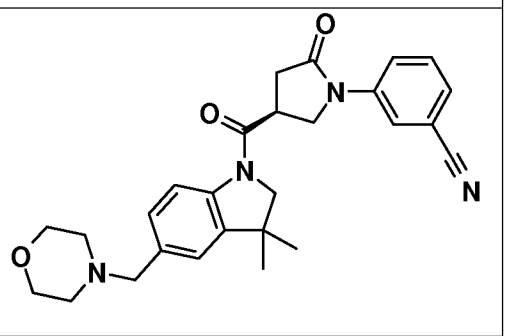
7a1 **8a1**

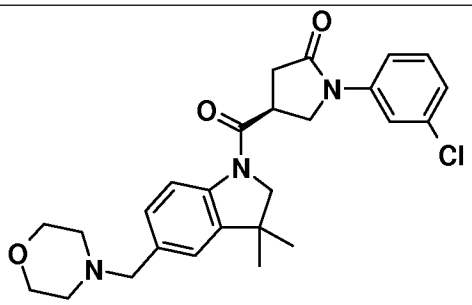
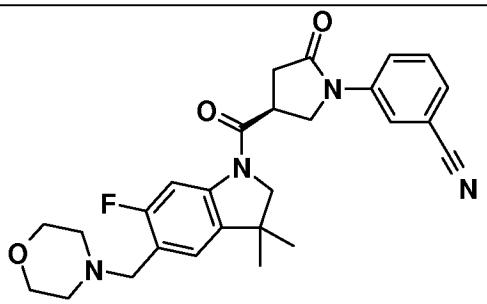
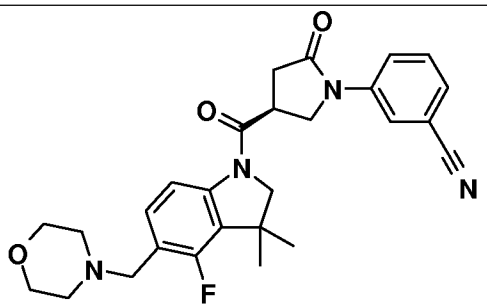
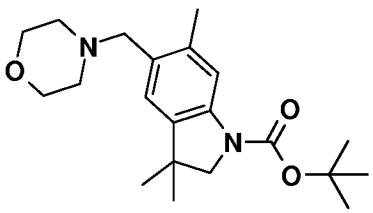
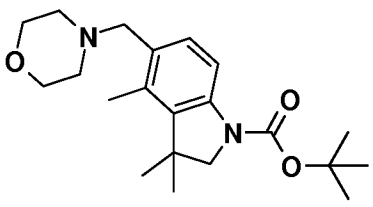
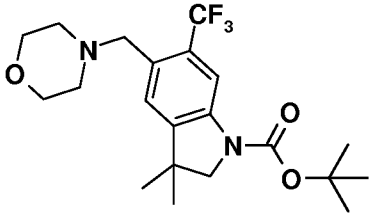
Step 1:

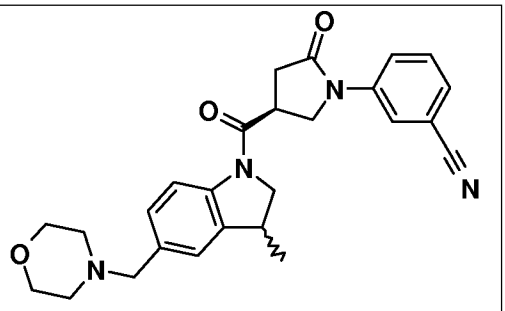
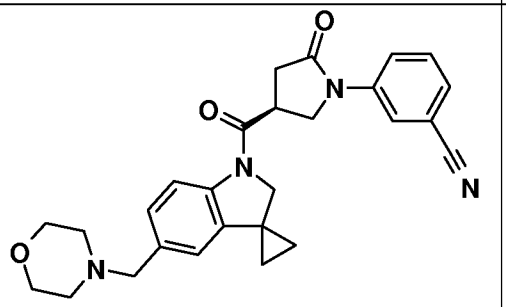
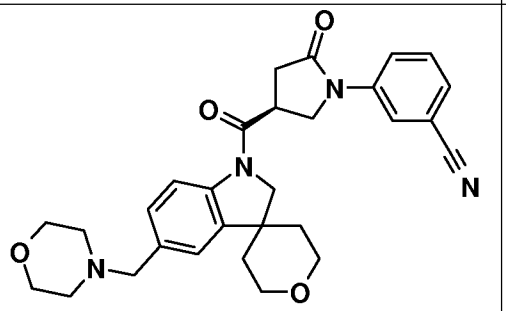
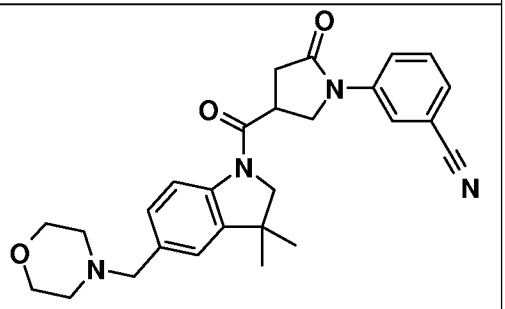
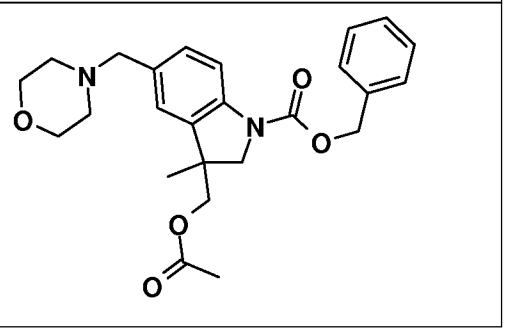
A pressure vessel equipped with a Teflon stir bar is charged with **7a1** (700 mg; 1.4 mmol),

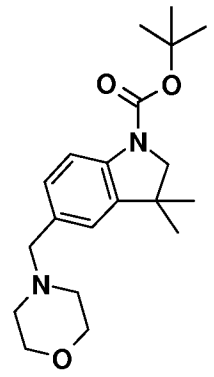
potassium (morpholin-4-yl)methyltrifluoroborate (350 mg, 1.7 mmol), cesium carbonate (1.4 g; 4.2 mmol), palladium (II) acetate (31 mg; 0.14 mmol) and 2-dicyclohexylphosphino-2',4',6'-tri-i-propyl-1,1'-biphenyl (130 mg; 0.28 mmol). Tetrahydrofuran (7 mL) and water (0.7 mL) are added and the solution is degassed by bubbling argon for 5 min. The vessel is sealed and heated at 80°C overnight. The reaction mixture is cooled to RT, filtered over Celite and washed with EtOAc. Water is added and the aqueous layer is extracted with EtOAc (3X). The combined organic layers are washed with brine, dried over $MgSO_4$, filtered and concentrated. Purification by Combiflash RF (25 g column, 70-100% EtOAc/Hex) gives **8a1** (t_R = 1.88 min, $(M+H)^+$ 522.2).

The following intermediates are prepared analogously to the procedure described in **Example 8** starting from the appropriate bromoindoline derivative.

8b1	
8c1	
8d1	

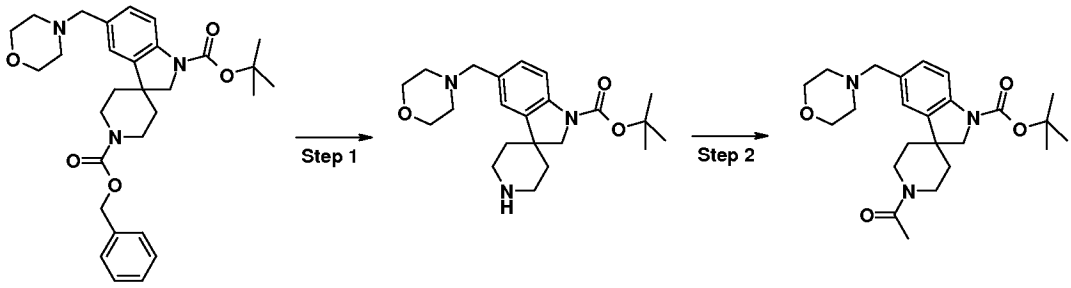
8e1	
8f1	
8g1	
8h1	
8i1	
8j1	

8k1		
8l1		t_R (min) 3.73; $(M+H)^+$ 457
8l2		
8m1		
8n1		

8o1	

Example 9

Preparation of intermediate 9a2



8a1 9a1 9a2

Step 1:

8a1 (600 mg, 1.1 mmol) is dissolved in EtOH (12 mL) and purged under argon. Pd/C (10 % w/w, 182 mg, 0.2 mmol) is added. The mixture is purged under argon and then placed under H_2 (1 atm) for 2 h. The reaction mixture is filtered through a pad of celite and washed with MeOH. The filtrate is concentrated to dryness to afford **9a1** (t_R = 0.95 min, $(M+H)^+$ 388.3).

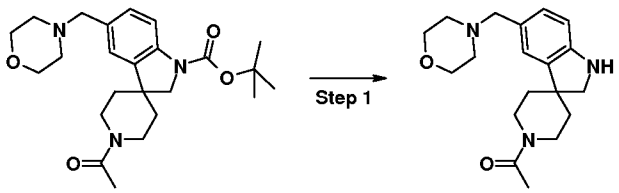
Step 2:

9a1 (430 mg, 1.1 mmol) is dissolved in DCM (44 mL) and treated with acetyl chloride (94 µL, 1.3 mmol) followed by triethylamine (0.31 mL, 2.2 mmol).

The mixture is stirred at RT for 16 h. Water and DCM are added and the layers are separated. The aqueous layer is extracted with DCM (3X). The combined organic layers are washed with water, brine, dried over $MgSO_4$, filtered and concentrated to afford **9a2** (t_R = 1.34 min, $(M+H)^+$ 430.3).

Example 10

Preparation of intermediate 10a1

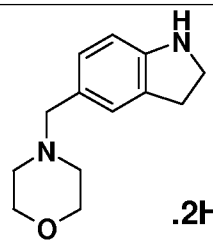
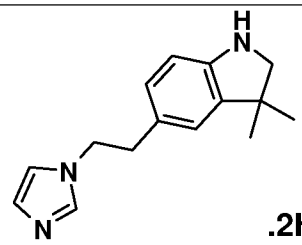
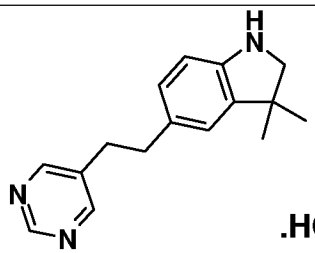
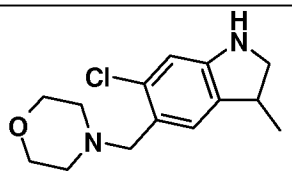


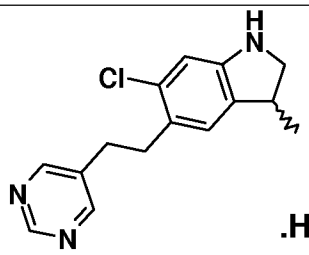
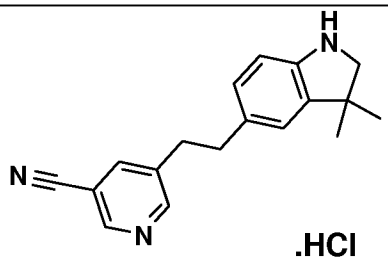
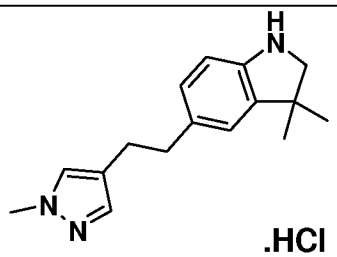
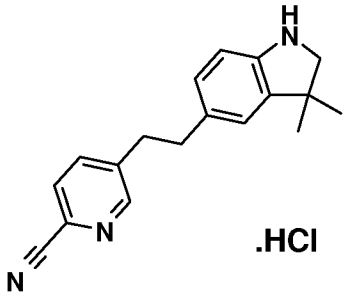
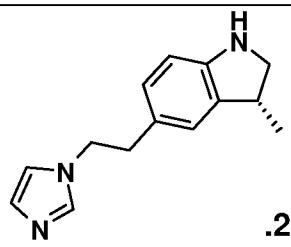
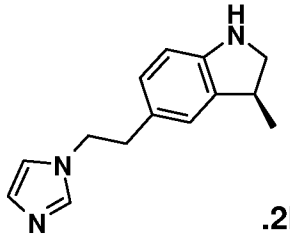
9a2 10a1

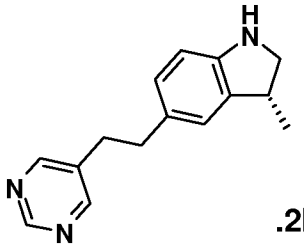
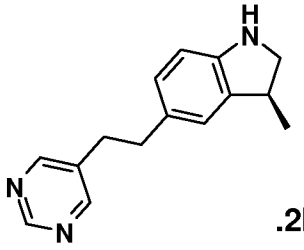
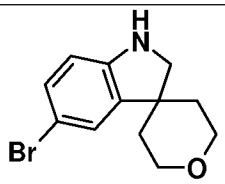
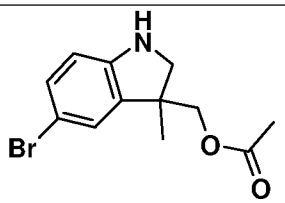
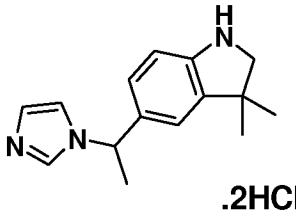
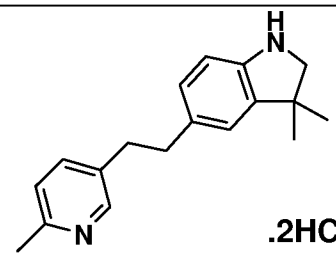
Step 1:

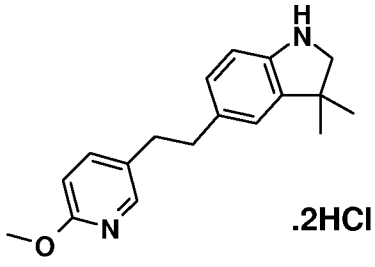
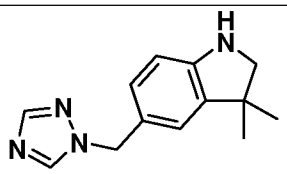
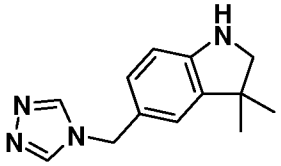
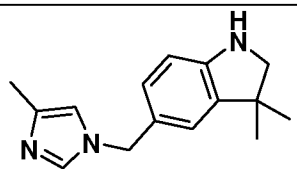
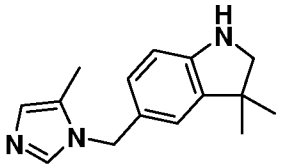
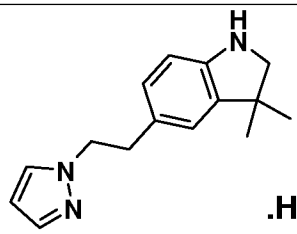
9a2 (50 mg, 0.1 mmol) is treated with a solution of HCl in 1,4-dioxane (4M, 1 mL, 4 mmol) at RT for 2 h. The mixture is concentrated to dryness to afford **10a1** (t_R = 0.95 min, $(M+H)^+$ 388.3).

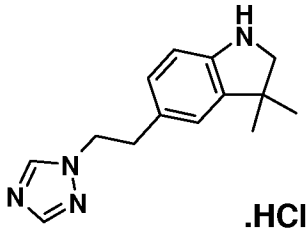
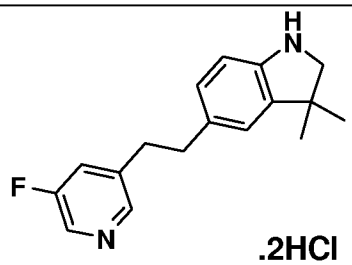
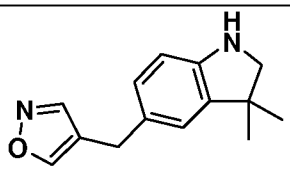
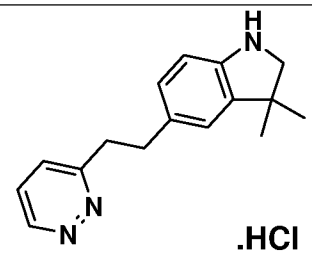
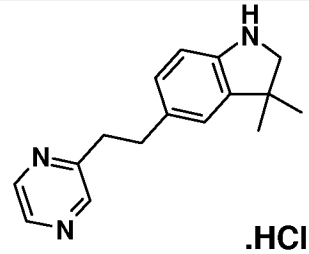
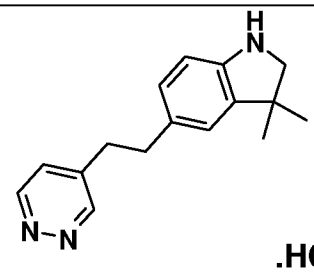
The following intermediates are prepared analogously to the procedure described in **Example 10** starting from the appropriate BOC derivative.

10b1	 .2HCl
10c1	 .2HCl
10d1	 .HCl
10e1	 .2HCl

10f1	 .HCl
10g1	 .HCl
10h1	 .HCl
10i1	 .HCl
10j1	 .2HCl
10k1	 .2HCl

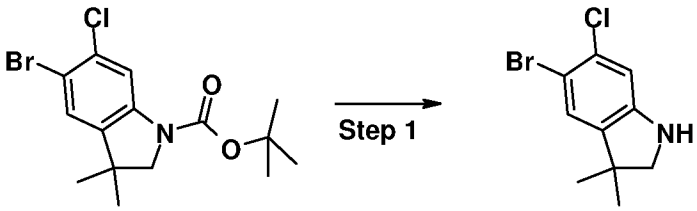
10l1	 .2HCl
10m1	 .2HCl
10n1	 .HCl
10o1	 .HCl
10p1	 .2HCl
10q1	 .2HCl

10r1	 .2HCl
10s1	 .HCl
10t1	 .HCl
10u1	 .2HCl
10v1	 .2HCl
10w1	 .HCl

10x1	 .HCl
10y1	 .2HCl
10z1	 .HCl
10aa1	 .HCl
10bb1	 .HCl
10cc1	 .HCl

Example 10-1

Preparation of intermediate 10-1a1

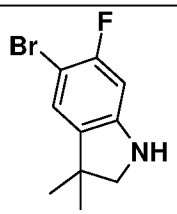
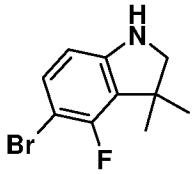
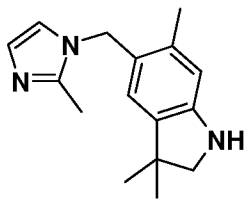


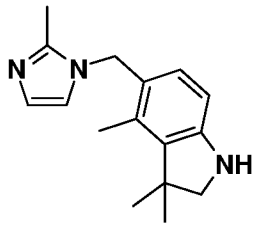
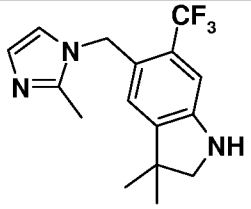
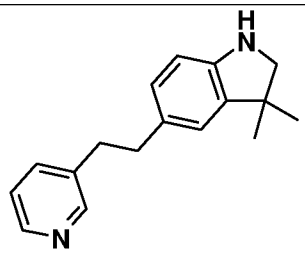
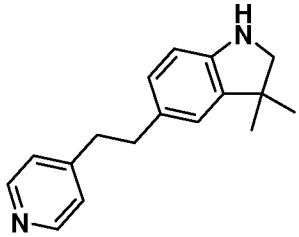
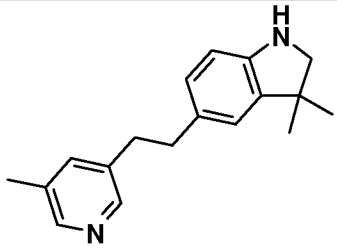
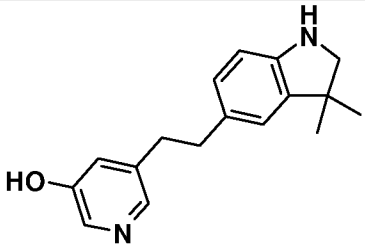
6a5 **10-1a1**

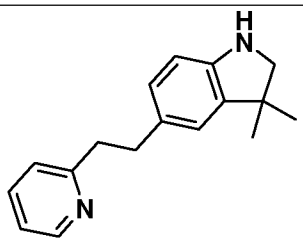
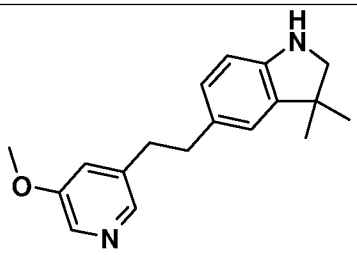
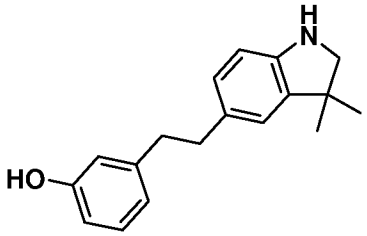
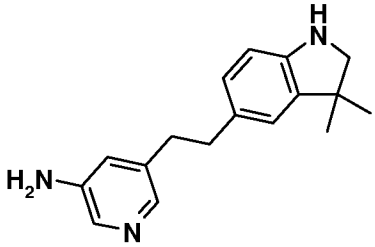
Step 1:

6a5 (1.1 g; 3.1 mmol) is dissolved in DCM (15 mL) and the solution is treated by dropwise addition of trifluoroacetic acid (15 mL). The mixture is stirred for 30 min and the solvent is evaporated. The crude product is taken in DCM (75 mL). A saturated aqueous $NaHCO_3$ solution is added and the mixture is stirred for 1 h. The layers are separated and the aqueous layer is extracted twice with DCM. The combined organic layers are dried over $MgSO_4$, filtered and concentrated to afford **10-1a1** (t_R = 1.71 min, $(M-H)^+$ 260; 261.9).

The following intermediates are prepared analogously to the procedure described in **Example 10-1** starting from the appropriate BOC derivative

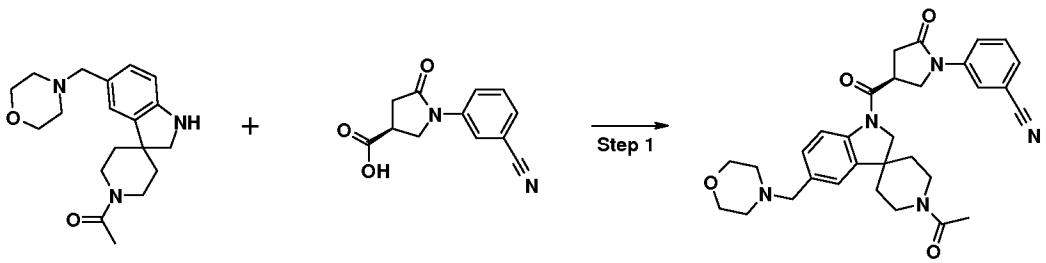
10-1b1	
10-1c1	
10-1d1	

10-1e1	
10-1f1	
10-1g1	
10-1h1	
10-1i1	
10-1j1	

10-1k1	
10-1l1	
10-1m1	
10-1n1	

Example 11

Preparation of 11a1



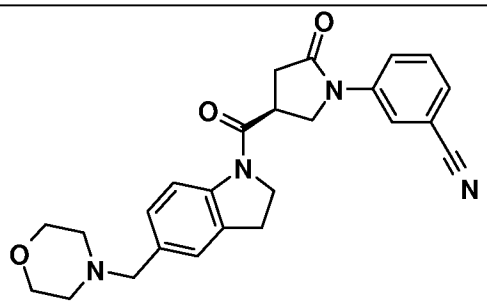
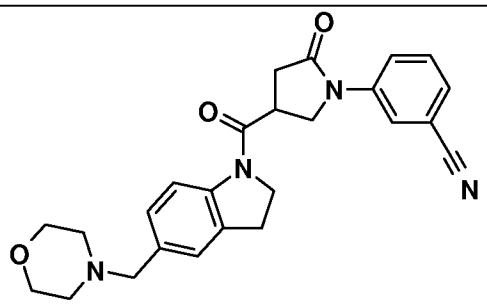
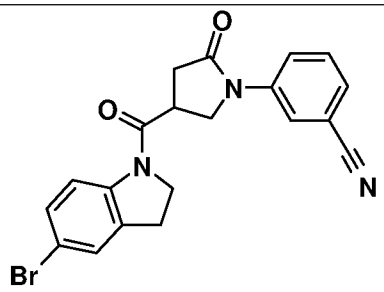
10a1 3a4 11a1

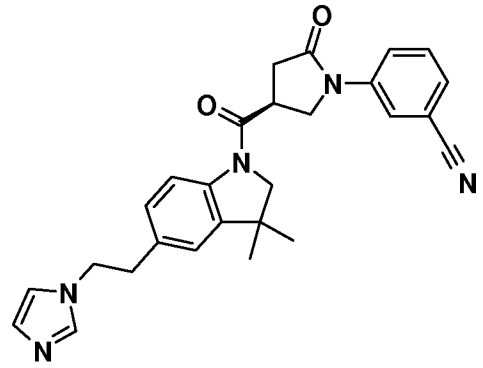
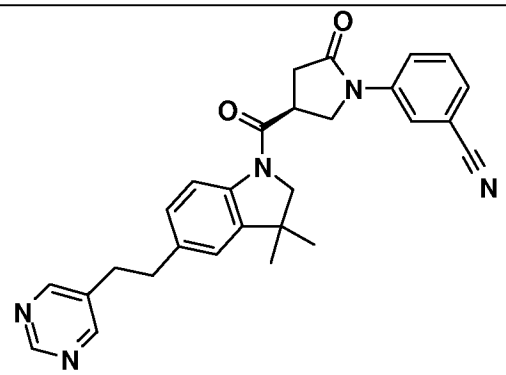
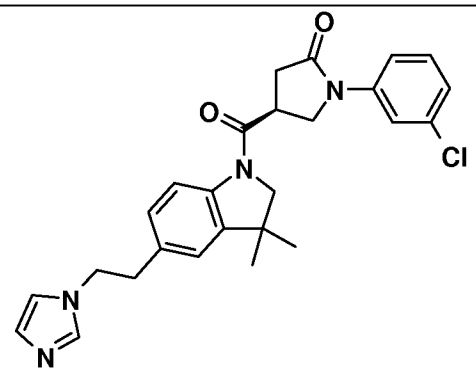
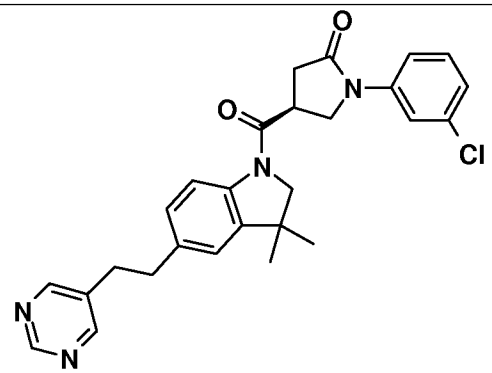
Step 1:

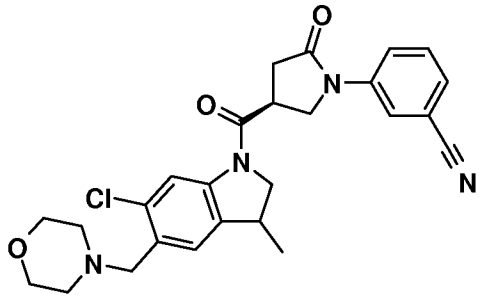
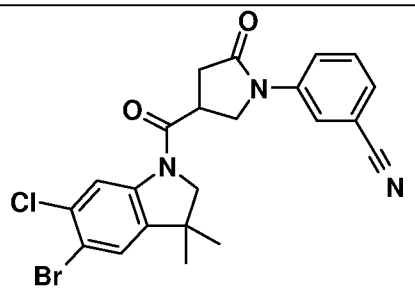
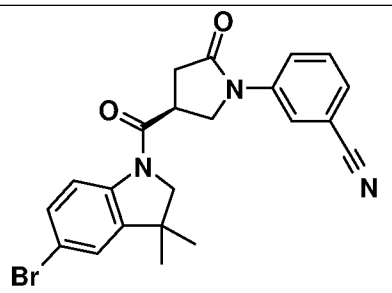
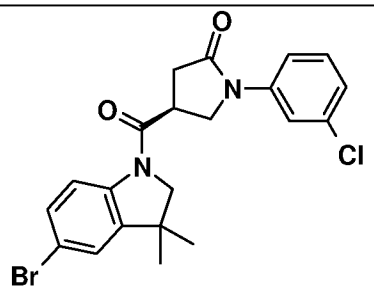
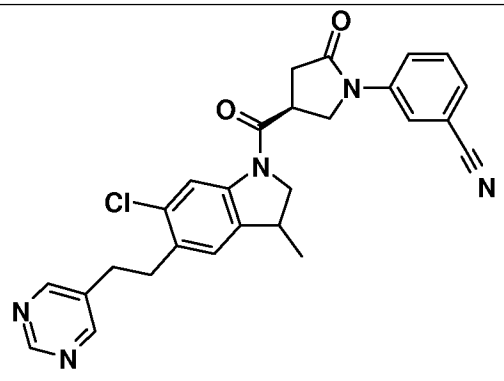
To the acid **3a4** (24 mg, 0.11 mmol) in NMP (1 mL) is added HATU (80 mg, 0.2 mmol) and 2,6-lutidine (73 μL, 0.63 mmol). A solution of the amine **10a1** (42 mg, 0.12 mmol) in NMP (0.25 mL) is added and the mixture is stirred at RT for 2.5 h.

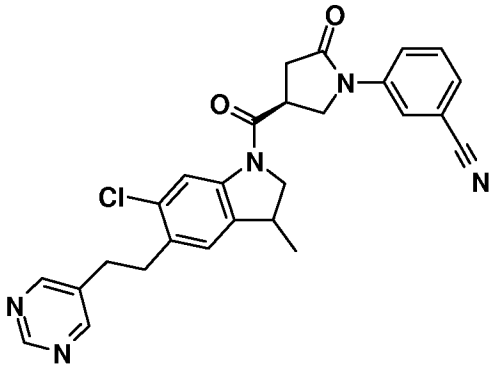
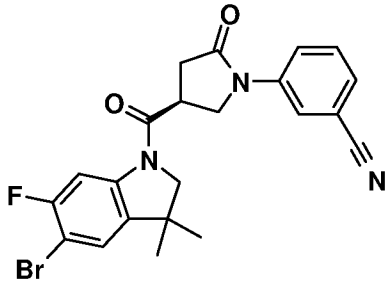
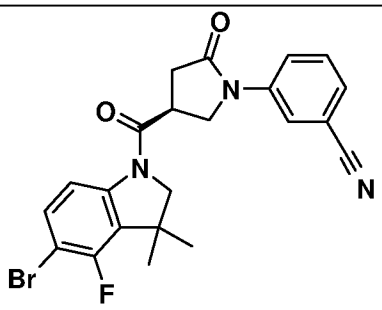
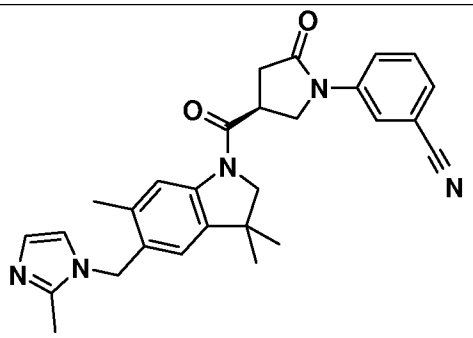
The reaction mixture is diluted with AcOH / MeOH (to provide 2 mL of solution), filtered through an Acrodisc filter and purified by preparative-HPLC MeOH / H_2O (containing 5mM of ammonium formate). The pure fractions are combined, concentrated, diluted with a mixture of MeCN / H_2O, frozen and lyophilized to afford **11a1** (t_R = 1.07 min, $(M+H)^+$ 542.5).

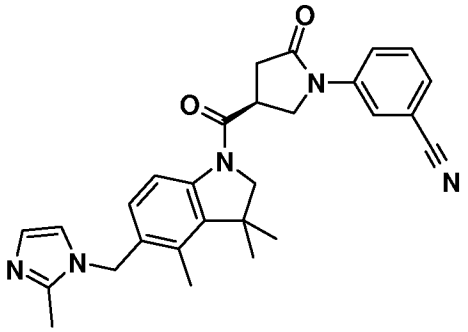
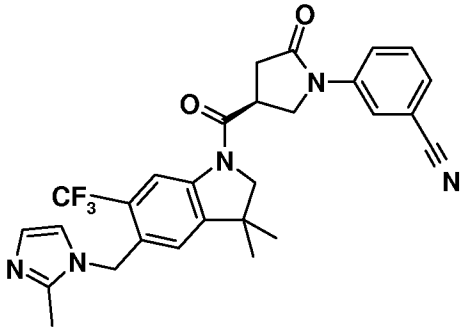
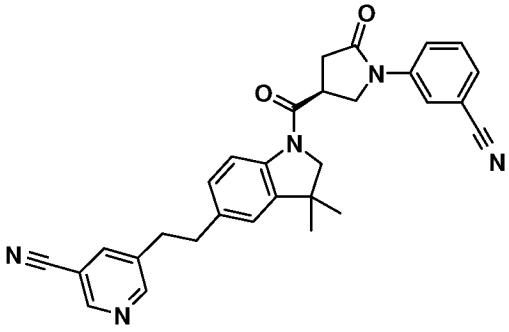
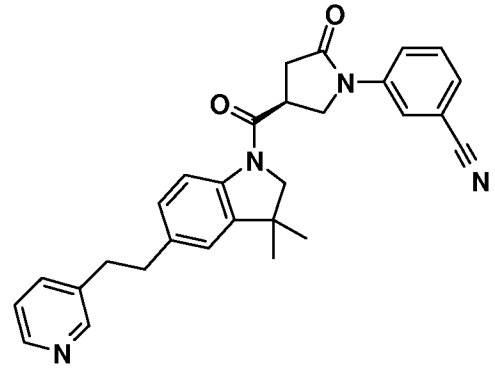
The following compounds are prepared analogously to the procedure described in **Example 11** starting from the appropriate acid and indoline derivative.

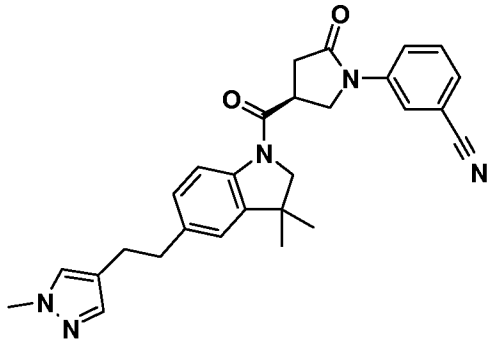
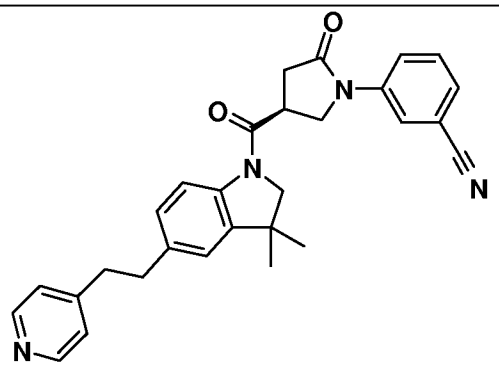
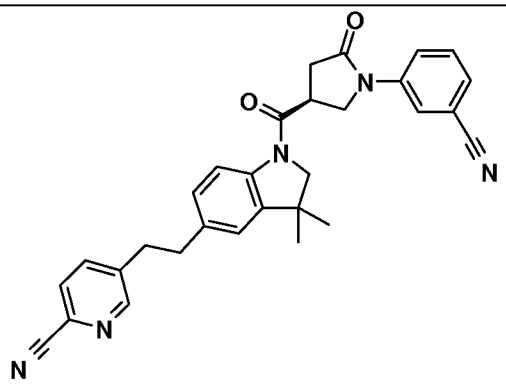
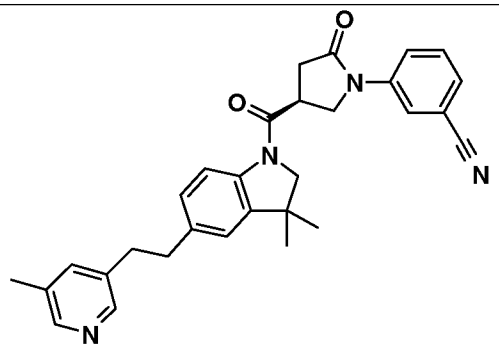
11b1		
11c1		t_R (min) 1.04; $(M+H)^+$ 431.1
11d1		

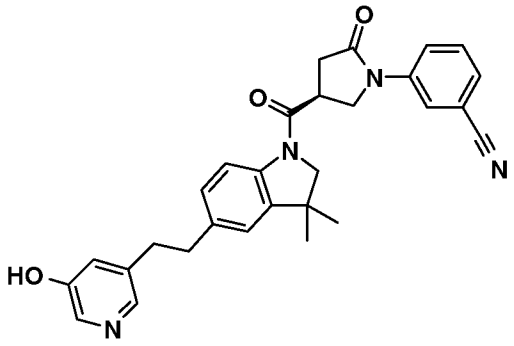
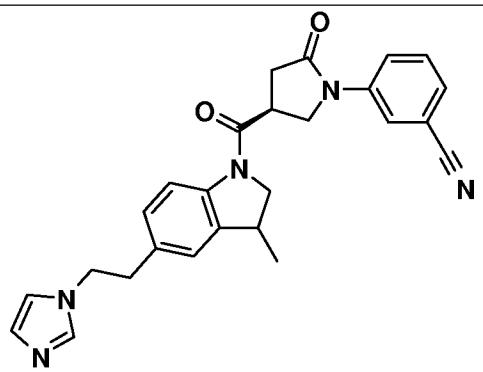
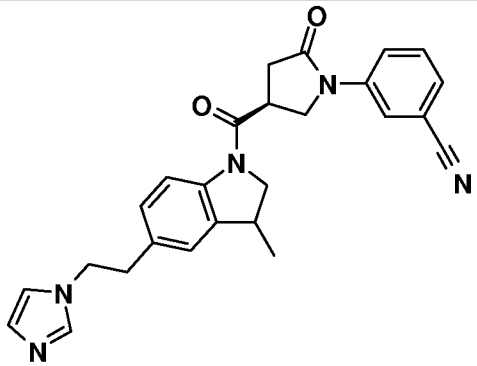
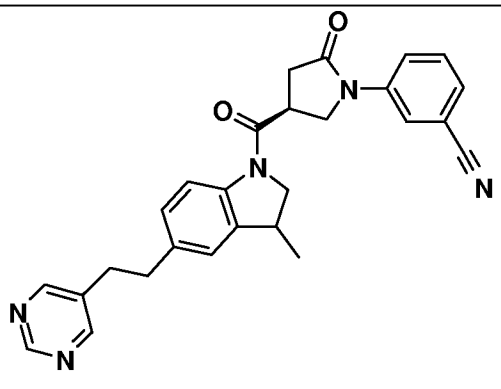
11e1		t_R (min) 0.94; $(M+H)^+$ 454.2
11f1		t_R (min) 1.27; $(M+H)^+$ 466.2
11g1		t_R (min) 1.12; $(M+H)^+$ 463.1
11h1		t_R (min) 1.44; $(M+H)^+$ 475.1

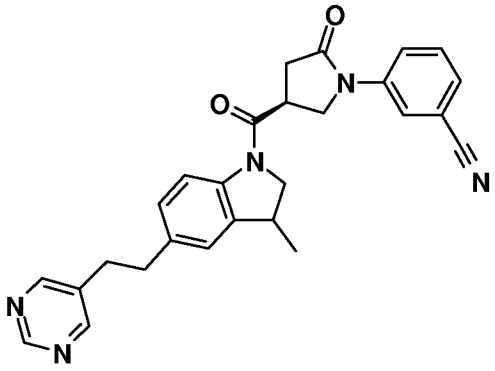
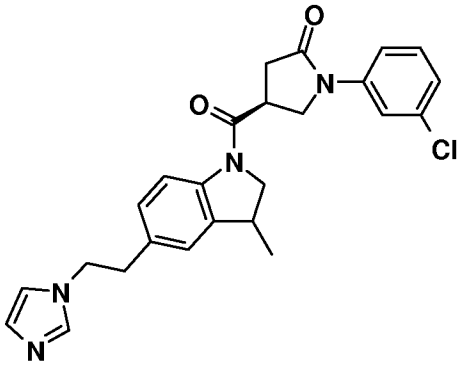
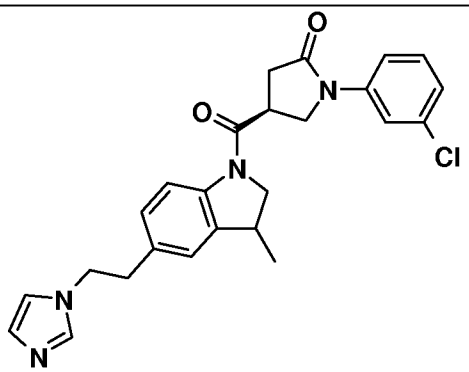
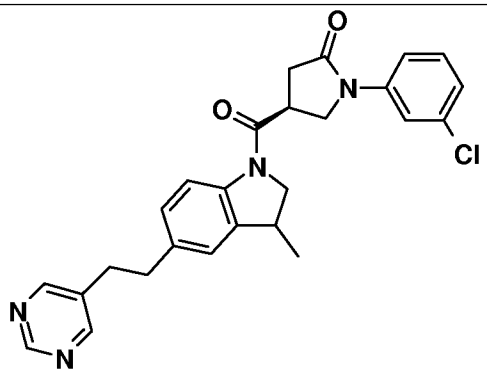
11i1		Racemic
11j1		
11k1		
11l1		
11m1		Diastereomer A t_R (min) 1.34; $(M+H)^+$ 486.1; 488.1

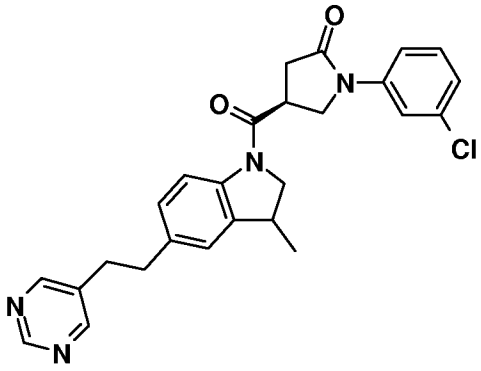
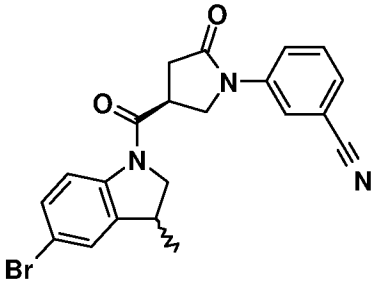
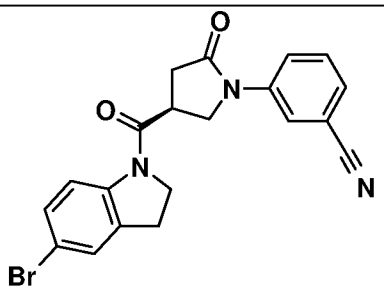
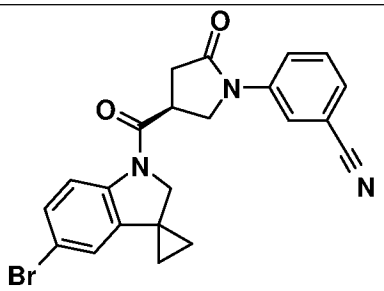
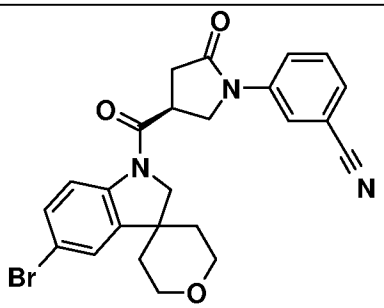
11n1		Diastereomer B t_R (min) 1.33; $(M+H)^+$ 486.1; 488.1
11o1		
11p1		
11q1		t_R (min) 0.99; $(M+H)^+$ 468.2

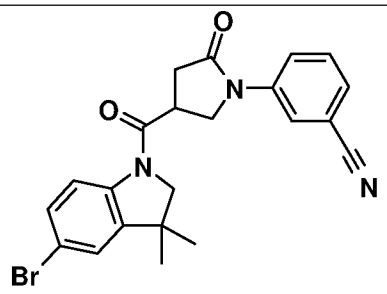
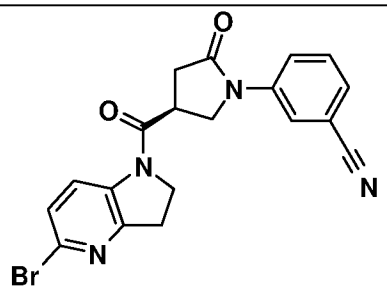
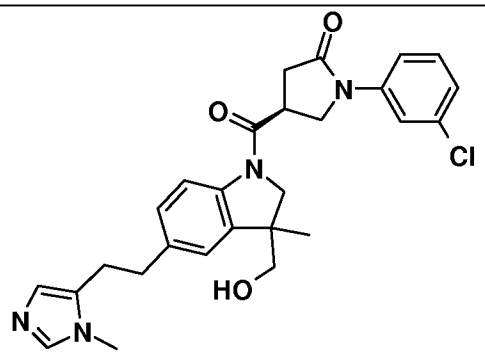
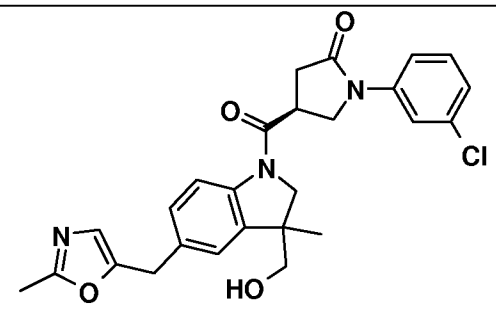
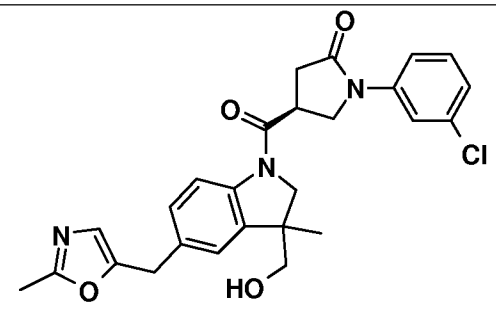
11r1		t_R (min) 0.99; $(M+H)^+$ 468.2
11s1		t_R (min) 1.08; $(M+H)^+$ 522.2
11t1		t_R (min) 1.77; $(M+H)^+$ 490.4
11u1		t_R (min) 1.39; $(M+H)^+$ 465.2

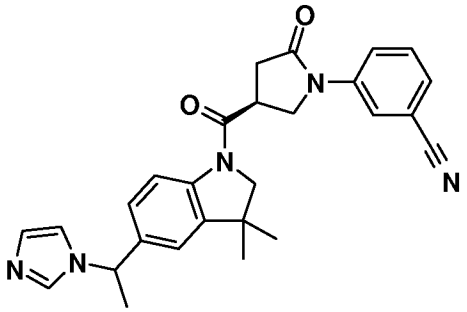
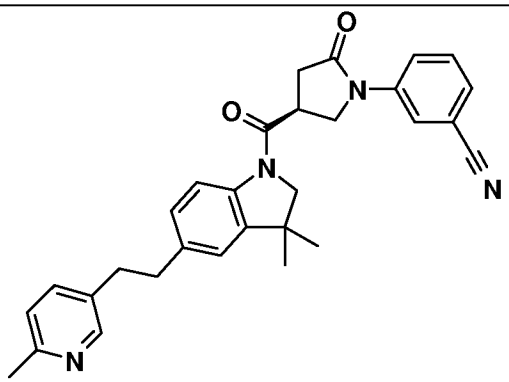
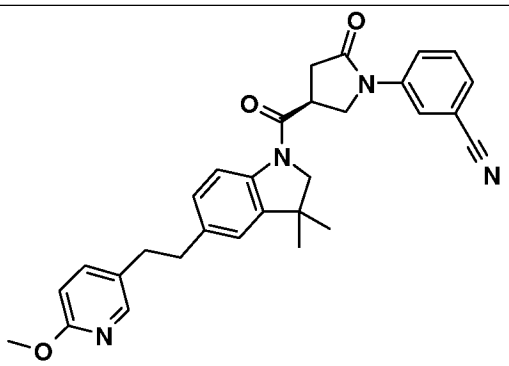
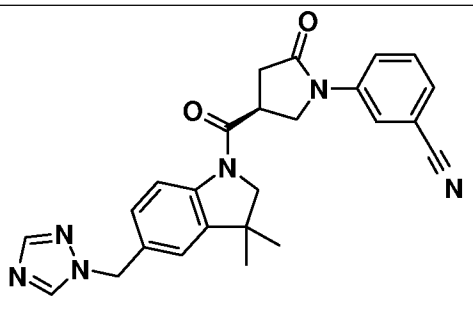
11v1		t_R (min) 1.42; $(M+H)^+$ 468.3
11w1		t_R (min) 1.31; $(M+H)^+$ 465.3
11x1		t_R (min) 1.77; $(M+H)^+$ 490.4
11y1		t_R (min) 1.41; $(M+H)^+$ 479.3

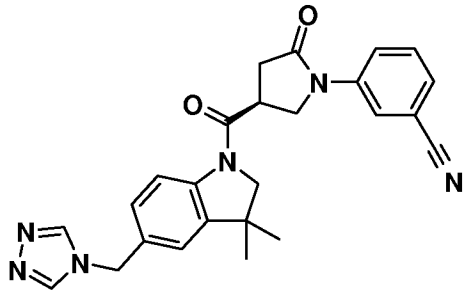
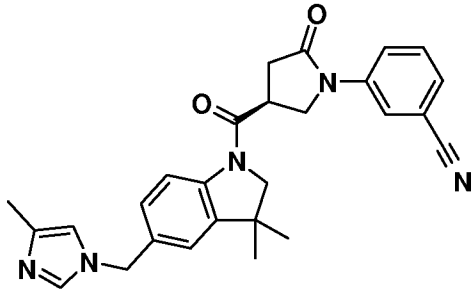
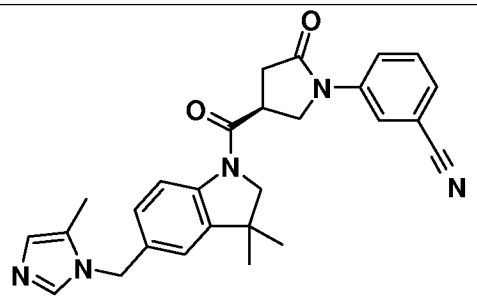
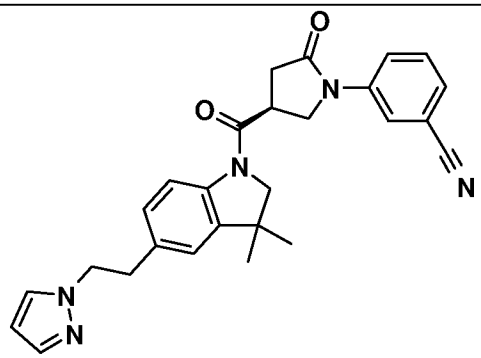
11z1		t_R (min) 1.22; $(M+H)^+$ 481.3
11aa1		Diastereomer A t_R (min) 1.21; $(M+H)^+$ 440.3
11bb1		Diastereomer B t_R (min) 1.21; $(M+H)^+$ 440.1
11cc1		Diastereomer A t_R (min) 1.61; $(M+H)^+$ 452.1

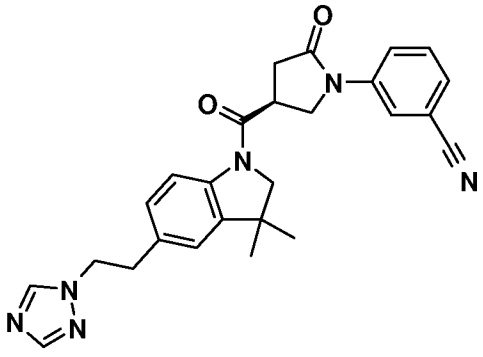
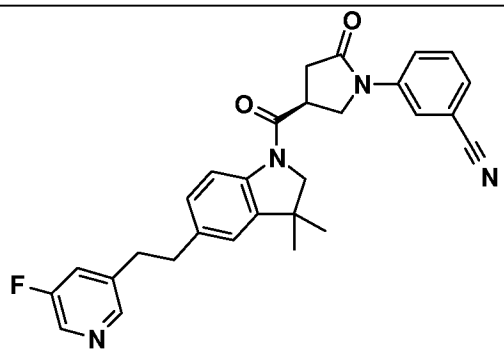
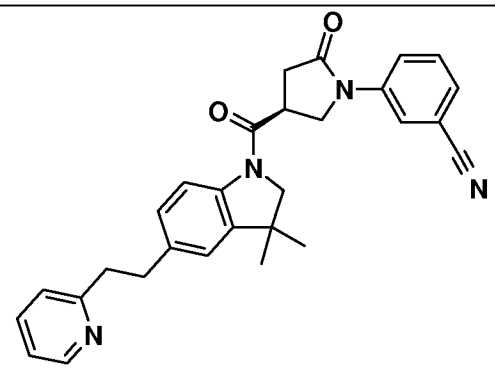
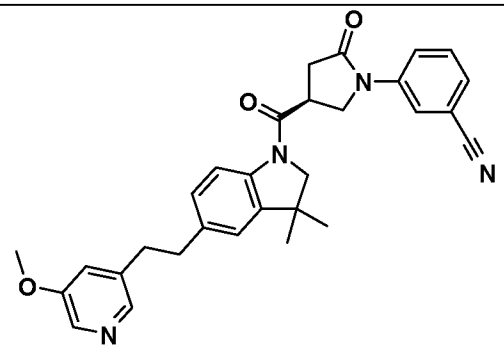
11dd1		Diastereomer B t_R (min) 1.60; $(M+H)^+$ 452.6
11ee1		Diastereomer A t_R (min) 1.47; $(M+H)^+$ 449.1
11ff1		Diastereomer B t_R (min) 1.48; $(M+H)^+$ 449.1
11gg1		Diastereomer A t_R (min) 1.82; $(M+H)^+$ 461.1

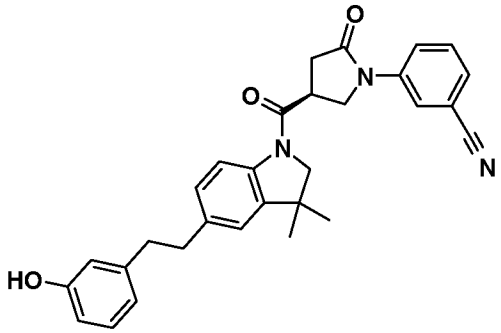
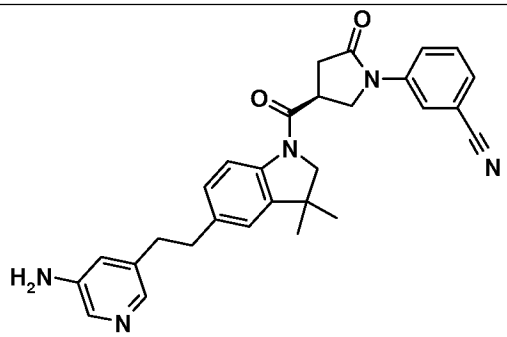
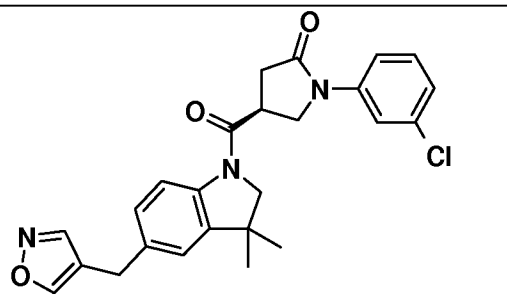
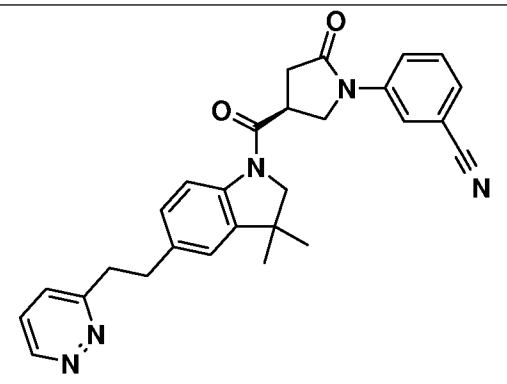
11hh1		Diastereomer B t_R (min) 1.80; $(M+H)^+$ 461.1
11ii1		t_R (min) 1.91; $(M+H)^+$ 425.9;427.9
11jj1		
11kk1		
11ll1		

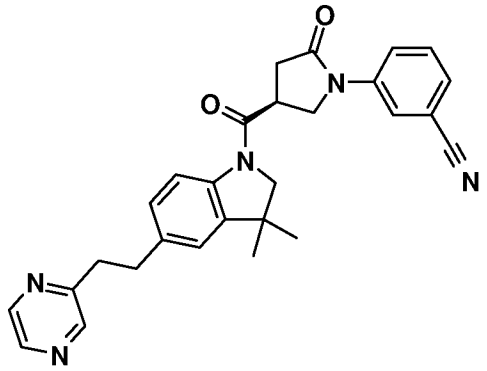
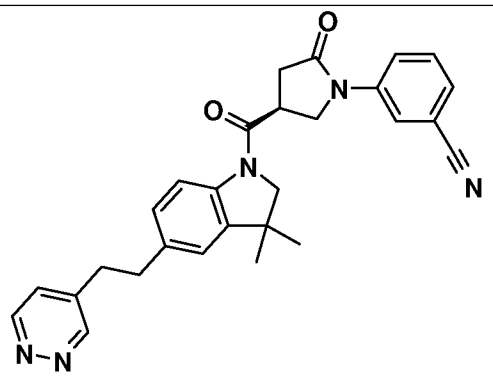
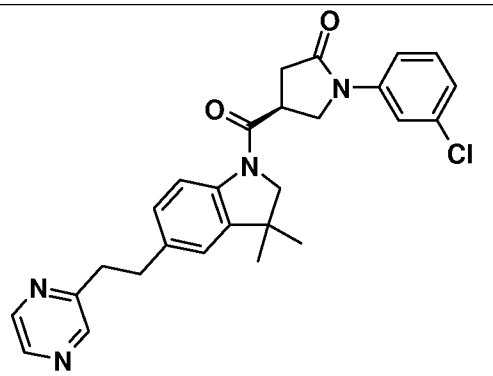
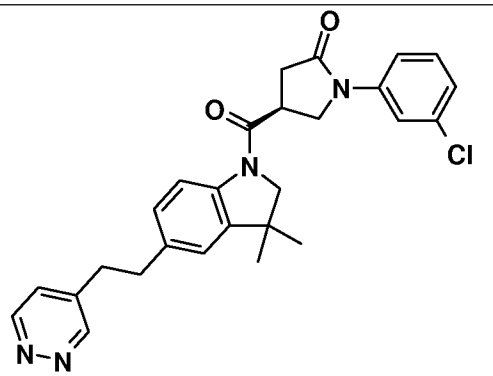
11mm1		
11nn1		
11oo1		t_R (min) 0.94; $(M+H)^+$ 493.2;495.2 Single diastereomer
11pp1		Diastereomer A t_R (min) 1.24; $(M+H)^+$ 480.1; 482.1
11qq1		Diastereomer B t_R (min) 1.29; $(M+H)^+$ 480.1; 482.1

11rr1		t_R (min) 1.25; $(M+H)^+$ 454.4 Racemic
11ss1		t_R (min) 1.72; $(M+H)^+$ 479.5
11tt1		t_R (min) 1.99; $(M+H)^+$ 495.4
11uu1		t_R (min) 1.46; $(M+H)^+$ 441.4

11vv1		t_R (min) 1.32; $(M+H)^+$ 441.3
11ww1		t_R (min) 1.23; $(M+H)^+$ 454.4
11xx1		t_R (min) 1.21; $(M+H)^+$ 454.4
11yy1		t_R (min) 1.70; $(M+H)^+$ 454.4

11zz1		t_R (min) 1.55; $(M+H)^+$ 455.5
11aaa1		t_R (min) 1.55; $(M+H)^+$ 483.2
11bbb1		t_R (min) 1.38; $(M+H)^+$ 465.2
11bbb2		t_R (min) 1.46; $(M+H)^+$ 495.2

11ccc1		t_R (min) 1.56; $(M+H)^+$ 480.1
11ddd1		t_R (min) 1.10; $(M+H)^+$ 480.2
11eee1		t_R (min) 1.59; $(M+H)^+$ 450.2;452.2
11fff1		t_R (min) 1.26; $(M+H)^+$ 466.2

11ggg1		t_R (min) 1.37; $(M+H)^+$ 466.2
11hhh1		t_R (min) 1.24; $(M+H)^+$ 466.2
11iii1		t_R (min) 1.54; $(M+H)^+$ 475.1
11jjj1		t_R (min) 1.40; $(M+H)^+$ 475.1

Example 12

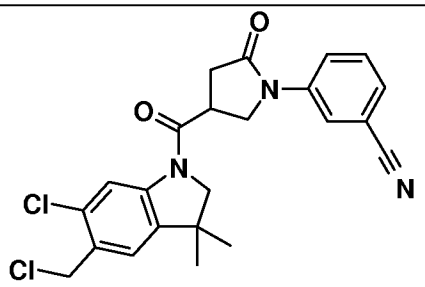
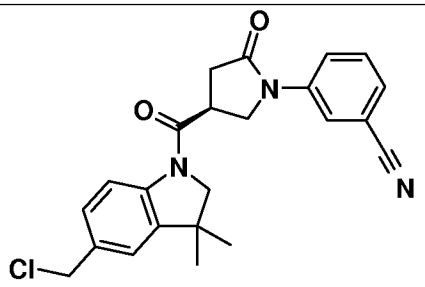
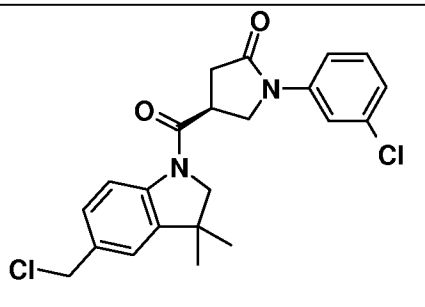
Preparation of intermediate 12a1

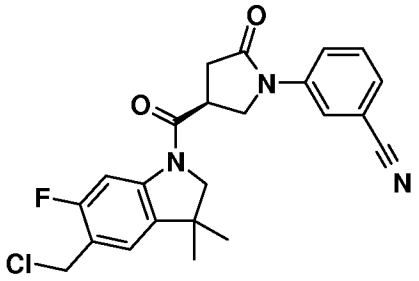
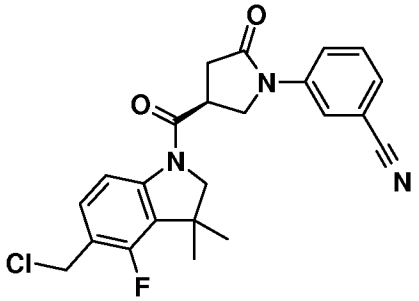
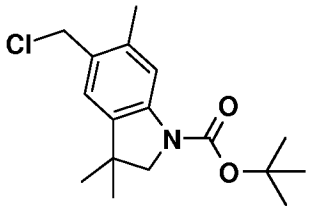
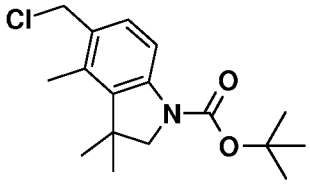
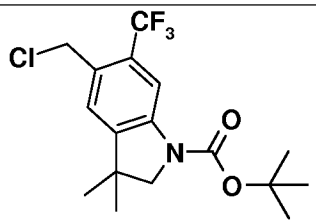
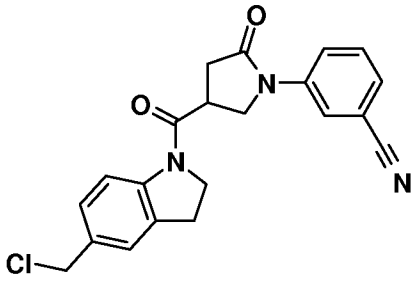
11b1 12a1

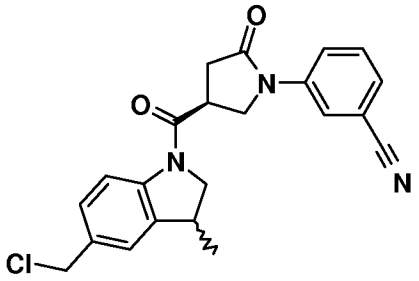
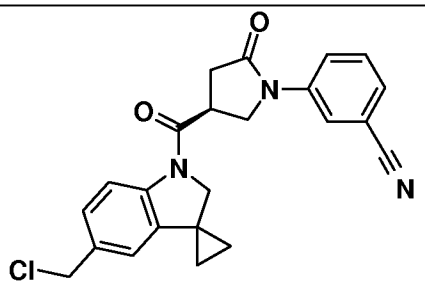
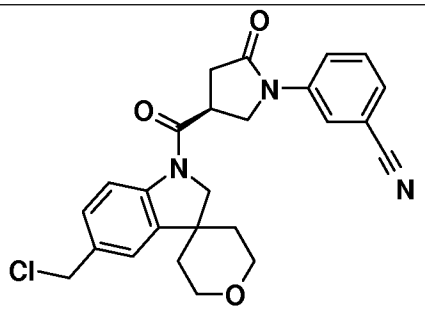
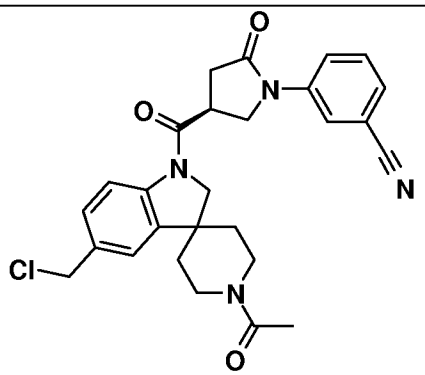
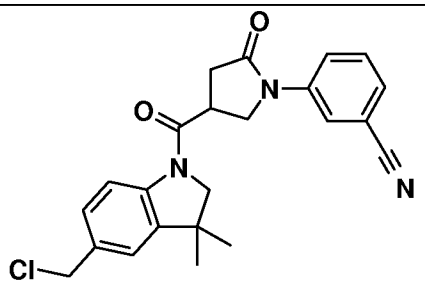
Step 1:

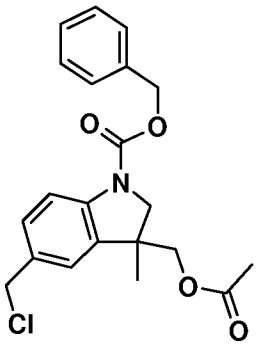
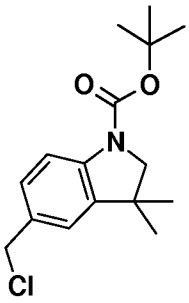
A rounded-bottom flask equipped with a Teflon stir bar is charged with **11b1** (750 mg, 1.7 mmol), chloroform (75 mL) and ethyl chloroformate (330 µL, 3.5 mmol). The mixture is refluxed for 3 h. The mixture is cooled to RT, diluted with DCM, washed with 1N HCl and brine, dried over $MgSO_4$, filtered and concentrated. Purification by Combiflash RF (25 g column, 0-20% MeCN/DCM) gives **12a1** (t_R = 0.93 min, $(M+H-Cl)^+$ 344.1).

The following intermediates are prepared analogously to the procedure described in **Example 12** starting from the appropriate morpholine derivative.

12b1	
12c1	
12d1	

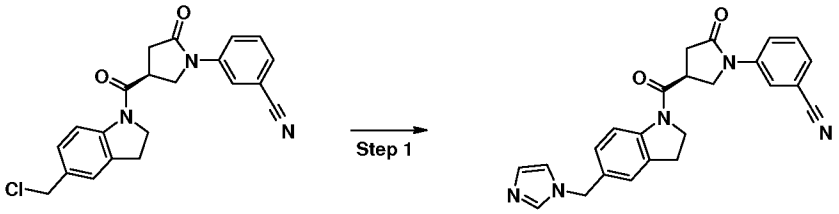
12e1	
12f1	
12g1	
12h1	
12i1	
12j1	

12k1	
12l1	
12m1	
12n1	
12o1	

12p1	
12q1	

Example 13

Preparation of 13a1

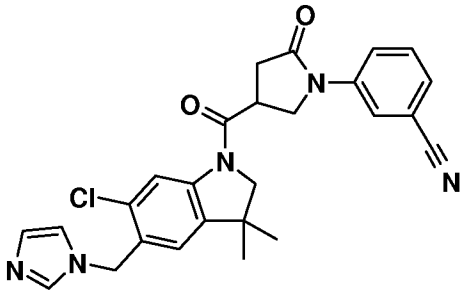
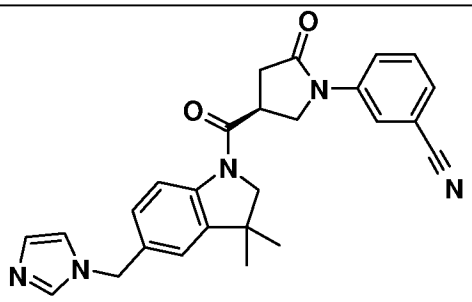
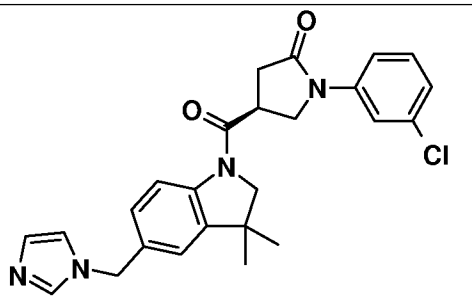
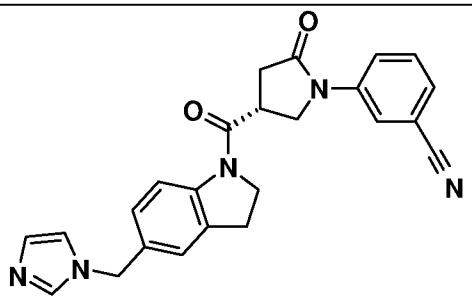
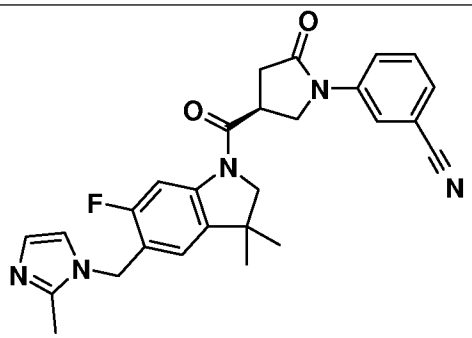


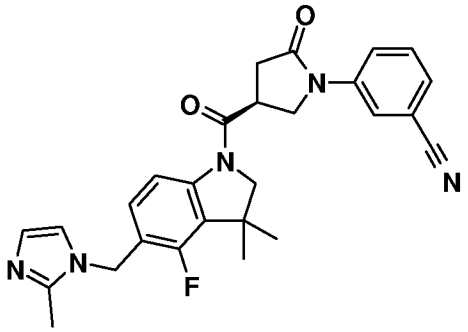
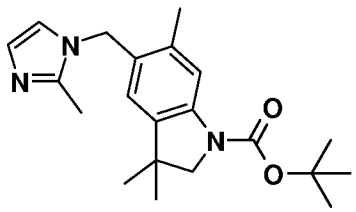
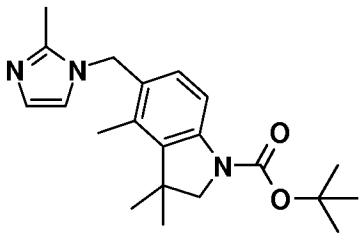
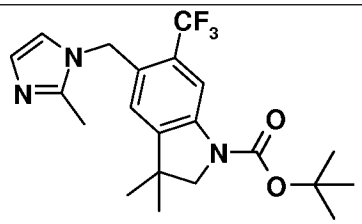
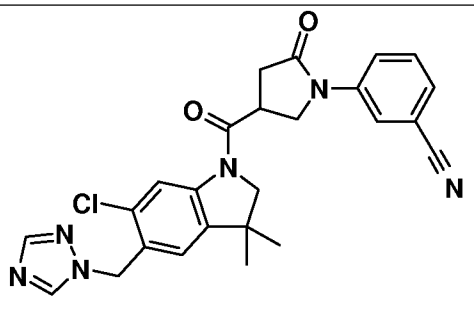
12a1 13a1

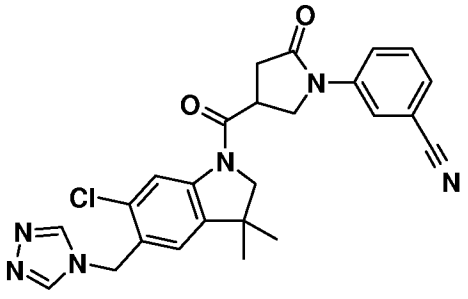
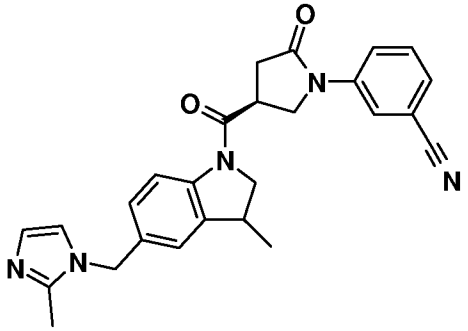
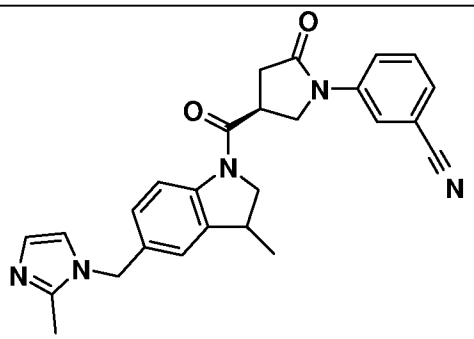
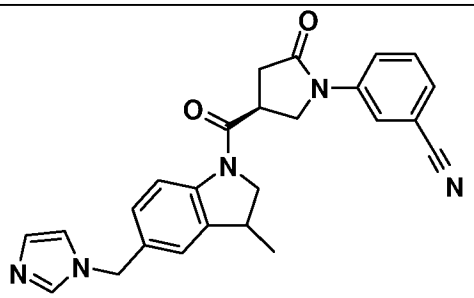
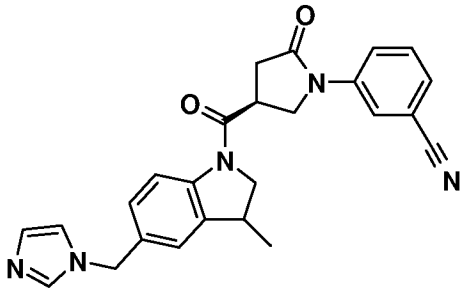
Step 1:

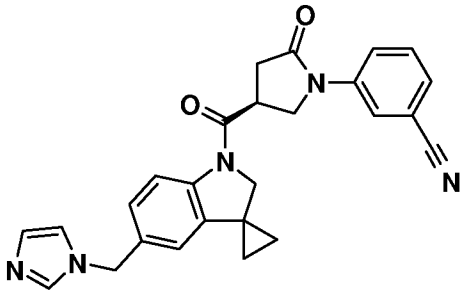
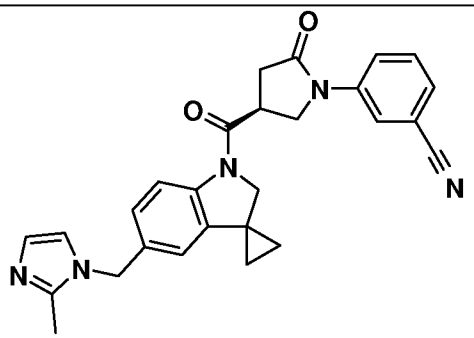
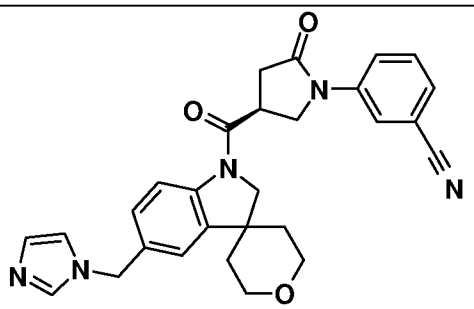
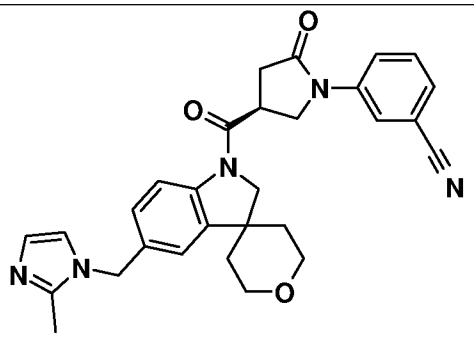
To **12a1** (560 mg, 1.5 mmol) in DMF (4.7 mL) is added imidazole (510 mg, 7.4 mol) and the mixture is stirred at 80°C for 1.5 h. The mixture is cooled to RT, diluted with AcOH / MeOH, filtered with an Acrodisc filter and purified by preparative-HPLC MeCN / H_2O (containing 5mM of ammonium formate). The pure fractions are combined, concentrated, diluted with a mixture of MeCN / H_2O, frozen and lyophilized to afford **13a1** (t_R = 0.76 min, $(M+H)^+$ 412.1).

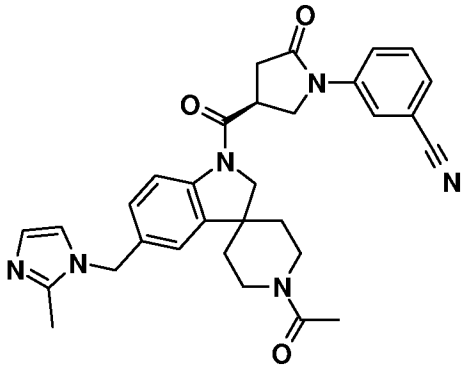
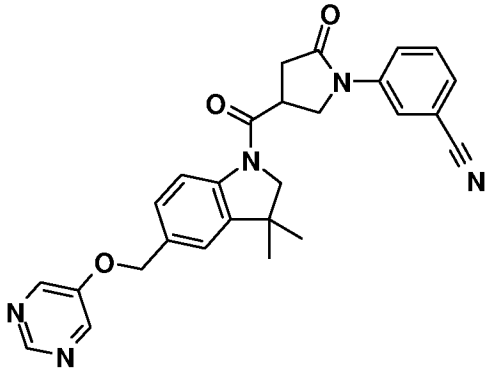
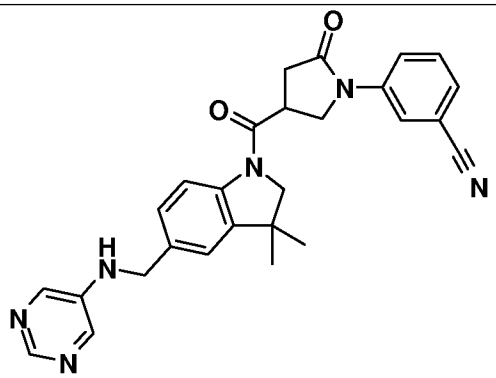
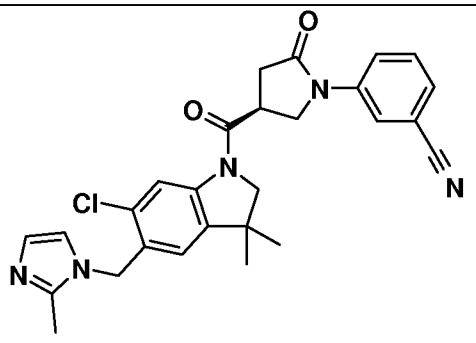
The following compounds are prepared analogously to the procedure described in **Example 13** starting from the appropriate chloro or mesylate derivative.

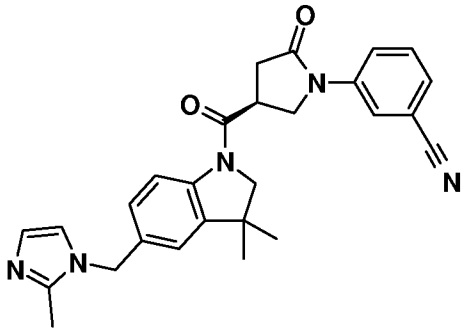
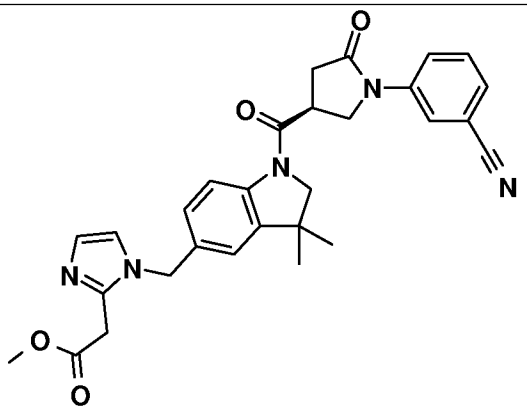
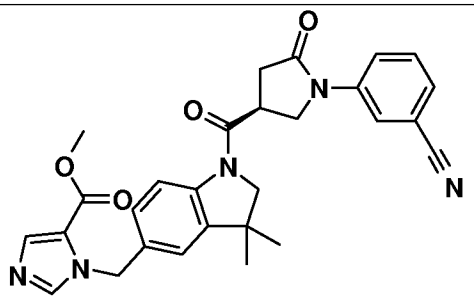
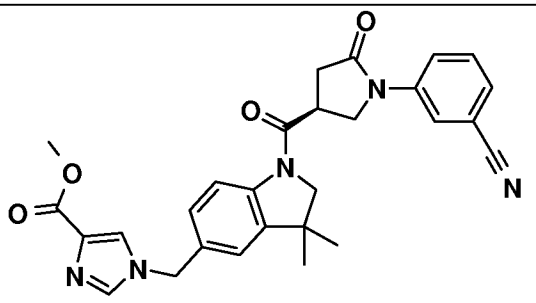
13b1		t_R (min) 1.02; $(M+H)^+$ 474.1;476.0
13c1		t_R (min) 0.90; $(M+H)^+$ 440.1
13d1		t_R (min) 1.09; $(M+H)^+$ 449.1;451.1
13e1		t_R (min) 1.07; (M+H)+ 412.1
13f1		t_R (min) 0.96; $(M+H)^+$ 472.2

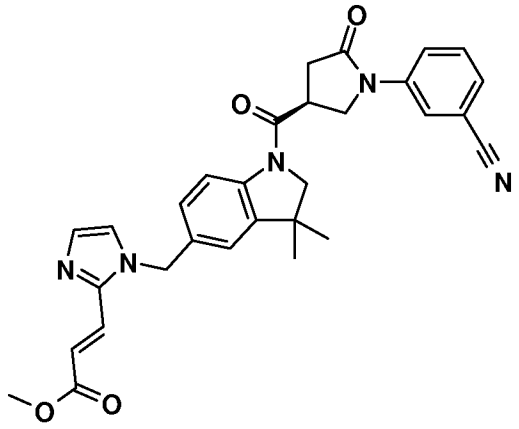
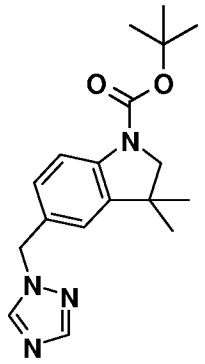
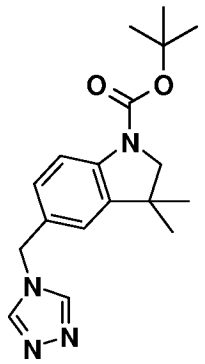
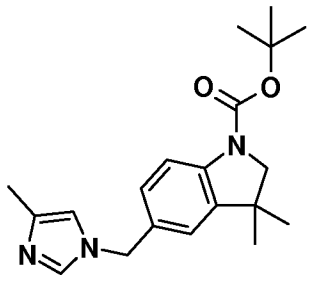
13g1		t_R (min) 0.97; $(M+H)^+$ 472.2
13h1		
13i1		
13j1		
13k1		t_R (min) 1.26 $(M+H)^+$ 475;477

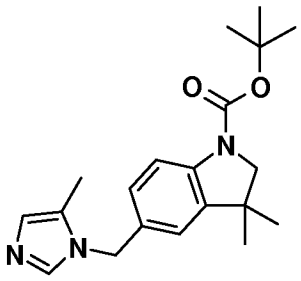
13l1		t_R (min) 1.13; $(M+H)^+$ 475;477
13n1		Diastereomer A t_R (min) 1.10; $(M+H)^+$ 440.1
13o1		Diastereomer B t_R (min) 1.12; $(M+H)^+$ 440.1
13p1		Diastereomer A t_R (min) 1.12; $(M+H)^+$ 426.1
13q1		Diastereomer B t_R (min) 1.09; $(M+H)^+$ 426.1

13r1		t_R (min) 1.17; (M+H)+ 438
13s1		t_R (min) 1.17; (M+H)+ 452
13t1		t_R (min) 1.11; (M+H)+ 482
13u1		t_R (min) 1.10; (M+H)+ 496

13v1		t_R (min) 1.08; (M+H)+ 537
13w1		t_R (min) 1.62; (M+H)+ 468.2
13w2		t_R (min) 1.47; (M+H)+ 467.2
13x1		t_R (min) 1.01; $(M+H)^+$ 488.2;490.1

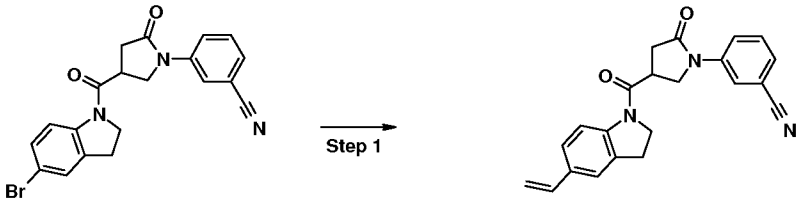
13y1		t_R (min) 0.89; $(M+H)^+$ 454.2
13z1		
13aa1		
13bb1		

13cc1	
13dd1	
13ee1	
13ff1	

13gg1	

Example 14

Preparation of intermediate 14a1

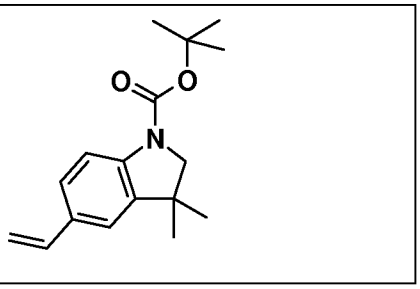


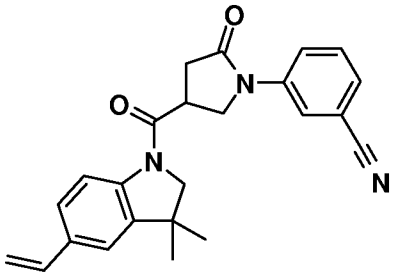
11d1 14a1

Step 1:

A pressure vessel equipped with a Teflon stir bar is charged with **11d1** (690 mg, 1.7 mmol), 2,4,6-trivinylcyclotriboroxane pyridine complex (420 mg, 1.7 mmol), sodium carbonate (2M in water, 5 mL, 10 mmol), $Pd(PPh_3)_4$ (180 mg; 0.15 mmol) and DME (20 mL). The solution is degassed by bubbling argon for 5 min. The vessel is sealed and heated at 80°C overnight. The reaction mixture is cooled to RT, poured into EtOAc, washed with water and brine, dried over $MgSO_4$, filtered and concentrated. Purification by Combiflash RF (24 g column, 0-30% MeCN/DCM) gives **14a1** (t_R = 1.78 min, $(M+H)^+$ 358).

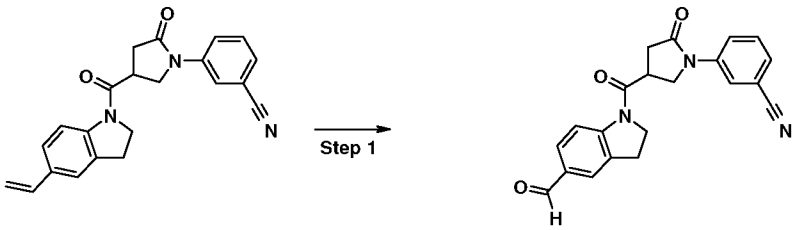
The following intermediates are prepared analogously to the procedure described in **Example 14** starting from the appropriate bromo and boronic acid derivatives.

14b1	

14c1	

Example 15

Preparation of intermediate 15a1

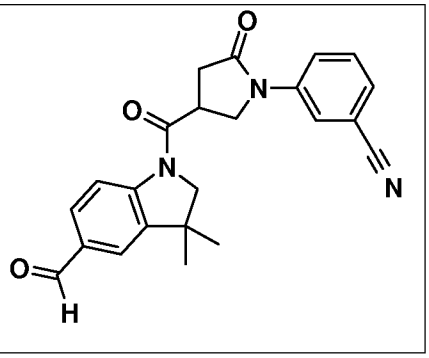


14a1 15a1

Step 1:

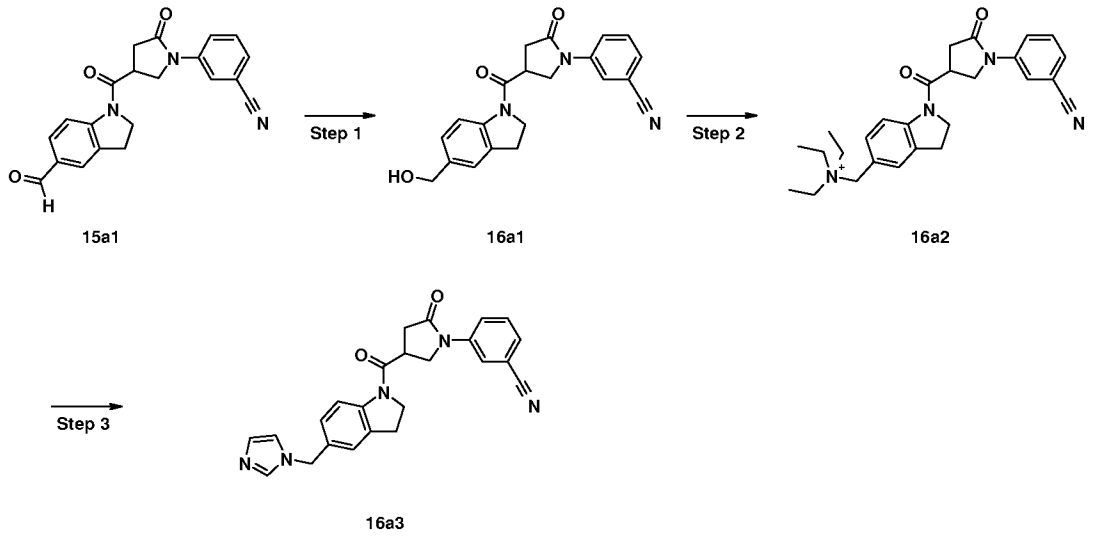
A mixture of the olefin **14a1** (470 mg, 1.3 mmo), a solution of OsO_4 in t-BuOH (0.1 M, 260 µL, 0.03 mmol) and a solution of $NaIO_4$ in water (0.5 M, 9.3 mL, 4.6 mmol) in THF (10 mL) are stirred at RT for 4 h. The mixture is poured in water and extracted twice with EtOAc. The organic layer is dried with $MgSO_4$, filtered and evaporated to generate **15a1** (t_R = 1.48 min, $(M+H)^+$ 360).

The following intermediate is prepared analogously to the procedure described in **Example 15** starting from the appropriate vinyl derivative.

15b1	

Example 16

Preparation of 16a3



Step 1:

A mixture of aldehyde **15a1** (390 mg, 1.1 mmol) in MeOH (10 mL) (1 mL of THF is added to complete the solubilization) is stirred at RT under N_2(g). $NaBH_4$ (81 mg, 2.1 mmol) is added and the mixture is stirred at RT for 2 h. The reaction mixture is neutralized with 1N HCl and then concentrated. EtOAc is added and the organic layer is washed with brine, dried over Na_2SO_4, filtered and evaporated. Purification by Combi-Flash Rf (0-50% MeCN/CH_2Cl_2 as eluent in 25 min with a 4 g column) affords **16a1** (t_R = 1.33 min, $(M+OMe)^+$ = 376.1).

Step 2:

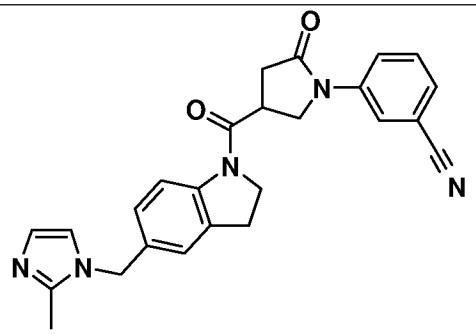
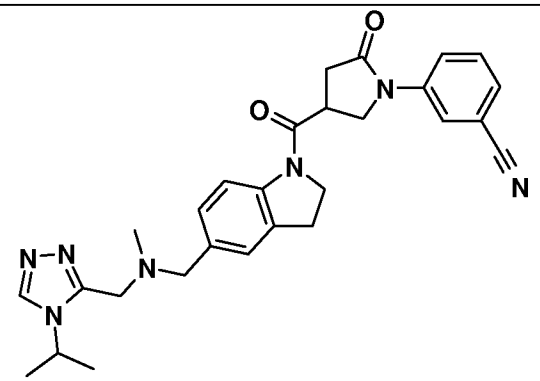
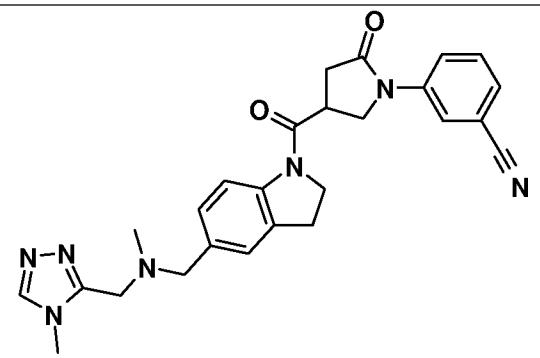
A solution of alcohol **16a1** (160 mg, 0.4 mmol) in CH_2Cl_2 (110 mL) is stirred at 0°C under N_2(g). Et_3N (0.15 mL, 1.1 mmol) is added followed by methanesulfonylchloride (50 µL, 0.65 mmol) over 15 min. The reaction mixture is warmed to RT over 2 h. Water is added and the layers are separated. The organic layer is washed with brine, dried over $MgSO_4$, filtered then evaporated to give **16a2** (t_R = 1.05 min, $(M+H)^+$ = 445.1).

Step 3:

To **16a2** (40 mg, 0.09 mmol) in DMF (2 mL) is added imidazole (31 mg, 0.45 mmol) and the mixture is stirred at 140°C for 16 h. The mixture is cooled to RT, diluted with AcOH / MeOH, filtered with an Acrodisc filter and purified by preparative-HPLC MeOH / H_2O (containing 5mM of ammonium formate). The pure fractions are combined, concentrated, diluted with a mixture of MeCN / H_2O, frozen and lyophilized to afford **16a3** ((t_R = 1.06 min, $(M+H)^+$ 412.0).

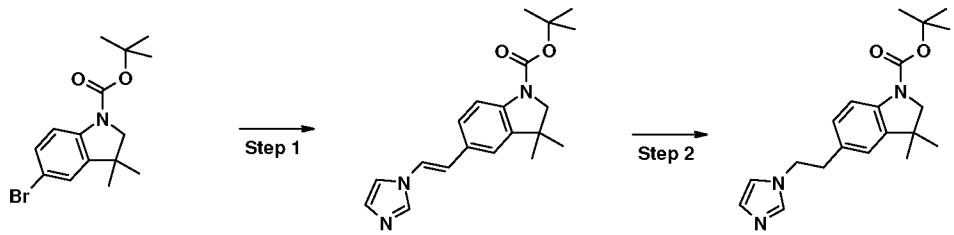
The following compounds are prepared analogously to the procedure described in **Example 16**

starting from the appropriate aldehyde derivative.

16b3		t_R (min) 1.06; $(M+H)^+$ 426.1
16c3		t_R (min) 1.45; $(M+H)^+$ 498.1
16d3		t_R (min) 1.22; $(M+H)^+$ 470.1

Example 17

Preparation of intermediate 17a1



6c5 17a1 17a2

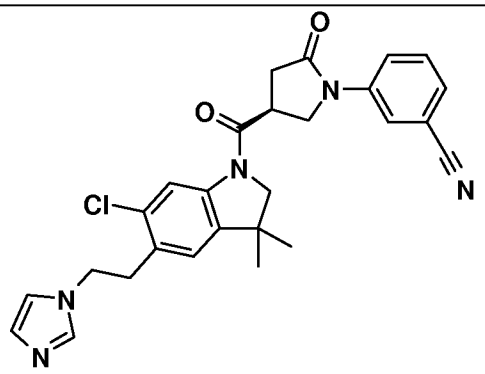
Step 1:

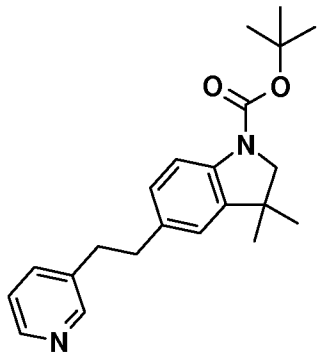
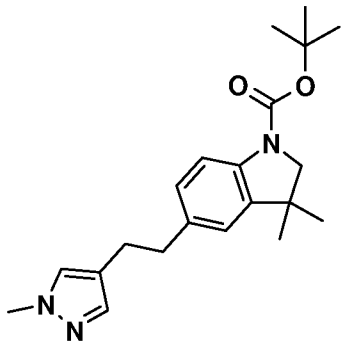
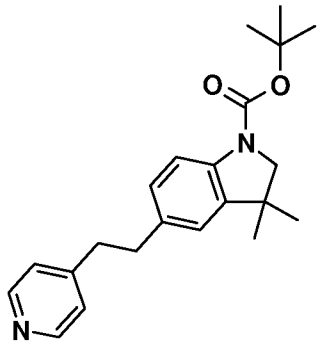
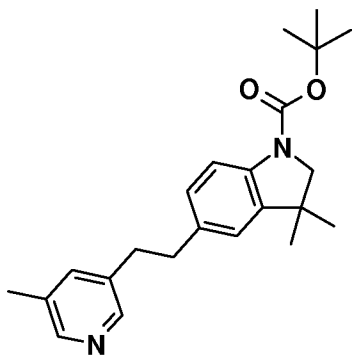
A pressure vessel equipped with a Teflon stir bar is charged with **6c5** (250 mg, 0.8 mmol), 1-vinylimidazole (90 mg, 1 mmol), tri-*o*-tolyphosphine (33 mg, 0.11 mmol), diisopropylamine (0.4 mL, 2.3 mmol), $Pd(OAc)_2$ (12 mg; 0.05 mmol) and DMF (18 mL). The solution is degassed by bubbling argon for 5 min. The vessel is sealed and heated at 110°C overnight. The reaction mixture is cooled to RT, poured into EtOAc and extracted with 0.1N HCl. The aqueous layer is basified with potassium carbonate and extracted with EtOAc. The organic layer is washed with brine, dried over $MgSO_4$, filtered and concentrated to afford **17a1** (t_R = 1.52 min, $(M+H)^+$ 340).

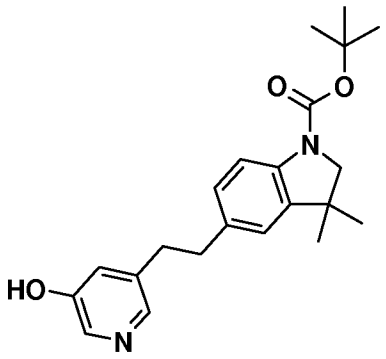
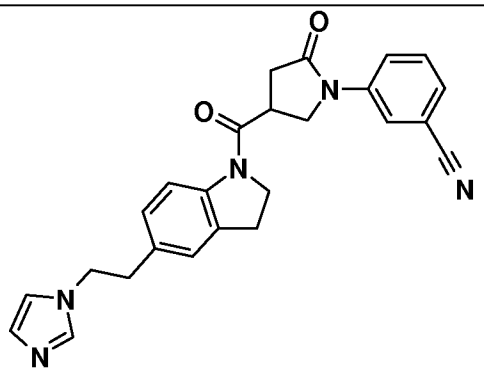
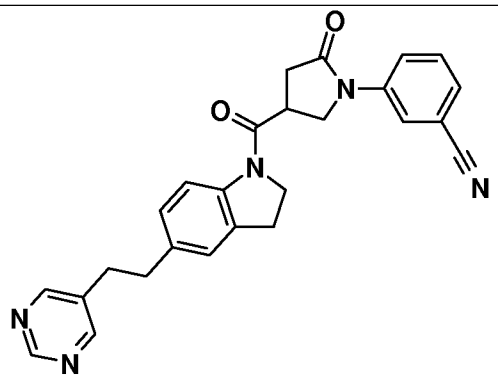
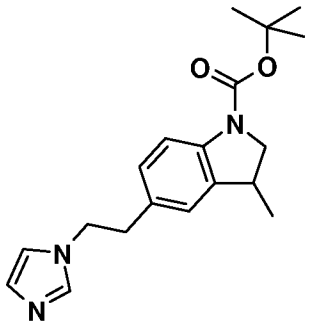
Step 2:

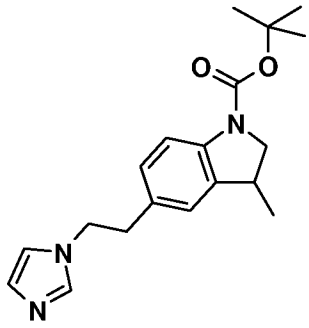
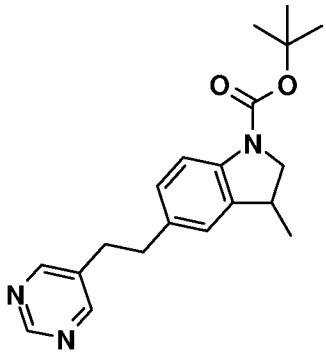
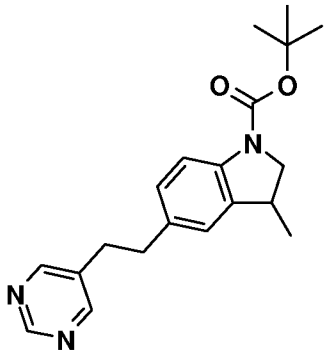
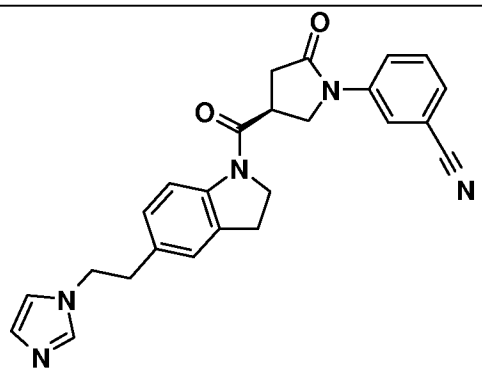
17a1 (190 mg, 0.55 mmol) is dissolved in EtOH (20 mL) and purged under argon. Pd/C (10 % w/w) is added. The mixture is purged under argon and then placed under H_2 (1 atm) for 16 h. The reaction mixture is filtered through a pad of celite and washed with MeOH. The filtrate is concentrated to dryness to afford **17a2** (t_R = 1.21 min, $(M+H)^+$ 342.2).

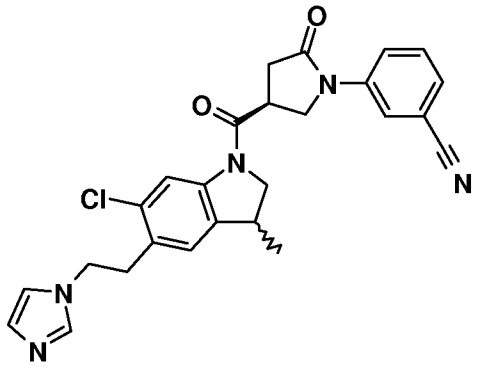
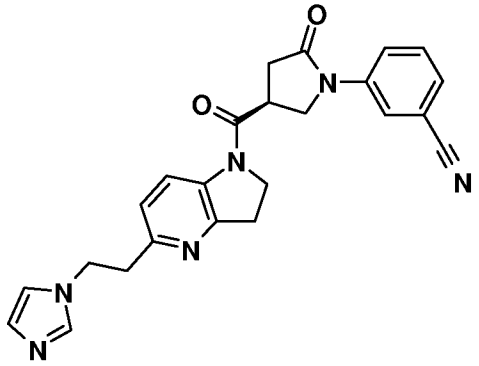
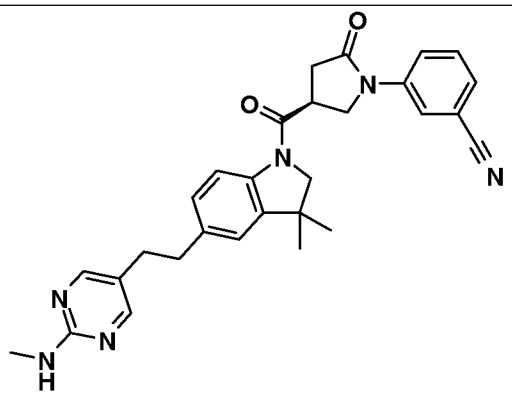
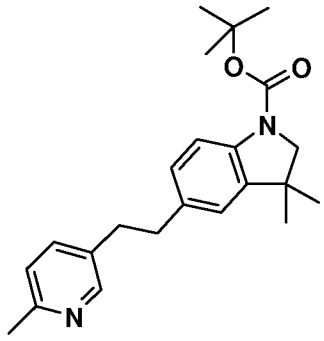
The following compounds are prepared analogously to the procedure described in **Example 17** starting from the appropriate bromo and vinylic derivatives.

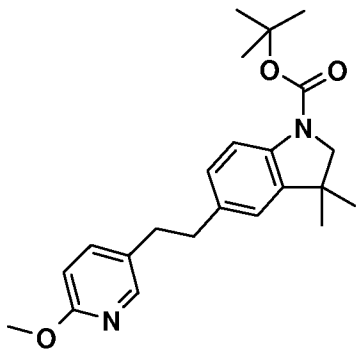
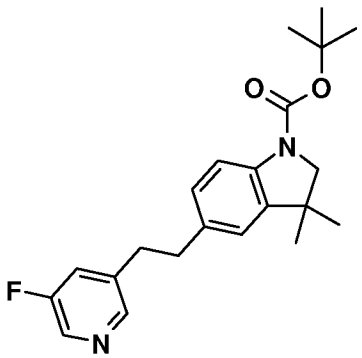
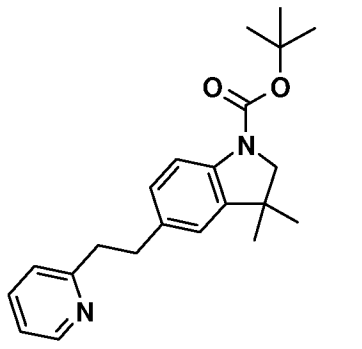
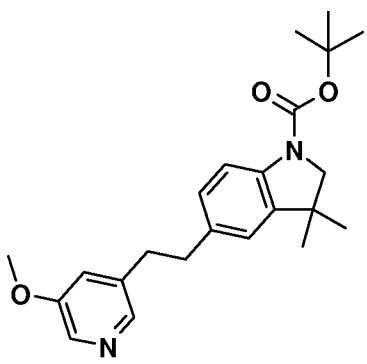
17b1		t_R (min) 1.06; $(M+H)^+$ 488.1;490.1

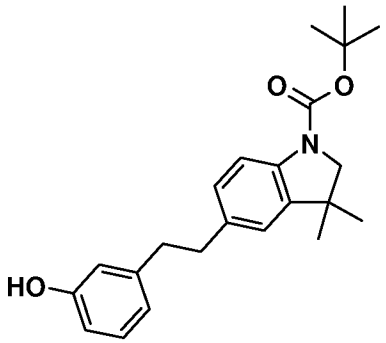
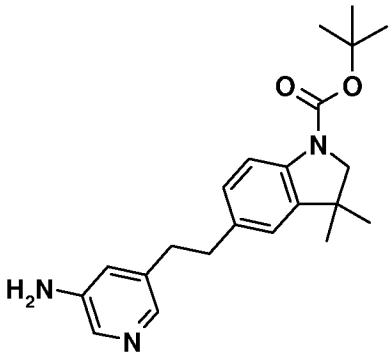
17c1	
17c1	
17d1	
17e1	

17e1		
17f1		t_R (min) 1.38; $(M+H)^+$ 424.0
17g1		t_R (min) 1.54; $(M+H)^+$ 438.1
17h1		Enantiomer A

17i1		Enantiomer B
17j1		Enantiomer A
17k1		Enantiomer B
17l1		t_R (min) 1.12; $(M+H)^+$ 426.1

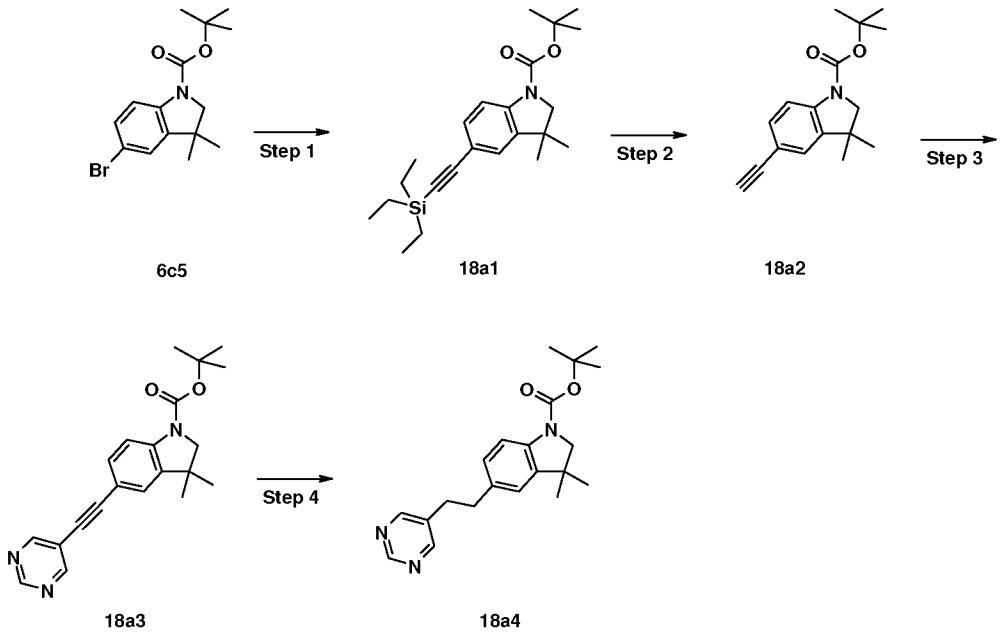
17m1		t_R (min) 0.99; $(M+H)^+$ 474.1;476.1 Mixture of diastereomers.
17n1		t_R (min) 0.69; $(M+H)^+$ 427.1
17o1		t_R (min) 1.33; $(M+H)^+$ 495.2
17p1		

17q1	
17r1	
17s1	
17t1	

17u1	
17v1	

Example 18

Preparation of intermediate 18a4



Step 1:

A pressure vessel equipped with a Teflon stir bar is charged with **6c5** (410 mg, 1.3 mmol),

(triethylsilyl)acetylene (220 mg, 1.6 mmol), diethylamine (650 µL, 6.3 mmol), copper iodide (24 mg, 0.13 mmol), $Pd(PPh_3)_4$ (130 mg; 0.12 mmol) and DMF (5.5 mL). The solution is degassed by bubbling argon for 5 min. The vessel is sealed and heated at 90°C overnight. The reaction mixture is cooled to RT and poured into EtOAc. The organic layer is washed with a 1N solution of citric acid and brine, dried over $MgSO_4$, filtered and concentrated. Purification by Combi-Flash Rf (0-2% EtOAc/Hexanes as eluent on a 12 g column) affords **18a1** (t_R = 2.52 min).

Step 2:

18a1 (450 mg, 1.2 mmol) is dissolved in MeOH (18 mL) and treated with a solution of TBAF in THF (1M, 1.3 mL, 1.3 mmol) at 70°C for 16 h. The reaction mixture is cooled to RT and concentrated. Purification by Combi-Flash Rf (0-10% EtOAc/Hexanes as eluent on a 12 g column) affords **18a2** (t_R = 1.93 min).

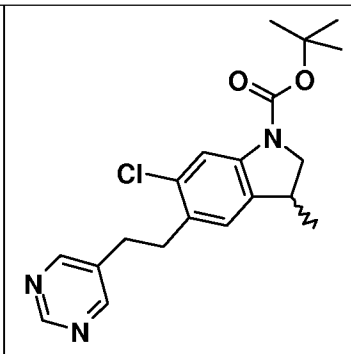
Step 3:

A pressure vessel equipped with a Teflon stir bar is charged with **18a2** (260 mg, 0.95 mmol), 5-bromopyrimidine (190 mg, 1.2 mmol), diethylamine (491 µL, 4.8 mmol), copper iodide (18 mg, 0.10 mmol), $Pd(PPh_3)_4$ (100 mg; 0.09 mmol) and DMF (4.0 mL). The solution is degassed by bubbling argon for 5 min. The vessel is sealed and heated at 90°C overnight. The reaction mixture is cooled to RT and poured into EtOAc. The organic layer is washed with a saturated aqueous solution of ammonium chloride and brine, dried over $MgSO_4$, filtered and concentrated. Purification by Combi-Flash Rf (0-20% EtOAc/Hexanes as eluent on a 12 g column) affords **18a3** (t_R = 1.88 min, $(M+H)^+$ = 350.1).

Step 4:

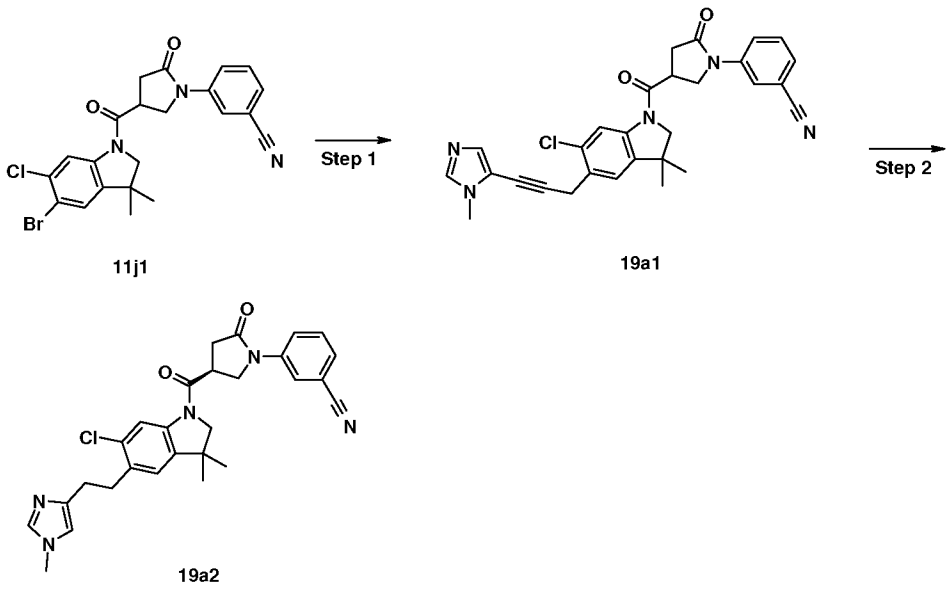
18a3 (205 mg, 0.59 mmol) is dissolved in EtOH (20 mL) and purged under argon. Pd/C (10 % w/w) is added. The mixture is purged under argon and then placed under H_2 (1 atm) for 16 h. The reaction mixture is filtered through a pad of celite and concentrated to dryness. Purification by Combi-Flash Rf (0-50% EtOAc/Hexanes as eluent on a 4 g column) affords **18a4** (t_R = 1.65 min, $(M+H)^+$ = 298.1).

The following intermediates are prepared analogously to the procedure described in **Example 18** starting from the appropriate bromo derivative.

18b4	

Example 19

Preparation of 19a2



Step 1:

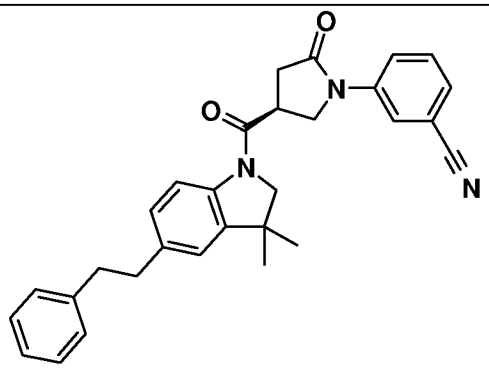
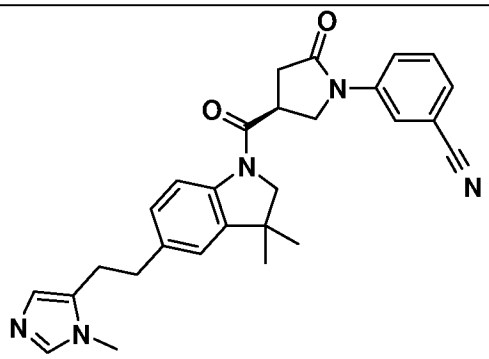
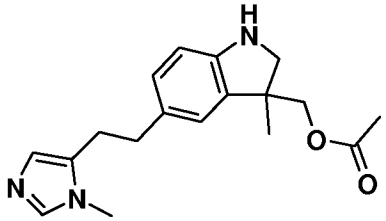
A pressure vessel equipped with a Teflon stir bar is charged with **11j1** (100 mg, 0.21 mmol), 5-ethynyl-1-methyl-1H-imidazole (28 mg, 0.26 mmol), diethylamine (109 μL, 1.1 mmol), copper iodide (4 mg, 0.02 mmol), $Pd(PPh_3)_4$ (22 mg; 0.02 mmol) and DMF (1 mL). The solution is degassed by bubbling argon for 5 min. The vessel is sealed and heated at 90°C overnight. The reaction mixture is cooled to RT and poured into EtOAc and water. The residue is filtered and the filtrate is dried under hign vacuum to afford **19a1** (t_R = 1.38 min, $(M+H)^+$ = 498; 500).

Step 2:

19a1 (25 mg, 0.05 mmol) is dissolved in a mixture of MeOH (1 mL) and THF (1 mL). The slurry is treated with 20 % Pd/C w/w (Degussa type E101 NE/W, 4 mg), purged under argon and then

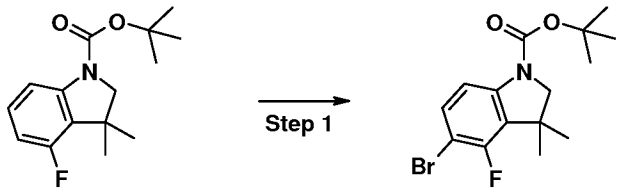
placed under H_2 (1 atm) for 16 h. The reaction mixture is filtered through an Acrodisc filter and concentrated to dryness. The residue is diluted with DMSO and purified by preparative-HPLC MeCN / H_2O (containing 5 mM of ammonium formate). The pure fractions are combined, concentrated, diluted with a mixture of MeCN / H_2O, frozen and lyophilized to afford **19a2** as a racemic mixture. The enantiomers are separated by SFC (multiple stacked injections): SFC-MS: Waters Prep 15, Column: IA 10 x 250 mm at 40ºC, Eluent A: CO_2, Eluent B: MeOH – 2mM ammonium bicarbonate, Gradient: Isocratic 50:50 CO_2:MeOH + 2 mM AmBic at 10 mL / min, Back Pressure Regulator: 150 Bars, Run Time: 12 min.
The desired fractions are collected and concentrated *in vacuo* to afford **19a2** (t_R = 1.09 min, $(M+H)^+$ 502.1;504.0).

The following compounds are prepared analogously to the procedure described in **Example 19** starting from the appropriate bromoindoline derivative.

19b2		t_R (min) 2.14; $(M+H)^+$ 464.1
19c2		t_R (min) 1.33; $(M+H)^+$ 468.1
19d2		

Example 20

Preparation of intermediate 20a1

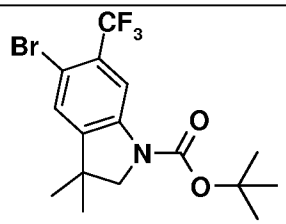
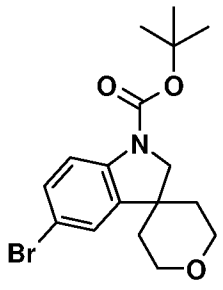
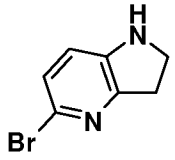


7b1 **20a1**

Step 1:

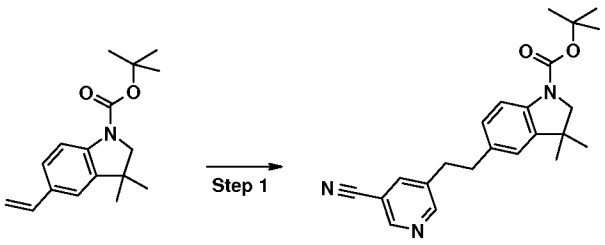
7b1 (450 mg, 1.7 mmol) is dissolved in acetonitrile (55 mL) and 1-bromo-pyrrolidine-2,5-dione (330 mg; 1.9 mmol) is added. The mixture is stirred at RT for 45 min. The reaction mixture is concentrated to about 20 mL of MeCN, diluted with EtOAc, washed with saturated aqueous $Na_2S_2O_3$, 1N NaOH (3X) and brine, dried over $MgSO_4$, filtered and concentrated to afford **20a1** (t_R = 2.14 min, $(M+H)^+$ 331; 333).

The following intermediates are prepared analogously to the procedure described in **Example 20** starting from the appropriate derivative.

20b1	
20c1	
20d1	

Example 21

Preparation of intermediate 21a1

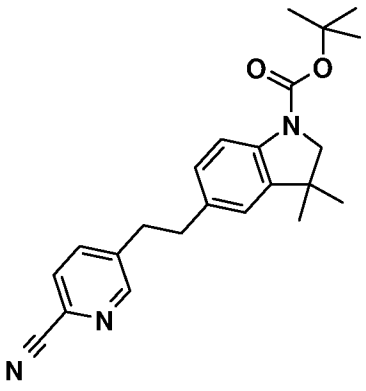


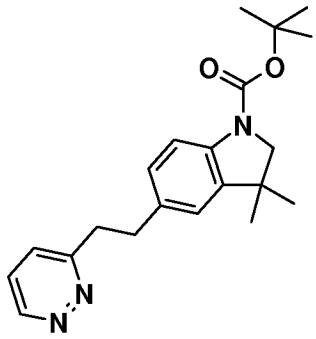
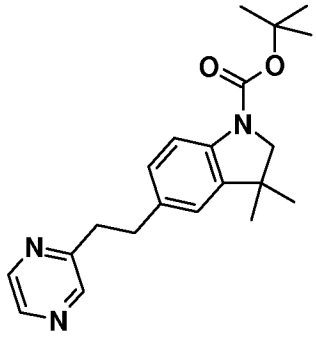
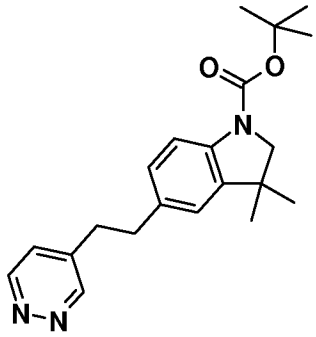
14c1 21a1

Step 1:

A solution of **14c1** (42 mg, 0.15 mmol) and 9-BBN (0.5M in THF, 1.2 mL, 0.6 mmol) is stirred at RT for 1 h. 65 µL of water is added and this mixture is stirred at RT for 10 min. A solution of K_2CO_3 (2M in water, 250µL, 0.5 mmol) is added and this mixture is stirred for 25 min. A solution of 5-bromo-nicotinonitrile (42 mg, 0.23 mmol) and $Pd(PPh_3)_4$ (8.9 mg, 0.01 mmol) in THF (0.4 mL) are added. The solution is degassed by bubbling N_2 and stirred under microwave irradiation for 20 min at 120°C. The mixture is concentrated and the residue is dissolved in EtOAc and water. The organic layers are washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product is purified by combi-flash RF (4 g column eluting 0-40% EtOAc/Hexanes) to afford **21a1** (t_R = 1.88 min, $(M+H)^+$ 378.2).

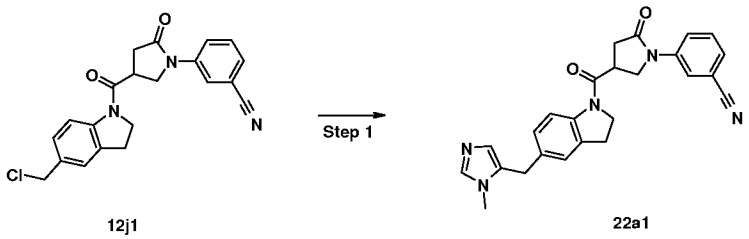
The following intermediates are prepared analogously to the procedure described in **Example 21** starting from the appropriate halo and vinylic derivatives.

21a1	

21b1	
21c1	
21d1	

Example 22

Preparation of 22a1



12j1 22a1

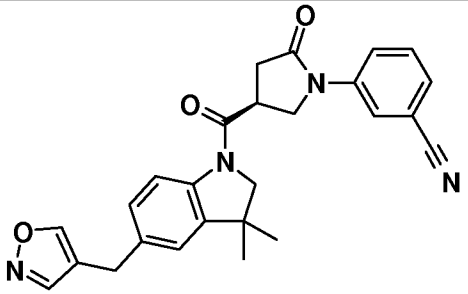
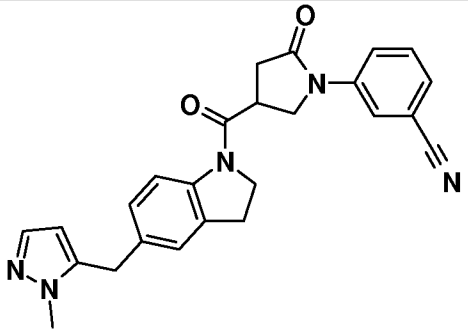
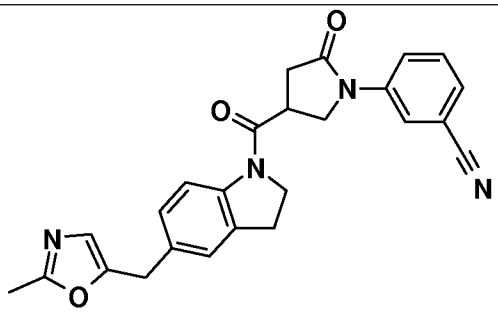
Step 1:

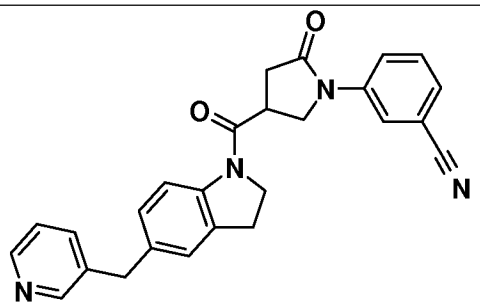
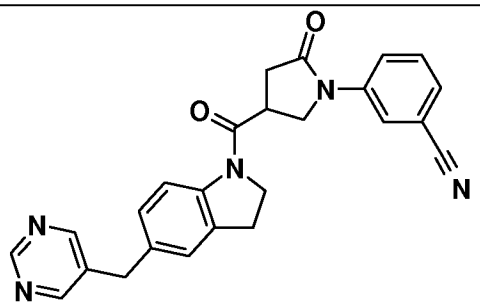
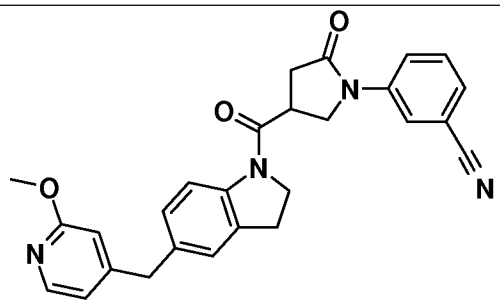
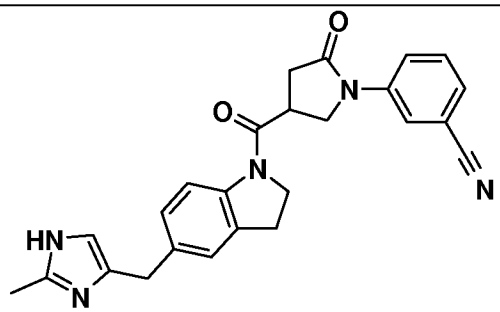
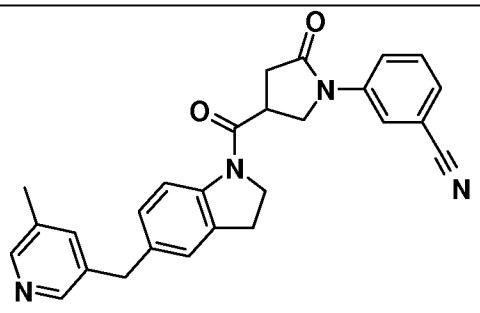
A pressure vessel equipped with a Teflon stir bar is charged with **12j1** (25 mg, 0.07 mmol), (1-methyl-1H-imidazol-5-yl)boronic acid (17 mg, 0.13 mmol), K_3PO_4 (84 mg, 0.39 mmol), $Pd(OAc)_2$

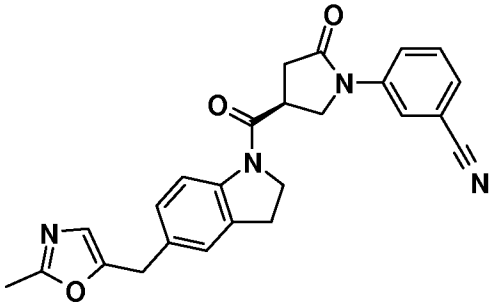
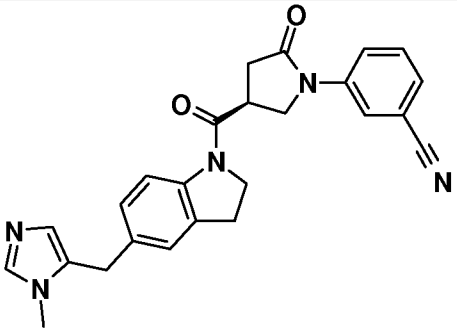
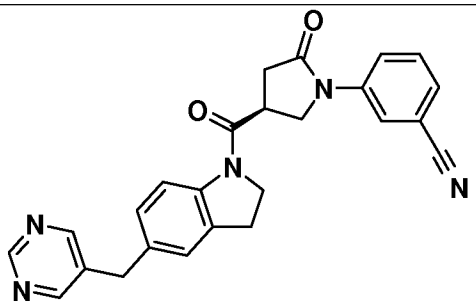
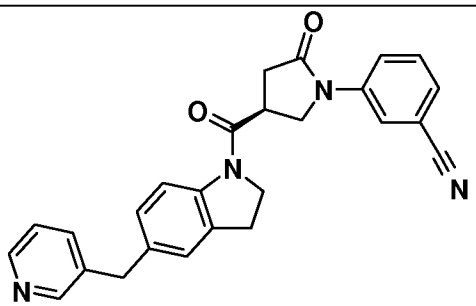
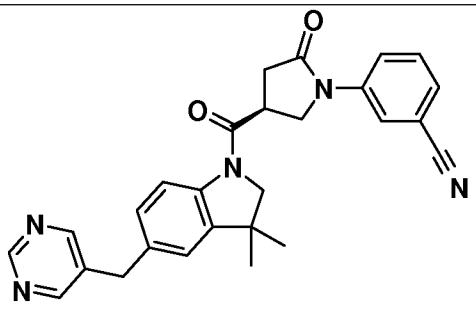
(3 mg; 0.01 mmol), triphenylphosphine (6.9 mg, 0.03 mmol) and DMF (1.6 mL). The solution is degassed by bubbling argon for 5 min. The vessel is sealed and heated under microwave irradiation at 110°C for 10 min. The reaction mixture is cooled to RT, filtered through an Acrodisc filter and purified by preparative-HPLC MeCN / H_2O (containing 5mM of ammonium formate). The pure fractions are combined, concentrated, diluted with a mixture of MeCN / H_2O, frozen and lyophilized to afford **22a1** (t_R = 1.13 min, $(M+H)^+$ 426.1).

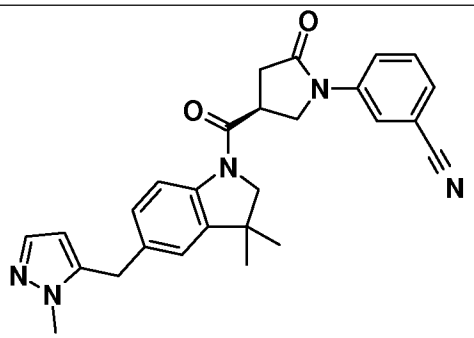
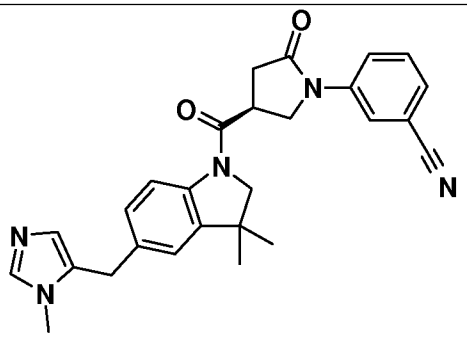
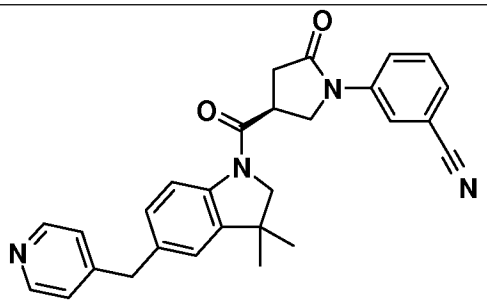
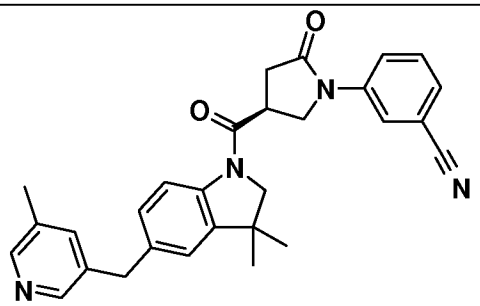
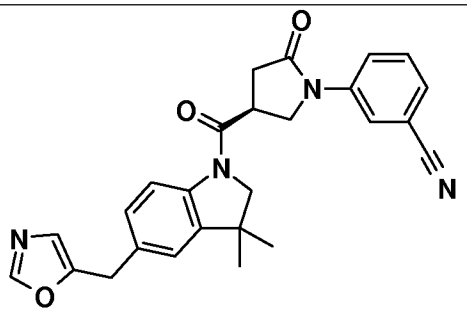
The enantiomers can be separated on SFC-MS using specific conditions from the matrix of conditions described in the general SFC procedures.

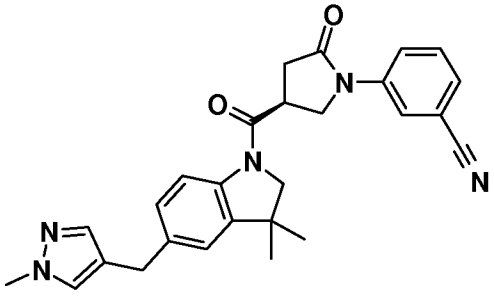
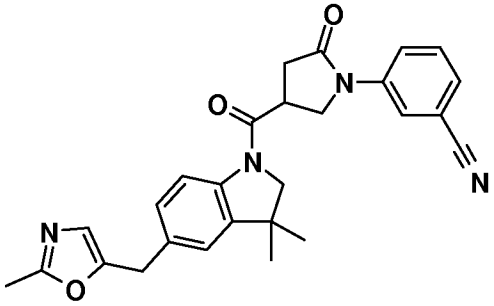
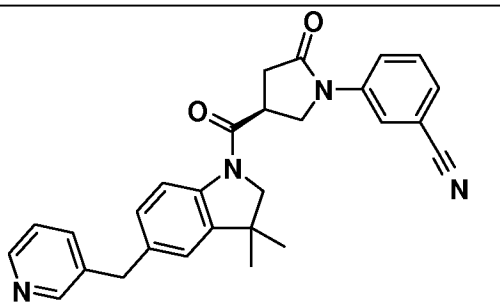
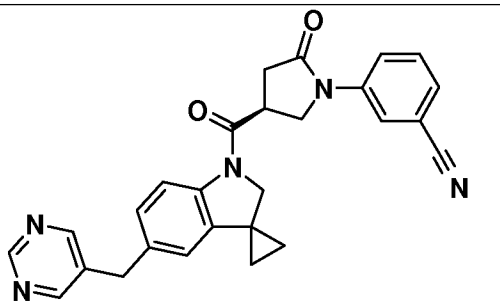
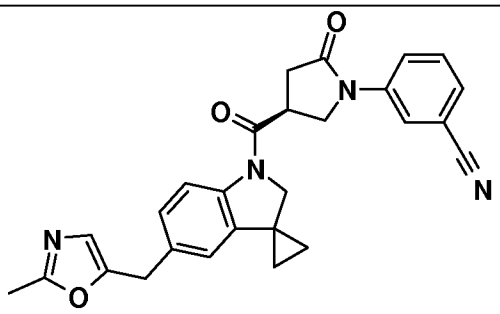
The following compounds are prepared analogously to the procedure described in **Example 22** starting from the appropriate chloro and boronic acid derivatives.

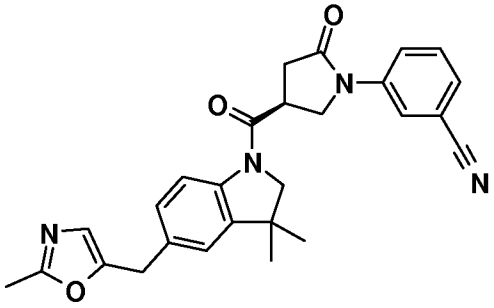
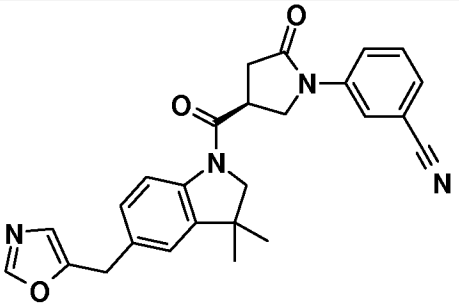
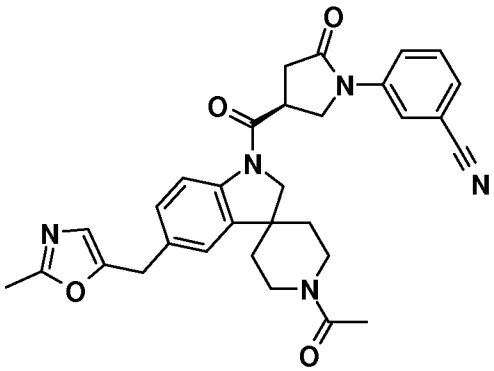
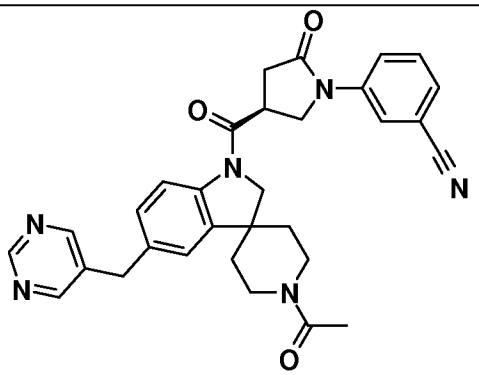
22a2		t_R (min) 1.68; $(M+H)^+$ 441.1
22b1		t_R (min) 1.13; $(M+H)^+$ 426.1
22c1		t_R (min) 1.22 $(M+H)^+$ 427.2

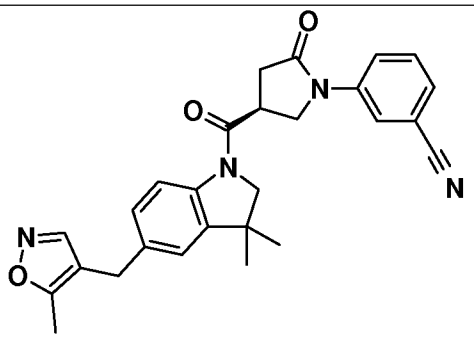
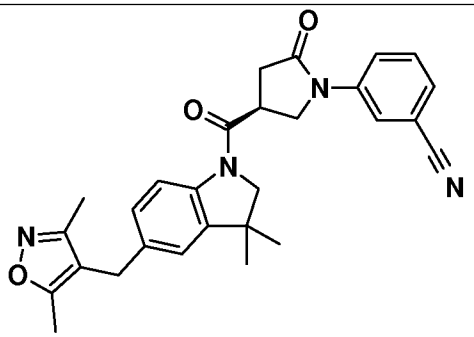
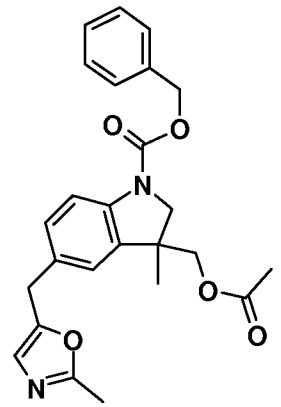
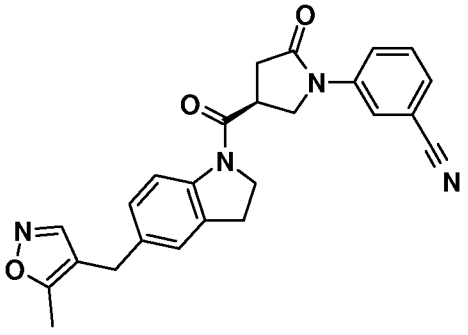
22d1		t_R (min) 1.14 $(M+H)^+$ 423.2
22e1		t_R (min) 1.07 $(M+H)^+$ 424.2
22f1		t_R (min) 1.43 $(M+H)^+$ 453.2
22g1		t_R (min) 0.81 $(M+H)^+$ 426.2
22h1		t_R (min) 1.18 $(M+H)^+$ 437.2

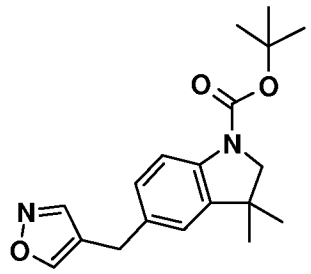
22i1		t_R (min) 1.63 $(M+H)^+$ 427.1
22j1		t_R (min) 1.08 $(M+H)^+$ 426.1
22k1		t_R (min) 1.44 $(M+H)^+$ 424.1
22l1.1		t_R (min) 1.54 $(M+H)^+$ 423.1
22l1.2		t_R (min) 1.08 $(M+H)^+$ 452.3

22m1		t_R (min) 1.17; $(M+H)^+$ 454.3
22n1		t_R (min) 0.68; $(M+H)^+$ 454.3
22o1		t_R (min) 0.76 $(M+H)^+$ 451.3
22p1		t_R (min) 0.82 $(M+H)^+$ 465.3
22q1		t_R (min) 1.15; $(M+H)^+$ 440.3

22r1		t_R (min) 1.17; $(M+H)^+$ 454.3
22s1		t_R (min) 1.20; $(M+H)^+$ 455.3
22t1		t_R (min) 0.69 $(M+H)^+$ 451.1
22u1		t_R (min) 1.57 $(M+H)^+$ 450
22v1		t_R (min) 1.75; $(M+H)^+$ 453

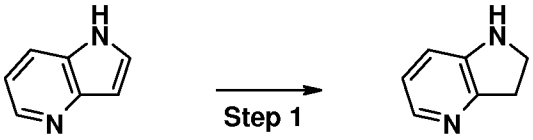
22w1		t_R (min) 1.20; $(M+H)^+$ 455.3
22x1		t_R (min) 1.17; $(M+H)^+$ 441.2
22y1		t_R (min) 1.62; (M+H)+ 538
22z1		t_R (min) 1.47; (M+H)+ 535

22aa1		t_R (min) 1.74; $(M+H)^+$ 455.1
22bb1		t_R (min) 1.79; $(M+H)^+$ 469.2
22cc1		
22dd1		t_R (min) 1.29; $(M+H)^+$ 427.1

22ee1	

Example 23

Preparation of intermediate 23a2



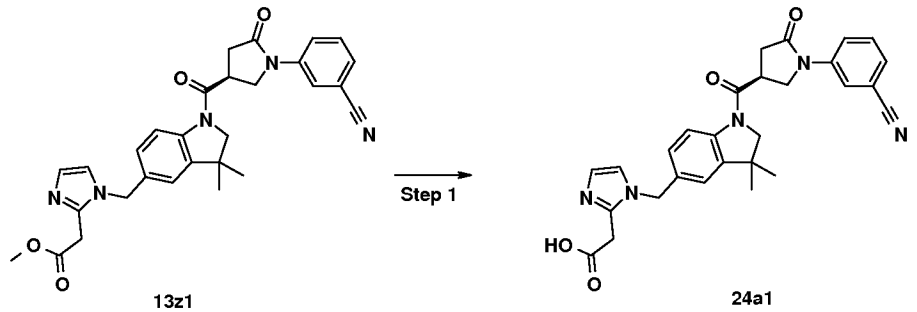
23a1 **23a2**

Step 1:

To a solution of **23a1** (Matrix, 8 g, 68 mmol) in anhydrous THF (68 mL), a 1M solution of BH_3 in THF (410 mL, 410 mmol) is added over the period of 15 min at RT. This mixture is stirred under reflux for 6 h. After cooling to RT, the reaction mixture is neutralized with addition of MeOH and concentrated under reduced pressure. The residue is dissolved in MeOH and refluxed overnight. The mixture is concentrated. The residue is dissolved in EtOAc, washed with water and brine, and dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude material is purified by flash column chromatography (silica gel 230-400 mesh; 0-3% gradient of MeOH in EtOAc) to provide **23a2**.

Example 24

Preparation of 24a1

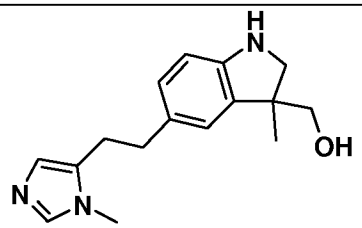
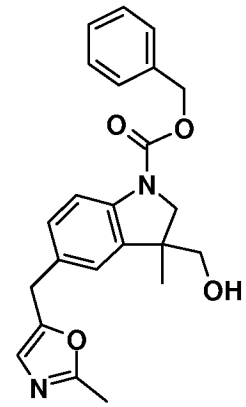
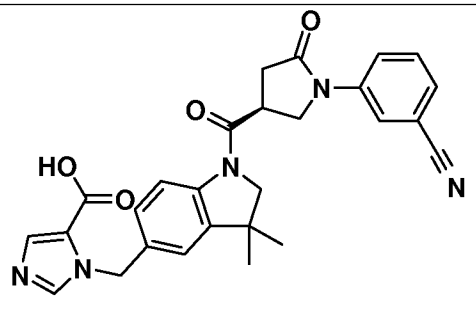


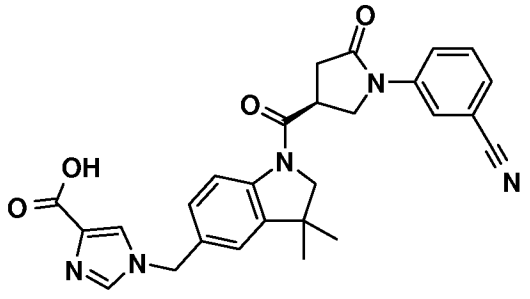
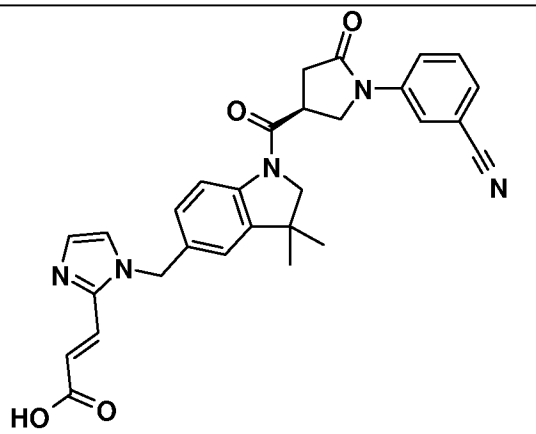
13z1 24a1

Step 1:

To **13z1** (51 mg, 0.10 mmol) in a mixture of MeOH and THF is added an aqueous solution of LiOH (2.5 M, 100 μL, 0.26 mmol). The reaction mixture is stirred at RT for 16 h, then DMSO and aqueous ammonium formate solution (5mM) are added. The solution is filtered through an Acrodisc filter and purified by preparative-HPLC MeCN / H_2O (containing 5mM of ammonium formate). The pure fractions are combined, concentrated, diluted with a mixture of MeCN / H_2O, frozen and lyophilized to afford **24a1** (t_R = 0.82 min, $(M+H)^+$ 498.3).

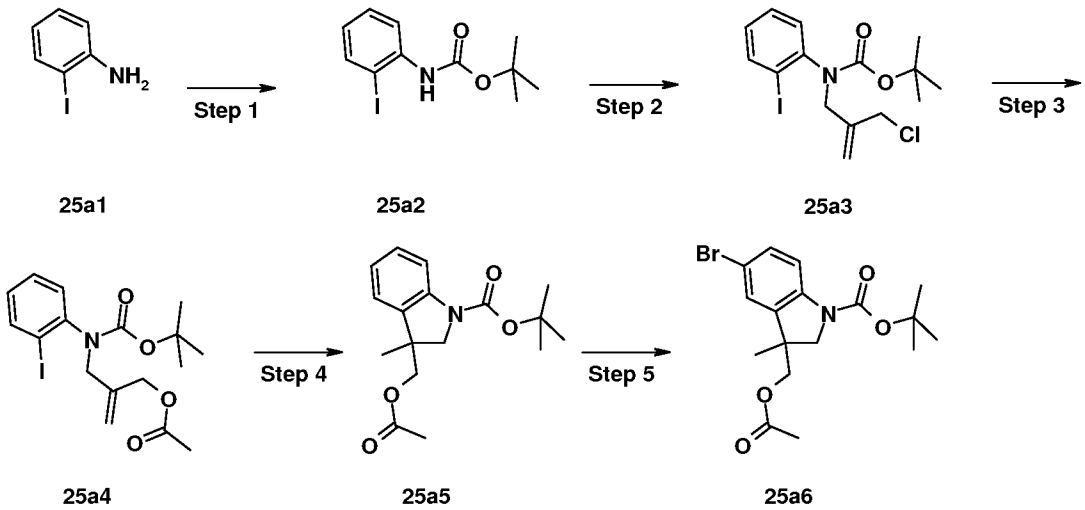
The following compounds are prepared analogously to the procedure described in **Example 24** starting from the appropriate ester derivative.

24b1		
24c1		
24d1		t_R (min) 0.84; $(M+H)^+$ 484.1

24e1		t_R (min) 0.90; $(M+H)^+$ 484.2
24f1		

Example 25

Preparation of intermediate 25a6



Step 1:

2-iodo-phenylamine **25a1** (Aldrich, 5 g, 23 mmol) dissolved in tetrahydrofuran (240 mL) is treated with boc anhydride (15 g; 68 mmol) and DMAP (280 mg, 2.3 mmol). The mixture is refluxed overnight. The reaction mixture is cooled to RT, diluted with EtOAc, washed with an aqueous solution of 10 % citric acid, water (2X) and brine, dried over $MgSO_4$, filtered and

concentrated.

The crude bis-boc product is taken into MeOH (240 mL), treated with potassium carbonate (9.5 g; 68 mmol) and refluxed for 2 h. The reaction mixture is cooled to RT and concentrated. The crude product is dissolved in EtOAc and an aqueous solution of 10 % citric acid is added. The layers are separated and the organic layer is washed with water and brine, dried over $MgSO_4$, filtered and concentrated to afford **25a2** (t_R = 1.78 min, $(M-H)^+$ 317).

Step 2:

25a2 (2 g, 6.3 mmol) is dissolved in DMF (40 mL) and cooled to 0°C. NaH (60% in mineral oil, 780 mg; 19 mmol) is added. The mixture is stirred for 15 min at 0°C and then 15 min at RT. 3-chloro-2-(chloromethyl)-1-propene (Aldrich, 2.3 mL; 20 mmol) is added and the mixture is stirred at RT for 3 h. The reaction mixture is neutralized with water and EtOAc then diluted with EtOAc and water. The layers are separated and the organic layer is washed with water (4X) and brine, dried over $MgSO_4$, filtered and concentrated to afford **25a3** (t_R = 2.13 min).

Step 3:

25a3 (2.6 g, 6.3 mmol) is dissolved in DMF (20 mL) and potassium acetate (800 mg, 8.2 mmol) is added. The mixture is stirred for 16 h at 65°C. The reaction mixture is neutralized with addition of water and extracted with EtOAc (3X). The combined organic layers are washed with water (4X) and brine, dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography eluting 10% EtOAc/Hex affords **25a4** (t_R = 1.78 min, $(M-OtBu)^+$ 375).

Step 4:

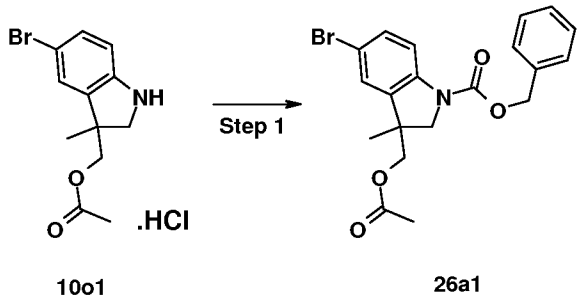
25a4 (600 mg; 1.4 mmol) is dissolved in toluene (30 mL). Triphenyltinhydride (590 mg; 1.7 mmol) is added followed by ACCN (51 mg; 0.21 mmol) and the mixture is degassed by bubbling nitrogen for 15 min. The mixture is stirred at 80°C for 1 h. Silica is added and the solvent is evaporated. Purification by flash chromatography eluting 3-5% EtOAc/Hex affords **25a5**.

Step 5:

25a5 (280 mg, 0.9 mmol) is dissolved in acetonitrile (4 mL) and 1-bromo-pyrrolidine-2,5-dione (170 mg; 0.9 mmol) is added. The mixture is stirred at RT for 60 min. The reaction mixture is concentrated, diluted with EtOAc, washed with brine, dried over $MgSO_4$, filtered and concentrated to afford **25a6** (t_R = 1.88 min).

Example 26

Preparation of intermediate 26a1



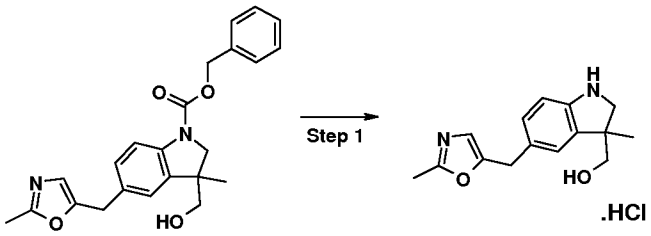
10o1 26a1

Step 1:

10o1 (109 mg, 0.38 mmol) is dissolved in acetonitrile (5.5 mL) and potassium carbonate (110 mg, 0.77 mmol) and benzyl chloroformate (60 µL, 0.42 mmol) are added. The mixture is stirred for 2 h, diluted with EtOAc, washed with water, 0.5N HCl and brine, dried over $MgSO_4$, filtered and concentrated. The crude product is purified by combi-flash RF (4 g column eluting 10% EtOAc/Hexanes) to afford **26a1** (t_R = 1.88 min, $(M+H)^+$ 417.9; 419.9).

Example 27

Preparation of intermediate 27a1



24c1 27a1

Step 1:

24c1 (26 mg, 0.07 mmol) is dissolved in THF (1mL) and MeOH (1 mL) and purged under argon. Pd/C (10 % w/w, catalytic) is added. The mixture is purged under argon and then placed under H_2 (1 atm) for 16 h. The reaction mixture is filtered through a pad of celite and washed with MeOH. The filtrate is concentrated to dryness. HCl in diethyl ether is added and the solid is collected to afford **27a1** (t_R = 1.01 min).

Example 28

Preparation of intermediate 28a2

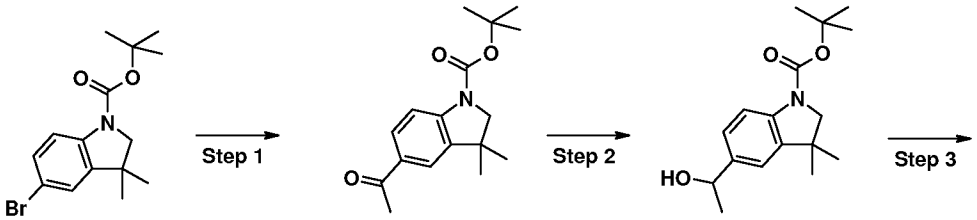
28a1 28a2

Step 1:

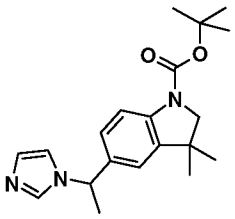
The acid **28a1** (Aldrich, 130 mg, 0.9 mmol) is weighed directly in an 8 mL vial, dissolved with MeOH (3 mL) and a 4M HCl solution in 1,4-dioxane (0.5 mL; 2 mmol) is added. The reaction mixture is allowed to stir overnight at 60 °C. The solvent is removed under reduced pressure to afford **28a2**.

Example 29

Preparation of intermediate 29a1



6c5 29a1 29a2



29a3

Step 1:

A pressure vessel equipped with a Teflon stir bar is charged with **6c5** (305 mg, 0.93 mmol), tributyl-(1-ethoxy-vinyl)-stannane (0.41 mL, 1.2 mmol), $PdCl_2(PPh_3)_2$ (98 mg; 0.14 mmol) and DMF (4.5 mL). The solution is degassed by bubbling argon for 5 min. The vessel is sealed and heated under microwave irradiation at 145°C for 30 min. The reaction mixture is cooled to RT. A 1N HCl solution (2.8 mL, 2.8 mmol) is added and this mixture is stirred at RT for 1 h. EtOAc is added. The mixture is filtered over Celite and concentrated *in vacuo*. EtOAc and water are added, the layers separated and the aqueous layer is extracted with EtOAc (2X). The combined organic layers are washed with water (2X), brine, dried over $MgSO_4$, filtered and concentrated. The crude product is purified by combi-flash RF (12 g column eluting 0-20% EtOAc/Hexanes) to

afford **29a1** (t_R = 2.04 min, $(M+H)^+$ 290.3).

Step 2:

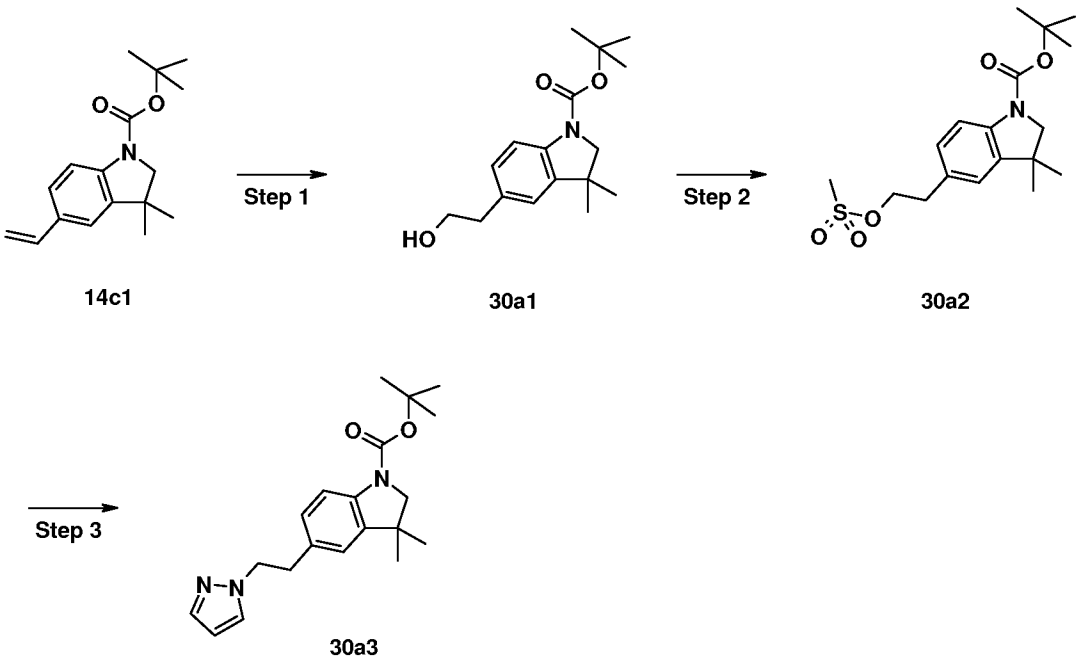
To **29a1** (60 mg, 0.21 mmol) in MeOH (2 mL) is added sodium borohydride (16 mg, 0.41 mmol) and the mixture is stirred overnight at RT. The reaction mixture is neutralized with a saturated aqueous solution of NH_4Cl. EtOAc is added and the aqueous layer is extracted with EtOAc (3X). The organic layers are washed with brine, dried with $MgSO_4$, filtered and concentrated. The crude product is purified by combiflash RF (4 g column using 0-30% EtOAc/Hex) to afford **29a2** ((t_R = 1.91 min, $(M-OH)^+$ 274.2).

Step 3:

To **29a2** (50 mg, 0.17 mmol) in THF (2 mL) is added di-imidazol-1-yl-methanone (56 mg, 0.34 mmol) and the mixture is stirred overnight at reflux. The reaction mixture is cooled to RT. EtOAc and water are added and the layers are separated. The aqueous layer is extracted with EtOAc (3X). The organic layers are washed with brine, dried with $MgSO_4$, filtered and concentrated. The crude product is purified by combiflash RF (4 g column using 0-8% MeOH/DCM) to provide **29a3** (t_R = 1.66 min, $(M+H)^+$ 342.3).

Example 30

Preparation of intermediate 30a1



14c1 30a1 30a2

30a3

Step 1:

A solution of the alkene **14c1** (200 mg, 0.73 mmol) and 9-BBN (0.5M in THF, 7.3 mL, 3.7 mmol) in THF (7 mL) is stirred at 0°C for 0.5 h and at RT for 3 h. The mixture is cooled to 0°C and 1N NaOH solution (7.3 mL, 7.3 mmol) and hydrogen peroxide solution (30% in water, 3.3 mL, 29 mmol) are added. The mixture is allowed to reach RT and stirred for 2 h. The reaction mixture is neutralized with an aqueous solution of 10% $Na_2S_2O_3$ at 0°C. The mixture is stirred at RT for 10 min and concentrated. The aqueous residue is extracted with EtOAc (3X). The combined organic layers are washed with brine, dried with $MgSO_4$, filtered and concentrated. The crude product is purified by Combiflash RF (12 g column eluting 0-40% EtOAc/Hexanes) to afford **30a1** (t_R = 1.95 min, $(M+H)^+$ 292.3).

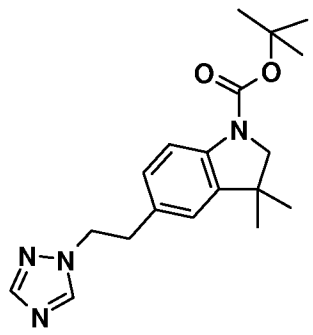
Step 2:

A solution of the alcohol **30a1** (190 mg, 0.63 mmol) and triethylamine (0.11 mL, 0.82 mmol) in DCM (3 mL) is stirred at 0°C and methanesulfonyl chloride (54 μL, 0.7 mmol) is added. The mixture is allowed to reach RT and stirred for 16 h. The reaction mixture is poured into a mixture of DCM and water and the layers are separated. The aqueous layer is extracted with DCM (3X). The combined organic layers are washed with brine, dried with $MgSO_4$, filtered and concentrated. The crude product is purified by Combiflash RF (12 g column eluting 0-40% EtOAc/Hexanes) to afford **30a2** (t_R = 1.97 min, $(M+H)^+$ 370.2).

Step 3:

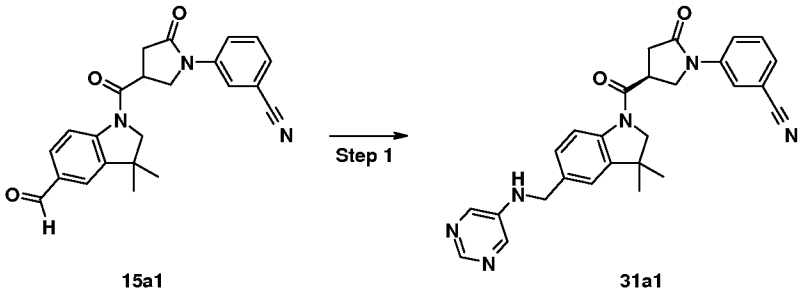
To a solution of *1H*-pyrazole (Aldrich, 18 mg, 0.27 mmol) in DMF (1.5 mL) at 0°C, is added sodium hydride (60 %, 11 mg, 0.27 mmol). This mixture is stirred at RT for 20 min. **30a2** (90 mg, 0.24 mmol) in DMF (1 mL) is added and the mixture is stirred for 1 h. The reaction mixture is poured into a mixture of EtOAc and water and layers are separated. The aqueous layer is extracted with EtOAc (3X). The combined organic layers are washed with water (2X), brine, dried with $MgSO_4$, filtered and concentrated. The crude product is purified by Combiflash RF (12 g column eluting 0-40% EtOAc/Hexanes) to afford **30a3** (t_R = 2.06 min, $(M+H)^+$ 342.0).

The following intermediates are prepared analogously to the procedure described in **Example 30** starting from the appropriate alkene and azole derivatives.

30b3	

Example 31

Preparation of 31a1



15a1 31a1

Step 1:

A 0.5-2.0 mL microwave vessel equipped with a Teflon stir bar is charged with **15a1** (20 mg; 0.05 mmol), pyrimidin-5-ylamine (25 mg; 0.26 mmol), a mixture of 2-MeTHF:AcOH 95:5 (0.80 mL) and SiliaBond Cyanoborohydride (100 mg; 0.1 mmol). The vessel is capped and heated under microwave irradiation at 120°C for 10 min. The reaction mixture is filtered through an Acrodisc filter (DMSO rinsed) and purified by preparative HPLC (Sunfire column; MeCN/AmFor at 45°C). The desired fractions are collected and concentrated. The enantiomers are separated by SFC (multiple stacked injections): SFC-MS: Waters Prep 100, Column: IB 10 x 250 mm at 40ºC, Eluent A: CO_2, Eluent B: MeOH, Gradient: Isocratic 50:50 CO_2:MeOH at 50 mL / min, Back Pressure Regulator: 150 Bars, Run Time: 10 min.

The desired fractions are collected and concentrated *in vacuo* afford to afford **31a1** (t_R = 1.01 min, $(M+H)^+$ 467.3).

EXAMPLE A

Expression vector, protein expression and purification

The codon optimized UL54 HCMV polymerase gene from strain AD169 for expression in insect cells is obtained from DNA 2.0 (Menlo Park, CA) and subcloned in 3' of the Glutathione-S-transferase (GST) gene in a pFastBac-derived vector. Bacmids and baculoviruses are generated and expression performed in Sf21 insect cells cultured in SF900 II SFM media. Infection using the baculoviruses is performed using an MOI of 5-10 and the cells are harvested 48 h post-infection and frozen.

Reagents and Materials (equivalents are acceptable):

Product	Company	Catalog #	Storage
SF900 II SFM media	Invitrogen	10902104	4 ℃
Tris	Sigma	T1503	RT
TCEP	Thermo Fisher Scientific	77720	4 °C
EDTA	Ambion	AM9262	RT
NaCl	Sigma	S6191	RT
Glycerol	Thermo Fisher Scientific	BP229-4	RT
PMSF	VWR	PB0425	RT
Leupeptin	Cedarlane	N-1000.0025	-20 °C
Antipain	MP Biomedicals	152843	-20 °C
Pepstatin A	MP Biomedicals	195368	-20 °C
Glutathione	Thermo Fisher Scientific	BP229-4	RT
Glutathione Sepharose 4B	GE Healthcare	17-0756-05	4 °C
HiTrap DEAE-Sepharose FF dolumn	GE Healthcare	17-5055-01	4 °C

All purification procedures are performed at 4℃. The cell pellet from 1 L of culture (1 x 10^9 cells) is resuspended in 25 mL of 50 mM Tris pH 7.5, 1 mM TCEP, 0.1 mM EDTA, 150 mM NaCl, 10% Glycerol, 1 mM PMSF, 2 µg/mL Leupeptin, 2 µg/mL Antipain, 2 µg/mL Pepstatin A. The solution is homogenized using a Dounce tissue grinder. Following homogenization, the volume is increased to 40 mL followed by centrifugation at 750 x g for 5 min to remove nuclei. The supernatant is then transferred and 3 cc of 50% slurry of glutathione-sepharose 4B resin is added and the mixture is incubated on a rotator for 1 h. The slurry is centrifuged at 500 g for 5 min. The supernatant is discarded and the pellet is resuspended in 10 x volume of wash buffer (50 mM Tris pH 7.5, 1 mM TCEP, 0.1 mM EDTA, 150 mM NaCl, 10% Glycerol) and incubated for 5 min. The slurry is centrifuged at 500 g for 5 min and the supernatant is discarded. The

wash step is performed 5 times. The elution is performed by adding 1.5 volume of elution buffer (50 mM Tris pH 7.5, 1 mM TCEP, 0.1 mM EDTA, 150 mM NaCl, 10% Glycerol, 20 mM glutathione) and then incubating on a rotator for 15 min. The slurry is centrifuged at 500 g for 5 min and the supernatant is removed and kept. The elution step is performed four times. The supernatant are pooled and centrifuged at 500 x g for 5 min to remove resin particles and are frozen at -80 °C.

The frozen protein is thawed and the NaCl concentration reduced to 37.5 mM by the addition of 3 volumes of DEAE buffer A (50 mM Tris pH 7.5, 1 mM TCEP, 0.1 mM EDTA, 10% Glycerol). The protein is loaded on a HiTrap DEAE-Sepharose FF column and eluted using a gradient with DEAE buffer B (50 mM Tris pH 7.5, 1 mM TCEP, 0.1 mM EDTA, 10% Glycerol, 1 M NaCl). UL54 eluted at 140 mM NaCl. The DEAE fractions are pooled, frozen and stored at -80°C. The protein concentration is determined by OD_{280} (A_{280} = 1.03 mg/mL).

EXAMPLE B

HCMV Polymerase LANCE TR-FRET Assay

This non-radiometric assay determines the enzymatic activity of purified recombinant HCMV polymerase from strain AD169 (UL54) using a Digoxigenin-labeled oligonucleotide priming a heteropolymeric template. The enzymatic activity is determined by incorporating Biotin-dUTP in the nascent complementary strand. The signal is generated by Fluorescence Resonance Energy Transfer from the donor (Anti-Digoxigenin-Europium Chelate binding with the primer) to the acceptor Streptavidin-AlloPhycoCyanin (SA-APC) binding to the biotin of the labeled nucleotides incorporated in proximity.

Reagents and Materials (equivalents are acceptable):

Product	Company	Catalog #	Storage
384-well white PP	SeaHorse	S30033W	RT
1M Hepes	Invitrogen	15630-080	4 °C
10 mg/mL BSA	New England Biolabs	B9001S	-20 °C
0.5 M TCEP pH 7.0	Thermo Fisher Scientific	77720	4 °C
0.5 M EDTA pH 8.0	Ambion	AM9262	RT
DMSO	VWR (EMD Chemicals)	CAMX1457-6	RT
KCl	Sigma	P9541	RT

NaCl	Sigma	S6191	RT
$MgCl_2$	VWR (EMD Chemicals)	CAMX0045-1	RT
Glycerol	Thermo Fisher Scientific	BP229-4	RT
Tris	Sigma	T1503	RT
10% Tween-20	Bio-Rad	161-0781	RT
Heteropolymeric template	Integrated DNA Technologies	Custom	-20 °C
Digoxigenin-labeled primer	Integrated DNA Technologies	Custom	-20 °C
100 mM Deoxynucleotide Solution	New England Biolabs	N0446S	-20 °C
1 mM Biotin-16-dUTP	Roche	11093070910	-20 °C
Streptavidin-APC	PerkinElmer	CR130-100	4 °C
Anti-Dig-Europium	PerkinElmer	Custom	4 °C
GST-UL54	Purified as described in Example A		-80 °C

Preparation of compounds:

Serial dilutions of the DMSO stock compound solution are performed using DMSO in columns 2-11 and 14-23. DMSO alone is present in columns 1, 12, 13 and 24. Three µL of the DMSO serial dilutions is transferred and diluted using 21 µL of compound dilution buffer (10 mM Hepes pH 7.5, 25 mM KCl, 5 mM $MgCl_2$, 1 mM TCEP) to obtain 12.5% DMSO. 4 µL per well of the 12.5% DMSO serial dilution compound solution is added to the assay plate. The plate is centrifuged at 200 x g for 30 sec.

LANCE TR-FRET Assay:

The assay conditions are the following: 10 mM HEPES pH 7.5, 25 mM KCl, 7.5 mM NaCl, 5 mM $MgCl_2$, 0.2 mg BSA/mL, 1 mM TCEP, 1.5% glycerol, 5% DMSO, 235 nM dATP, 350 nM dCTP, 350 nM dGTP, 235 nM dTTP, 12 nM biotin-16-dUTP, 23.5 nM Dig-primer/template, 2 nM GST-UL54. The assay volume is 10 µL. Each reagent is added as follow: 4 µL a + 3 µL b + 3 µL c; a: compound diluted in compound dilution buffer to obtain 12.5% DMSO; b: enzyme (GST-UL54) in 10 mM Hepes pH 7.5, 25 mM KCl, 5 mM $MgCl_2$, 25 mM NaCl, 5% Glycerol, 0.67 mg BSA/mL, 1mM TCEP w/o DMSO (2 nM GST-UL54 is present in the assay); c: substrate in 10 mM HEPES pH 7.5, 25 mM KCl, 5 mM $MgCl_2$, 1 mM TCEP, 783 nM dATP, 1166 nM dCTP, 1166 nM dGTP,

783 nM dTTP, 40 nM biotin-16-dUTP, 78 nM Dig-primer (5'-/Dig/ AGC TCG TTT AGT GAA CC-3' (SEQ ID NO: 1))/template (5'-GAG GTC AAA ACA GCG TGG ATG GCG TCT CCA GGC GAT CTG ACG GTT CAC TAA ACG AGC T-3' (SEQ ID NO: 2)) w/o DMSO. The primer and template are annealed in 10 mM Tris-HCl pH 7.5, 50 mM NaCl at a respective concentration of 50 µM. They are incubated at 95°C for 5 min in a dry batch block. The block is removed from the dry bath and allowed to cool to RT. Aliquots are made and stored at -20 °C.

To perform the assay, 3 µL of the enzyme solution is added to columns 2-12 and 14-24. The enzyme is substituted by the blank solution (b solution without enzyme) for columns 1 and 13 (blanks). The plate is centrifuged at 200 x g for 30 sec. 3 µL of substrate solution is added to each well. The plate is centrifuged at 200 x g for 30 sec. Plates are incubated at 37 ºC for 30 min. 5 µL of conjugate solution is added (25 mM Hepes pH 7.5, 0.1 M NaCl, 0.25% Tween-20, 1 mg/mL BSA, 12 mM EDTA, 24 nM Sreptavidin-APC, 342 ng/mL Anti-Dig-Europium). The plates are incubated at RT for at least 120 min. The signal is read on the Envision plate reader (Perkin-Elmer) or equivalent.

All compounds of the invention are tested in the assay described in Example B and show IC_{50} values in the range of 5 µM or less. Representative data is shown in the table below:

Cmpd #	IC_{50} (nM) Example B
11a1	580
16c3	600
11e1	240
11f1	95
11g1	200
11h1	94
17b1	330
13b1	34
19a2	350
13d1	110
13a1	150
13f1	140
13g1	2100
11q1	49
11r1	480
11s1	590
22a2	260
13l1	230
11t1	370
11v1	510
11bbb1	310

Cmpd #	IC_{50} (nM) Example B
19b2	990
19c2	420
13o1	3200
22l1.2	380
22o1	2900
22s1	550
13r1	360
13t1	730
22u1	570
22v1	790
22w1	470
13v1	1600
22z1	1300
22bb1	350
13w1	840
13x1	50
17n1	540
17o1	240
24a1	690
11oo1	1600
11qq1	750

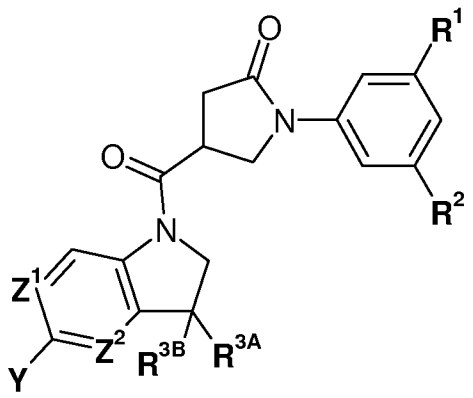
11ccc1	87
11ddd1	38
11aa1	100
11dd1	71
22j1	480
11ee1	63
11hh1	150

24d1	550
22dd1	290
31a1	86
11rr1	350
11ss1	130
11vv1	160
11zz1	99

Each reference, including all patents, patent applications, and publications cited in the present application is incorporated herein by reference in its entirety, as if each of them is individually incorporated. Further, it would be appreciated that, in the above teaching of invention, the skilled in the art could make certain changes or modifications to the invention, and these equivalents would still be within the scope of the invention defined by the appended claims of the application.

CLAIMS

1. A compound of Formula (I) or a racemate, enantiomer, diastereomer or tautomer thereof:



(I)

wherein

R^1 and R^2 are each independently selected from the group consisting of H, halo and -CN;

R^{3A} and R^{3B} are each independently selected from the group consisting of H, (C_{1-6})alkyl and (C_{3-7})cycloalkyl, wherein each said alkyl and cycloalkyl are optionally mono-, di-, or tri-substituted with R^{32};

or R^{3A} and R^{3B}, together with the C to which they are attached, are linked to form a (C_{3-7})heterocyclyl or (C_{3-7})cycloalkyl; wherein each said heterocyclyl and cycloalkyl are optionally mono-, di-, or tri-substituted with R^{32};

R^{32} is each independently selected from the group consisting of halo, -CN, OH, -O-(C_{1-6})alkyl, -C(=O)-(C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})haloalkyl and (C_{1-6})alkyl optionally mono- or di-substituted with OH, CN, -O-(C_{1-6})alkyl, $-NH_2$, -NH(C_{1-6})alkyl or -N$((C_{1-6})alkyl)_2$;

Z^1 is C(R^4) or N;

R^4 is H, halo, -CN, (C_{1-6})alkyl, OH, -O-(C_{1-6})alkyl or (C_{1-6})haloalkyl;

Y is -(C_{1-6})alkyl-R^5, -(C_{1-6})alkyl-O-R^5, -(C_{1-6})alkyl-N(R^{51})-(C_{1-6})alkyl-R^5 or -(C_{1-6})alkyl-N(R^{51})-R^5;

R^{51} is H or (C_{1-6})alkyl;

R^5 is aryl, heterocyclyl or heteroaryl; wherein each said aryl, heterocyclyl and heteroaryl are

optionally mono-, di-, or tri-substituted with $\mathbf{R^{52}}$;

$\mathbf{R^{52}}$ is each independently selected from the group consisting of (C_{1-6})alkyl, (C_{2-6})alkenyl, -CN, -OH, -O(C_{1-6})alkyl, halo, -C(=O)OH, -O-(C_{1-6})alkyl, (C_{3-7})cycloalkyl, -O-(C_{3-7})cycloalkyl, (C_{1-6})haloalkyl, $-NH_2$, -NH(C_{1-6})alkyl, -N$((C_{1-6})\text{alkyl})_2$, -$(C_{1-6})$alkyl-C(=O)OH, -$(C_{2-6})$alkenyl-C(=O)OH, -C(=O)-O-(C_{1-6})alkyl and $-C(=O)-NH_2$;

$\mathbf{Z^2}$ is C($\mathbf{R^6}$) or N;

$\mathbf{R^6}$ is H, halo, -CN, (C_{1-6})alkyl, OH, -O-(C_{1-6})alkyl or (C_{1-6})haloalkyl;

or a salt thereof.

2. The compound according to claim 1, wherein one of $\mathbf{R^1}$ and $\mathbf{R^2}$ is halo or –CN and the other of $\mathbf{R^1}$ and $\mathbf{R^2}$ is H;

or a pharmaceutically acceptable salt thereof.

3. The compound according to claim 2, wherein one of $\mathbf{R^1}$ and $\mathbf{R^2}$ is Cl or –CN and the other of $\mathbf{R^1}$ and $\mathbf{R^2}$ is H;

or a pharmaceutically acceptable salt thereof.

4. The compound according to any one of claims 1 to 3, wherein $\mathbf{R^{3A}}$ and $\mathbf{R^{3B}}$ are each independently selected from the group consisting of H or (C_{1-6})alkyl, optionally mono- or di-substituted with OH or –O-(C_{1-6})alkyl;

or $\mathbf{R^{3A}}$ and $\mathbf{R^{3B}}$, together with the C to which they are attached, are linked to form a (C_{3-7})cycloalkyl; optionally mono- or di-substituted with halo, -CN, OH, -O-(C_{1-6})alkyl, -C(=O)-(C_{1-6})alkyl, (C_{1-6})haloalkyl and (C_{1-6})alkyl;

or a pharmaceutically acceptable salt thereof.

5. The compound according to claim 4, wherein $\mathbf{R^{3A}}$ and $\mathbf{R^{3B}}$ are each independently selected

from the group consisting of H and (C_{1-6})alkyl;

or a pharmaceutically acceptable salt thereof.

6. The compound according to any one of claims 1 to 5, wherein $\mathbf{Z^1}$ is C($\mathbf{R^4}$); $\mathbf{R^4}$ is H, halo, -CN, (C_{1-6})alkyl, OH, -O-(C_{1-6})alkyl or (C_{1-6})haloalkyl;

or a pharmaceutically acceptable salt thereof.

7. The compound according to claim 6, wherein $\mathbf{Z^1}$ is CH;

or a pharmaceutically acceptable salt thereof.

8. The compound according to any one of claims 1 to 7, wherein **Y** is -(C_{1-6})alkyl-$\mathbf{R^5}$ or -(C_{1-6})alkyl-N($\mathbf{R^{51}}$)-$\mathbf{R^5}$ and $\mathbf{R^{51}}$ is H or (C_{1-6})alkyl;

or a pharmaceutically acceptable salt thereof.

9. The compound according to claim 8, wherein **Y** is (C_{1-6})alkyl-$\mathbf{R^5}$**;**

or a pharmaceutically acceptable salt thereof.

10. The compound according to any one of claims 1 to 9, wherein $\mathbf{R^5}$ is a heterocyclyl or heteroaryl, wherein each said heterocyclyl and heteroaryl are optionally mono-, di-, or tri-substituted with $\mathbf{R^{52}}$**;**

$\mathbf{R^{52}}$ is each independently selected from the group consisting of (C_{1-6})alkyl, -CN, -OH, -O(C_{1-6})alkyl, halo, -C(=O)OH, -O-(C_{1-6})alkyl, (C_{1-6})haloalkyl, $-NH_2$, -NH(C_{1-6})alkyl, -N$((C_{1-6})\text{alkyl})_2$, -$(C_{1-6})$alkyl-C(=O)OH, (C_{2-6})alkenyl and -(C_{2-6})alkenyl-C(=O)OH;

or a pharmaceutically acceptable salt thereof.

11. The compound according to claim 10, wherein $\mathbf{R^5}$ is a 5- or 6-membered heteroaryl, optionally mono-, di-, or tri-substituted with $\mathbf{R^{52}}$;

$\mathbf{R^{52}}$ is each independently selected from the group consisting of (C_{1-6})alkyl, -CN, -OH, -O(C_{1-6})alkyl, halo, -C(=O)OH, -O-(C_{1-6})alkyl, (C_{1-6})haloalkyl, $-NH_2$, -NH(C_{1-6})alkyl and -N$((C_{1-6})\text{alkyl})_2$;

or a pharmaceutically acceptable salt thereof.

12. The compound according to any one of claims 1 to 11, wherein $\mathbf{Z^2}$ is C($\mathbf{R^6}$); $\mathbf{R^6}$ is H, halo, -CN, (C_{1-6})alkyl, OH, -O-(C_{1-6})alkyl or (C_{1-6})haloalkyl;

or a pharmaceutically acceptable salt thereof.

13. The compound according to claim 12, wherein $\mathbf{Z^2}$ is CH;

or a pharmaceutically acceptable salt thereof.

14. The compound according to any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, as a medicament.

15. Use of a compound according to any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prevention of CMV disease and/or infection in a human being.

16. A pharmaceutical composition comprising a compound according to any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/067670

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 C07D403/08 C07D403/14 C07D413/14 C07D471/04
C07D487/10 C07D491/107 A61P31/22 A61K31/404 A61K31/407
A61K31/421 A61K31/4178 A61K31/4439 A61K31/4196 A61K31/497

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	US 4 423 050 A (VERHEYDEN JULIEN P H [US] ET AL) 27 December 1983 (1983-12-27) examples 2-3 claim 1	1-16
A	WO 2004/106345 A2 (UPJOHN CO [US]; SCHNUTE MARK E [US]; CUDAHY MICHELE M [US]; EGGEN MARI) 9 December 2004 (2004-12-09) claims 1, 39	1-16
A	WO 03/059911 A2 (UPJOHN CO [US]; CUDAHY MICHELE M [US]; SHNUTE MARK E [US]; TANIS STEVE) 24 July 2003 (2003-07-24) claims 1, 76, 90	1-16

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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

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