

Compounds and Their Use in Treating Cancer

FIELD

5 This specification relates to certain Proteolysis Targeting Chimera (PROTAC) compounds and, as a minimum, their ability to degrade the Androgen Receptor (AR) and therefore their use for the treatment of diseases or disorders dependent on the androgen receptor in mammals. Degradation of androgen receptors may provide, for example, an anti-tumour effect and accordingly this specification relates in part to the use of such compounds for the treatment of cancer and to pharmaceutical compositions containing them. It also relates to
10 intermediate compounds that may be useful in the preparation of such PROTACs.

BACKGROUND

15 Traditional small molecule drugs reversibly (or sometimes irreversibly) bind to a target protein as a means of modulating a given biological activity. In contrast, PROTACs bind to their target proteins, but then bring about the target protein's degradation. Having achieved this effect, the PROTAC is in theory able to repeat this process with another target protein. Accordingly, unlike with "traditional small molecule" inhibitors, the PROTAC-driven degradation mechanism can in theory operate in a sub-stoichiometric manner – meaning that more modest exposures of a PROTAC compound could still achieve a desired level of efficacy
20 *in vivo*. In practice this can mean that the degradation power (DC_{50} and D_{max}) of a PROTAC can have an improved effect than that reflected only by its binding affinity.

 At a simplistic level, PROTAC molecules are often described as having three parts – (1) a part that is capable of binding to the target protein to be degraded, (2) a second part that is capable of binding to an E3 ubiquitin ligase, and finally, a linker that connects (1) and (2) together.

25 In use, the PROTAC binds to both the target protein and E3 ubiquitin ligase simultaneously to form a ternary complex. The E3 ligase then recruits an E2 conjugating enzyme to the ternary complex, which ubiquitinates the target protein. This has the effect of labelling the target protein for degradation by the cell's proteasome machinery. A PROTAC can then dissociate from the target protein and initiate another cycle of this process in a catalytic manner. Meanwhile, the ubiquitinated target proteins are recognized and degraded
30 by the cell's proteasome machinery.

 This PROTAC-mediated approach may be valuable as a method of treating certain diseases where the targeted degradation of specific bodily proteins may be beneficial, for example in the treatment of cancer. One such cancer-related target is the androgen receptor.

35 The androgen receptor (AR) belongs to the steroid hormone group of nuclear receptors and is a ligand-dependent transcription factor which controls the expression of a range of genes involved in growth and survival of prostate cells. AR is composed of four distinct domains: the N-terminal domain (NTD), DNA binding domain (DBD), a hinge region which allows the N- and C-termini to interact and a C-terminal ligand binding domain (LBD). Androgens such as testosterone and its derivative dihydrotestosterone (DHT) bind to the AR ligand binding domain which releases AR chaperone proteins allowing AR to dimerise and translocate
40 from the cytoplasm into the nucleus. Within the nucleus receptor dimers bind to androgen response elements

(AREs) in the promoters of androgen responsive genes such as PSA and FKBP5. The AR signalling pathway is critical for normal prostate development and male sexual differentiation fails to occur in the absence of androgens or without a functioning AR.

5 The relationship between androgens and prostate cancer was first discovered in a seminal study by Huggins and Hodges in 1941 and subsequent work has shown that androgen deprivation therapy is highly effective in the treatment of recurrent prostate cancer. However, despite good responses initially most tumour cells adapt to low androgen levels and patients relapse within a few years developing a disease state known as castrate resistant prostate cancer (CRPC). Several second generation antiandrogens have been approved by the US FDA for the treatment of CRPC. These include enzalutamide, apalutamide and darolutamide, which all
10 compete with androgens for binding to the ligand binding domain. As well as antagonising the AR, preventing its activation, they also inhibit nuclear translocation and DNA binding thus effectively shutting down AR signalling. In contrast abiraterone acetate is an androgen biosynthesis inhibitor which targets cytochrome p450 enzyme 17 α -hydroxylase-17,20-lyase (CYP17). Testosterone is processed in the testes and adrenal glands by CYP17 and therefore inhibition of this enzyme inhibits prostate tumour growth by decreasing circulating
15 androgen levels.

Whilst the above-mentioned drugs significantly prolong survival of patients with late stage prostate cancer they are not curative and resistance inevitably occurs. However, it is clear that the AR remains central to the progression of CRPC meaning there is still a need to develop alternative AR inhibitors. Several resistance mechanisms have been identified including AR amplification, mutation or the generation of splice
20 variants that lack the ligand binding domain. Mutations in the ligand binding domain, for example F877L or L702H, can convert antagonists into agonists or allow the receptor to utilise alternative steroid hormones such as glucocorticoids or progesterone. Agents that degrade AR, removing it from the cell could therefore help tackle these forms of resistance. As such, AR PROTACs, which bind the ligand binding domain of the androgen receptor and simultaneously recruit an E3 ligase such as cereblon leading to ubiquitination and
25 degradation of AR via the proteasome, could offer therapeutic benefit to patients with prostate cancer, particularly metastatic CRPC. AR PROTACs may also be useful against AR+ breast cancer.

Given that the above-mentioned resistance mutations that can occur in the ligand binding domain and may limit the effectiveness of known CRPC treatments, it would be beneficial to develop AR degrading PROTACs that do not just target the “wild-type” AR, but which are also effective in degrading clinically
30 relevant mutated forms of AR too.

Whichever target protein binding unit (1) is used at one end of a PROTAC’s linker unit, a fundamental element that must always be present at the other end of a PROTAC molecule is a unit (2) that helps to direct the tagging of the target protein for degradation, for example an E3 ubiquitin ligase cereblon binder unit. Scientific endeavours have already provided a number of such E3 ubiquitin ligase cereblon binder
35 units and further examples are demonstrated hereinafter by the present researchers.

WO2018/071606 describes certain PROTAC compounds said to be AR degraders.

As with “traditional small molecule” binders and PROTACs alike, there is always the issue of “off-target” activity *in vivo* which can be important to avoid in the development of safe and effective drug treatments. In other words, a given binding unit may be very potent against the intended target, but if it is

inadvertently potent against other unintended biological targets in the human body, it may cause unacceptable toxicities, side effects and so on.

It is therefore an ongoing challenge to develop potent molecules for pharmaceutical use that are also suitably selective – i.e. avoiding inhibition/binding/degradation of unintended biological targets *in vivo*.

5 For example, the present researchers have surprisingly found that certain compounds of this specification show beneficial selectivity that is expected to avoid or reduce the risk of mitotoxicity *in vivo*.

As part of developing current and future PROTAC drug treatments for medicinal use (e.g. cancer), there is still a need to develop androgen receptor PROTAC compounds that have a combination of beneficial/improved properties. As mentioned above, development of PROTACs that target both wild-type AR
10 and one or more clinically relevant mutated forms of AR is an example of such a combination effect.

Furthermore, there is a need to develop androgen receptor binder units that can be incorporated into a PROTAC, regardless of which an E3 ubiquitin ligase cereblon binder unit is selected for use at the other end of the molecule.

15 Other properties of interest during pharmaceutical discovery and development of such PROTACs may relate to selectivity profile, absorption/bioavailability, distribution, metabolism, elimination, toxicity and side-effect profile, stability, manufacturability and so on.

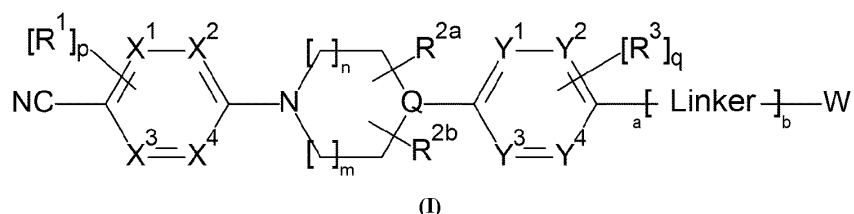
SUMMARY

20 The compounds of this specification provide, as a minimum, potent AR binding units suitable for incorporation into PROTAC compounds, and to PROTAC compounds containing such AR binding units together with an E3 ubiquitin ligase cereblon binder unit at the other end of the PROTAC molecule. Certain AR binding units are advantageously configured to degrade not only the wild-type AR, but also one or more clinically relevant mutant forms of AR too, for example L702H. Certain PROTAC compounds of this
25 specification also have a surprisingly beneficial combination of properties, e.g. relating to AR degradation and selectivity/safety profile in combination.

This specification relates to the above-mentioned AR-binding units and to PROTAC compounds (and pharmaceutically acceptable salts thereof) that incorporate such AR binding units together with an E3
ubiquitin ligase cereblon binder unit (the two units being linked by a linker).

30 This specification also relates to pharmaceutical compositions containing such PROTACs (and pharmaceutically acceptable salts thereof) and their use in methods of treatment in the human or animal body, for example in the treatment or prevention of cancer. This specification also relates to processes and intermediate compounds (and salts thereof) involved in the preparation of said PROTACs.

According to the first aspect of this specification there is provided a compound of Formula (I):



or a pharmaceutically acceptable salt thereof,

wherein:

X^1 is C & 0, 1 or 2 of X^2 , X^3 & X^4 is/are N, and are otherwise C;

or

5 X^3 & X^4 are both C and are substituted by $-X^5=X^6-X^7=X^8-$ with X^5 attached to X^3 and with X^8 attached to X^4 , where 1 or 2 of X^1 , X^2 , X^5 , X^6 , X^7 & X^8 is/are N, and are otherwise C;

p is 1 or 2 and X^1 is C attached to R^1 when X^3 & X^4 are not substituted by $-X^5=X^6-X^7=X^8-$; and otherwise p is 0, 1 or 2;

10 where:

each R^1 is a substituent on any C atom at X^1 , X^2 , X^3 & X^4 , (or at X^1 , X^2 , X^5 , X^6 , X^7 & X^8 when X^3 & X^4 are substituted by $-X^5=X^6-X^7=X^8-$), and is/are independently selected from F, Cl, C_{1-3} alkyl and C_{1-3} alkoxy, wherein said C_{1-3} alkyl and C_{1-3} alkoxy may be independently optionally substituted by one or more F;

15

n is 0, 1 or 2;

m is 0 or 1;

Q is CH or N when n & m are both other than 0 and otherwise Q is CH;

R^{2a} and R^{2b} are substituents on the same or different C atoms other than at Q , each independently selected from H, F and C_{1-3} alkyl, or R^{2a} & R^{2b} together form a $-(CH_2)_r-$ group where r is 1, 2 or 3;

20

0, 1 or 2 of Y^1 , Y^2 , Y^3 & Y^4 is/are N, and are otherwise C;

each R^3 is a substituent on any C atom at Y^1 , Y^2 , Y^3 & Y^4 , and is/are independently selected from F, Cl, CN, C_{1-3} alkyl and C_{1-3} alkoxy, wherein said C_{1-3} alkyl and C_{1-3} alkoxy may be independently optionally substituted by one or more F;

25

q is 0, 1 or 2;

Linker is a saturated or a partially or fully unsaturated framework comprising C and H atoms and at least one heteroatom, wherein said framework has end points of attachment 'a' and 'b' and a minimum length of from 6 to 26 atoms between 'a' and 'b'; wherein said framework may include one or more straight and/or branched chains and/or rings and is optionally substituted on any available C atom(s) by one or more F; and

30

W is an E3 ubiquitin ligase cereblon binder unit.

35

This specification also describes, in part, a pharmaceutical composition which comprises a compound of **Formula (I)**, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

This specification also describes, in part, a compound of **Formula (I)**, or a pharmaceutically acceptable salt thereof, for use in therapy.

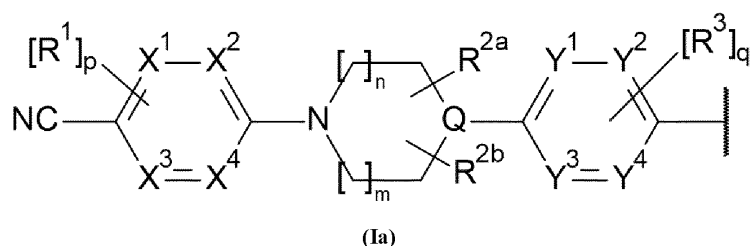
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This specification also describes, in part, a compound of **Formula (I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer.

This specification also describes, in part, a method for treating cancer in a warm-blooded animal in need of such treatment, which comprises administering to the warm-blooded animal a therapeutically effective amount of a compound of **Formula (I)**, or a pharmaceutically acceptable salt thereof.

As shown in the experimental section hereinafter, the present researchers have not just developed a range of beneficial AR binding units, but gained an understanding about where such binding units can incorporate a linker (leading to an E3 ubiquitin ligase cereblon binder unit) without it interfering with their AR binding capability. Accordingly the present researchers understand that when incorporating their AR binding units into a PROTAC, the linker of said PROTAC should not attach at the left or central rings in **Formula (I)** shown hereinabove, but may suitably attach at the specified position on the right-hand ring in the compound of **Formula (I)** as shown herein.

Therefore, in a further aspect of this specification there is provided a PROTAC compound or a pharmaceutically acceptable salt thereof, containing an E3 ubiquitin ligase cereblon binder unit and an AR binding unit of **Formula (Ia)**:



where **R¹**, **p**, **X¹**, **X²**, **X³**, **X⁴**, **n**, **m**, **R^{2a}**, **R^{2b}**, **Q**, **Y¹**, **Y²**, **Y³**, **Y⁴**, **R³** and **q** may take any of the values defined herein for each of these integers respectively.

For avoidance of doubt  in **Formula (Ia)** indicates a point of connection via a single covalent bond to the remainder of the PROTAC compound.

In one embodiment there is provided a PROTAC compound or a pharmaceutically acceptable salt thereof, containing an E3 ubiquitin ligase cereblon binder unit linked to an AR binding unit of **Formula (Ia)** as described herein.

As described herein, the link between an E3 ubiquitin ligase cereblon binder unit and an AR binding unit of **Formula (Ia)** as shown hereinabove preferably has a length corresponding to the length of a linear chain of from 6 to 26 atoms, said atoms being linked by single covalent bonds and each selected from carbon or a heteroatom (i.e. O, N or S).

As described herein, the link between an E3 ubiquitin ligase cereblon binder unit and an AR binding unit of **Formula (Ia)** as shown hereinabove preferably has a length corresponding to the length of a linear chain of from 7 to 14 atoms, said atoms being linked by single covalent bonds and each selected from carbon or a heteroatom (i.e. O, N or S).

In one embodiment, the link between an E3 ubiquitin ligase cereblon binder unit and an AR binding unit of **Formula (Ia)** as shown hereinabove preferably has a length corresponding to the length of a linear chain of from 6 to 26 atoms, said atoms being linked by single covalent bonds and each selected from C, N or O.

5 In one embodiment, the link between an E3 ubiquitin ligase cereblon binder unit and an AR binding unit of **Formula (Ia)** as shown hereinabove preferably has a length corresponding to the length of a linear chain of from 7 to 14 atoms, said atoms being linked by single covalent bonds and each selected from C, N or O.

10 It is to be understood that although a link length “corresponding to the length of [certain atoms in a chain]” it is not to be interpreted that this limits said link to said atoms, and for example sulfur atom(s) may also be present in the link even if S atoms are not included in the length descriptor.

As described herein, the link between an E3 ubiquitin ligase cereblon binder unit and an AR binding unit of **Formula (Ia)** as shown hereinabove preferably has a length of from 0.9 nm to 4 nm.

15 As described herein, the link between an E3 ubiquitin ligase cereblon binder unit and an AR binding unit of **Formula (Ia)** as shown hereinabove preferably has a length of from 1.0 nm to 2.2 nm.

In a further aspect of the specification there is provided an androgen receptor binding unit of **Formula (Ia)**, as described herein, for use in a PROTAC compound (or pharmaceutically acceptable salt thereof) that also contains an E3 ubiquitin ligase cereblon binder unit.

20 In a further aspect of the specification there is provided an androgen receptor binding unit of **Formula (Ia)**, as described herein, for use in a PROTAC compound (or pharmaceutically acceptable salt thereof) that is linked to an E3 ubiquitin ligase cereblon binder unit.

Accordingly, there is provided an androgen receptor binding unit of **Formula (Ia)**, as described herein, for use in a PROTAC compound (or pharmaceutically acceptable salt thereof) where said PROTAC compound also contains an E3 ubiquitin ligase cereblon binder unit.

25 Accordingly, there is provided an androgen receptor binding unit of **Formula (Ia)**, as described herein, for use in a PROTAC compound (or pharmaceutically acceptable salt thereof) where said PROTAC compound also contains an E3 ubiquitin ligase cereblon binder unit that is linked to said androgen receptor binding unit.

30 Accordingly, there is provided an androgen receptor binding unit of **Formula (Ia)**, as described herein, for incorporation into a PROTAC compound (or pharmaceutically acceptable salt thereof) where said PROTAC compound also contains an E3 ubiquitin ligase cereblon binder unit.

35 Accordingly, there is provided an androgen receptor binding unit of **Formula (Ia)**, as described herein, for incorporation into a PROTAC compound (or pharmaceutically acceptable salt thereof) where said PROTAC compound also contains an E3 ubiquitin ligase cereblon binder unit that is linked to said androgen receptor binding unit.

Therefore, there is provided an androgen receptor binding unit of **Formula (Ia)**, as described herein, contained within a PROTAC compound (or a pharmaceutically acceptable salt thereof) where said PROTAC compound also contains an E3 ubiquitin ligase cereblon binder unit.

40 Therefore, there is provided an androgen receptor binding unit of **Formula (Ia)**, as described herein, contained within a PROTAC compound (or a pharmaceutically acceptable salt thereof) where said PROTAC

compound also contains an E3 ubiquitin ligase cereblon binder unit that is linked to said androgen receptor binding unit.

- 5 In one embodiment the link between androgen receptor binding unit of **Formula (Ia)** [as described above] and an E3 ubiquitin ligase cereblon binder unit is a **Linker** as defined according to any embodiment or claim herein, where the point of attachment shown in **Formula (Ia)** above connects to the 'a' point of connection on any **Linker** as defined herein.

DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

- 10 Many embodiments of this disclosure are detailed throughout the specification and will be apparent to a reader skilled in the art.

- A pharmaceutically acceptable salt of a compound of **Formula (I)** or PROTAC compound described herein may be, for example, an acid-addition salt when said compound contains a basic functional group, such as an amine. An acid-addition salt may be formed using an inorganic acid or an organic acid. A
15 pharmaceutically acceptable salt of said compound may be, for example, a base-addition salt when said compound contains an acidic functional group, such as a carboxylic acid. An acid-addition salt may be formed using an inorganic base or an organic base. "Pharmaceutically acceptable salt" is used to specify that the salt is suitable for use in the human or animal body. An example list of pharmaceutically acceptable salts can be found in the *Handbook of Pharmaceutical Salts: Properties, Selection and Use*, P. H. Stahl and C. G. Wermuth, editors, Weinheim/Zurich: Wiley-VCH/VHCA, 2002. A pharmaceutically acceptable salt of a
20 compound of **Formula (I)** or PROTAC compound includes such salts that may be formed within the human or animal body after administration of said compound to said human or animal body.

- As used herein the term "alkyl" includes straight chain, branched chain and cyclic alkyl groups and combinations thereof having the specified number of carbon atoms. Therefore, C₁₋₃alkyl includes methyl,
25 ethyl, *n*-propyl, isopropyl and cyclopropyl; and C₁₋₉alkyl would include (4-isopropylcyclohexyl)methyl. The same principles apply to the term "alkoxy". Similarly, as used herein the term "alkoxy" includes straight chain, branched chain and/or cyclic alkoxy groups having the specified number of carbon atoms. Therefore, C₁₋₃alkoxy includes methoxy, ethoxy, *n*-propoxy, isopropoxy and cyclopropoxy.

- In this specification chemical abbreviations familiar to the skilled person may be used including for
30 example "Me" = methyl, "Et" = ethyl, "Pr" = propyl, "Bu" = butyl and "Ph" = phenyl.

- Where the term "optionally" is used, it is intended that the subsequent feature may occur or may not occur. As such, use of the term "optionally" includes instances where the feature is present, and also instances where the feature is not present. For example, "methyl optionally substituted by one or more F" includes -CH₃, -CH₂F, -CHF₂ and -CF₃.

- 35 The term "substituted" means that one or more hydrogens on the designated atom or group is replaced by the indicated substituent(s) provided that any atom(s) bearing such substituent(s) maintains its permitted valency where the skilled person understands that the standard valencies of carbon, nitrogen and oxygen are 4, 3 and 2 respectively. Therefore, "substituted on any available C atom(s)" is to be understood to mean that the substituent(s) is/are limited in their positioning (and/or potentially in their number) according to whether there

are any hydrogen atoms remaining on the designated atom or group which could be replaced by said substituent(s).

The dashed bonds included in **Z**, “-----”, indicate the possibility that the bond may in each case be a single covalent bond or a double covalent bond - in accordance with the atom (or group of atoms) present at each of the **X^E**, **X^F**, **X^G**, **X^H** and **X^J** positions. The skilled person understands that the standard valencies of carbon, nitrogen and oxygen are as mentioned above, and as such they can understand whether each dashed bond should be interpreted as a single bond or a double bond in any given **Z** group in the compound of **Formula (I)**. The same applies to the **X^{E2}**, **X^{F2}**, **X^{G2}**, **X^{H2}** and **X^{J2}** positions in **Z^A**.

The term “adjacent” or “adjacent position” - for example in reference to **X^G**, **X^H** and **X^J** of **Z** refers to the next closest position in the molecular chain/ring system. Accordingly, in the context of **Z**: **X^G** and **X^H** are adjacent each other, **X^H** and **X^J** are also adjacent each other, but **X^G** is not adjacent **X^J**.

The term “saturated” means that the atoms of the specified framework or group are linked only by single covalent bonds. Accordingly, the term “unsaturated” means that the specified framework or group contains double and/or triple covalent bonds. Examples of unsaturated molecular fragments that may be present within a partly or fully unsaturated group or framework are C=C, C=N, C=O, N=N, C≡C or C≡N in cases where nitrogen and oxygen heteroatoms are permitted/present, and may also include S=O in cases where sulfur heteroatoms are also permitted/present.

It is to be understood that “heteroatom” may represent an oxygen, nitrogen or sulfur atom unless explicitly further limited in a given context.

The term “minimum length of [...] atoms between ‘a’ and ‘b’” refers to the shortest chain of atoms in the chain between ‘a’ and ‘b’. Therefore, if the chain consisted of -CH₂CH₂CH₂-, the number of atoms in the chain is 3 (the hydrogen atoms are regarded as not being in the chain). Alternatively if the chain consisted of 1,3-phenylene, where the shorter route around the phenyl ring contains 3 C atoms and the long route around the phenyl ring contains 5 C atoms, the minimum length of such a chain would be counted as 3 atoms.

It is to be understood that the points of attachment ‘a’ and ‘b’ each represent single covalent bonds to the relevant adjacent groups/atoms.

It is to be understood that in this specification “rings” or “heterocyclic groups” may include single rings, fused rings, spirocyclic rings and bridged rings.

In reference to the **Linker**, as described herein, it is to be understood that the branching, where present may be present on a chain (even a chain of 1 atom length) and/or on a ring. The skilled person would generally interpret in this manner, but for the avoidance of doubt, it is to be understood that the “branching” that occurs inherently in order to form a ring is not considered “branching” in the context of the **Linker** embodiments described herein. It is to be understood that said branches may occur on the same or different atoms of the **Linker** framework. For example it is possible to have two “=O” branches on a sulfur heteroatom in order to form a SO₂ group within the **Linker** framework. **Linker #22** described hereinafter is an example where there is one branch (-Me) coming from a chain within the **Linker**.

It is further to be understood that ‘branches’ (and definitions for branches provided herein) refer to branches that branch off the main chain of atoms between ‘a’ and ‘b’, leading to a ‘dead end’ in the molecular structure.

In this specification it is to be understood that the point of attachment of a given group to some other group (via a single covalent bond) may be represented by a line meeting a bond substantially at right angles to said bond, for example as shown on the far right-hand side of **Formula (Ia)** herein, and for example at either end of **Linkers** 1 to 46 depicted hereinafter.

- 5 In this specification when “0, 1 or 2 of X^A , X^B , X^C , X^D , X^E & X^F is/are N where X^E & X^F are not both N, and are otherwise C” - certain of the C atoms are to be understood to implicitly possess a hydrogen atom where necessary in order to satisfy the standard valency (4) for carbon atoms. The skilled person will understand that such H atom cannot be present on a C at X^E or X^F or on a C at X^A , X^B , X^C or X^D when a substituent or **Linker** is attached to said carbon. The same principle applies in respect of X^1 , X^2 , X^3 , X^4 (and with X^5 , X^6 , X^7 & X^8 where present), and also with Y^1 , Y^2 , Y^3 & Y^4 . The same applies to X^{A2} , X^{B2} , X^{C2} , X^{D2} , X^{E2} , X^{F2} , X^{G2} , X^{H2} & X^{J2} .

In this specification a reference to a secondary or tertiary amine is intended to have the normal meaning in the art and therefore a nitrogen atom that is part of an amide group or a sulphonamide group, for example, is not to be regarded as a secondary or tertiary amine.

- 15 In this specification a saturated heterocyclic group refers to at least one ring of atoms (including bridged rings, spiro rings, fused rings, and single rings) containing carbon atoms and at least one heteroatom, where the heteroatom(s) is/are each independently selected from N, O and S, and where each atom in the ring is linked to its adjacent atoms by single covalent bonds. Therefore, an example of a heterocyclic group is a spiro heterocyclic group having two rings and a total of one heteroatom such as 9-azasprio[5.5]undecane.
- 20 Typically, a saturated heterocyclic group will have at least two carbon atoms separating each of the heteroatom(s) present in said group to ensure a suitable level of chemical stability for use in a pharmaceutical context. Where reference is made to a “nitrogen-containing saturated (or partially unsaturated) heterocyclic group” this requires the presence of at least one nitrogen heteroatom but does not limit the possibility of one or more non-nitrogen heteroatoms (i.e. S, O) being present in addition. In this specification a partially
- 25 unsaturated heterocyclic group refers to at least one ring of atoms (including bridged rings, spiro rings, fused rings, and single rings) containing carbon atoms and at least one heteroatom, where the heteroatom(s) is/are each independently selected from N, O and S, and where at least two atoms within the heterocyclic group are connected to each other via a double covalent bond. As the skilled person would understand, partially unsaturated does not include fully unsaturated heterocyclic groups – i.e. where the group contains the
- 30 maximum possible number of double bonds for the atomic framework in question. Where reference is made to a cyclic group (e.g. a heterocyclic group) having a specified number of ring atoms, this includes the atoms making up the ring (including atoms involved in the bridge of a bridged ring, and all atoms of a fused or spiro ring) but does not include any hydrogen atoms or other substituent atoms attached to the ring atoms. Therefore, for example, a cyclic group which is 1,4-piperazin-1,4-diyl has 6 ring atoms (4C
- 35 and 2N).

- In this specification an alkylene group (for example a C_{1-5} alkylene) is a saturated group consisting only of carbon and hydrogen atoms with two points of attachment to adjacent atoms/groups. They may include straight chain(s), branched chain(s) and/or ring(s). Accordingly C_1 alkylene represents $-CH_2-$, a C_2 alkylene can represent $-CH_2CH_2-$ or $-CH(Me)-$, C_{1-5} alkylene includes for example $-CH_2(cyclobut-1,3-diyl)-$. A “straight
- 40 chain C_{u1-u2} alkylene” corresponds to $-(CH_2)_n-$ where u is an integer from u1 to u2.

In this specification a hydrocarbyl group means any group consisting only of C and H atoms. For example, C₁₋₇-hydrocarbyl includes methyl, phenyl and *p*-tolyl.

The term “therapy” is intended to have its normal meaning of dealing with a disease in order to entirely or partially relieve one, some or all of its symptoms, or to correct or compensate for the underlying pathology. The term “therapy” also includes “prophylaxis” or “prophylactic” unless there are specific indications to the contrary. The terms “therapeutic” and “therapeutically” should be interpreted in a corresponding manner.

The term “prophylactic” is intended to have its normal meaning and includes primary prophylaxis to prevent the development of the disease and secondary prophylaxis whereby the disease has already developed and the patient is temporarily or permanently protected against exacerbation or worsening of the disease or the development of new symptoms associated with the disease.

The term “treatment” is used synonymously with “therapy”. Similarly the term “treat” can be regarded as “applying therapy” where “therapy” is as defined herein.

Some values of variable groups are as follows. One, two or more of such values, may be used in any combination with any other definitions, claims, aspects or embodiments herein (unless the context doesn't permit) to provide further embodiments/claims of the specification.

In one embodiment **X**¹ is C & 0 or 1 of **X**², **X**³ & **X**⁴ is N and are otherwise C; or **X**³ & **X**⁴ are both C and are substituted by **-X**⁵=**X**⁶-**X**⁷=**X**⁸- with **X**⁵ attached to **X**³ and **X**⁸ attached to **X**⁵, where 1 of **X**¹, **X**², **X**⁵, **X**⁶, **X**⁷ & **X**⁸ is N, and are otherwise C.

In one embodiment **X**¹ is C & 0, 1 or 2 of **X**², **X**³ & **X**⁴ is N and are otherwise C.

In one embodiment **X**¹ is C & 0 or 1 of **X**², **X**³ & **X**⁴ is N and are otherwise C.

In one embodiment **X**¹ is C & 1 or 2 of **X**², **X**³ & **X**⁴ is/are N and are otherwise C.

In one embodiment **X**¹ is C & 1 of **X**², **X**³ & **X**⁴ is N and are otherwise C.

In one embodiment **X**¹, **X**², **X**³ & **X**⁴ are all C.

In one embodiment **X**¹ & **X**² are C and **X**³ & **X**⁴ are both C and are substituted by **-X**⁵=**X**⁶-**X**⁷=**X**⁸- with **X**⁵ attached to **X**³ and **X**⁸ attached to **X**⁵, where 1 of **X**⁵, **X**⁶, **X**⁷ & **X**⁸ is N, and are otherwise C.

In one embodiment **X**³ & **X**⁴ are both C and are substituted by **-X**⁵=**X**⁶-**X**⁷=**X**⁸- with **X**⁵ attached to **X**³ and **X**⁸ attached to **X**⁵, **X**⁶ & **X**⁷ are all C and **X**⁸ is N.

In one embodiment each **R**¹ is a substituent on **X**¹, and when **p** is 2, on any other C atom at **X**², **X**³ & **X**⁴, (or each **R**¹ is a substituent at **X**¹, **X**², **X**⁵, **X**⁶, **X**⁷ or **X**⁸ when **X**³ & **X**⁴ are substituted by **-X**⁵=**X**⁶-**X**⁷=**X**⁸-), and in each case is independently selected from F, Cl, Me, cyclopropyl, CHF₂, CF₃ and OMe.

In one embodiment each **R**¹ is a substituent on **X**¹, and when **p** is 2, on any other C atom at **X**², **X**³ & **X**⁴ when **X**³ & **X**⁴ are not substituted by **-X**⁵=**X**⁶-**X**⁷=**X**⁸-, and the values of **R**¹ is/are otherwise as defined herein.

In one embodiment each **R**¹ is selected from Cl, F, C₁₋₃alkyl (optionally substituted by one or more F) and C₁₋₃alkoxy.

In one embodiment **p** is 1 or 2 and **X**¹ is C attached to **R**¹ when **X**³ & **X**⁴ are not substituted by **-X**⁵=**X**⁶-**X**⁷=**X**⁸-, and otherwise **p** is 1 or 2.

In one embodiment **p** is 1 or 2 and **X**¹ is C attached to **R**¹ when **X**³ & **X**⁴ are not substituted by

-X⁵=**X**⁶-**X**⁷=**X**⁸-, and otherwise **p** is 0 or 1.

- In one embodiment p is 1 or 2 and X^1 is C attached to R^1 when X^3 & X^4 are not substituted by $-X^5=X^6-X^7=X^8-$, and otherwise p is 0.
- In one embodiment p is 1 and X^1 is C attached to R^1 when X^3 & X^4 are not substituted by $-X^5=X^6-X^7=X^8-$, and otherwise p is 0, 1 or 2.
- 5 In one embodiment p is 2 and X^1 is C attached to R^1 when X^3 & X^4 are not substituted by $-X^5=X^6-X^7=X^8-$, and otherwise p is 0, 1 or 2.
- In one embodiment p is 2 and X^1 is C attached to R^1 when X^3 & X^4 are not substituted by $-X^5=X^6-X^7=X^8-$, and otherwise p is 0.
- 10 In one embodiment p is 0 and X^3 & X^4 are both C and are substituted by $-X^5=X^6-X^7=X^8-$ with X^5 attached to X^3 and X^8 attached to X^4 .
- In one embodiment p is 1 or 2 and X^3 & X^4 are not substituted by $-X^5=X^6-X^7=X^8-$.
- In one embodiment p is 1 or 2; X^3 & X^4 are not substituted by $-X^5=X^6-X^7=X^8-$, and X^1 is C attached to R^1 where R^1 is CF_3 .
- In one embodiment p is 1; X^3 & X^4 are not substituted by $-X^5=X^6-X^7=X^8-$, and X^1 is C attached to R^1 .
- 15 In one embodiment p is 1; X^3 & X^4 are not substituted by $-X^5=X^6-X^7=X^8-$, and X^1 is C attached to R^1 where R^1 is CF_3 .
- In one embodiment p is 1 and R^1 is selected from Cl, C_{1-3} alkyl (optionally substituted by one or more F) and C_{1-3} alkoxy.
- In one embodiment p is 1 and R^1 is selected from Cl, Me, cyclopropyl, CHF_2 , CF_3 and OMe.
- 20 In one embodiment p is 1, X^1 is C attached to R^1 , where R^1 is selected from Cl, Me, cyclopropyl, CHF_2 , CF_3 and OMe.
- In one embodiment p is 1, X^1 is C attached to R^1 , X^3 & X^4 are not substituted by $-X^5=X^6-X^7=X^8-$, and R^1 is selected from Cl, Me, cyclopropyl, CHF_2 , CF_3 and OMe.
- In one embodiment p is 1 or 2; X^3 & X^4 are not substituted by $-X^5=X^6-X^7=X^8-$; X^1 is C attached to an R^1 where said R^1 is selected from Cl, C_{1-3} alkyl (optionally substituted by one or more F) and C_{1-3} alkoxy, and if present (i.e. when p is 2) the other R^1 is F.
- 25 In one embodiment p is 1 or 2; X^3 & X^4 are not substituted by $-X^5=X^6-X^7=X^8-$; X^1 is C attached to an R^1 where said R^1 is selected from Cl, Me, cyclopropyl, CHF_2 , CF_3 and OMe, and if present (i.e. when p is 2) the other R^1 is F.
- 30 In one embodiment p is 1 or 2; X^3 & X^4 are not substituted by $-X^5=X^6-X^7=X^8-$; X^1 is C attached to R^1 where R^1 is selected from Cl, Me, cyclopropyl, CHF_2 , CF_3 and OMe, and if present (i.e. when p is 2) the additional R^1 substituent is F attached to X^2 where X^2 is C.
- In one embodiment p is 1 and R^1 is C_{1-3} alkyl optionally substituted by one or more F.
- In one embodiment p is 1 and R^1 is methyl, cyclopropyl, CF_3 or CHF_2 .
- 35 In one embodiment p is 1 and R^1 is CF_3 or CHF_2 .
- In one embodiment p is 1 and R^1 is CHF_2 .
- In one embodiment p is 1 and R^1 is CF_3 .
- In one embodiment p is 1 and R^1 is methyl.
- In one embodiment p is 1 and R^1 is cyclopropyl.
- 40 In one embodiment p is 1 and R^1 is methoxy.

The above 8 embodiments may for example be in the context where X^3 & X^4 are not substituted by $-X^5=X^6-X^7=X^8-$, X^1 is C and the above-mentioned R^1 is a substituent on said C at X^1 .

In one embodiment p is 2; X^1 & X^2 are both C; X^3 & X^4 are not substituted by $-X^5=X^6-X^7=X^8-$; and the values of R^1 are such that X^1 is substituted by CF_3 and X^2 is substituted by F.

- 5 In one embodiment p is 1; X^3 & X^4 are not substituted by $-X^5=X^6-X^7=X^8-$; X^1 , X^2 , X^3 & X^4 are all C and R^1 is a substituent on X^1 as defined herein.

In one embodiment p is 1; X^3 & X^4 are not substituted by $-X^5=X^6-X^7=X^8-$; X^1 , X^2 , X^3 & X^4 are all C and R^1 is a substituent on X^1 and is CF_3 .

In one embodiment p is 2, and one R^1 is CF_3 and the other R^1 is F or ethyl.

- 10 In one embodiment p is 2, and one R^1 is CF_3 and the other R^1 is F.

In one embodiment p is 2, and one R^1 is CF_3 and the other R^1 is ethyl.

In one embodiment p is 2, X^1 is C attached to a first R^1 and X^2 is C attached to a second R^1 .

In one embodiment p is 2, X^1 is C attached to a CF_3 and X^2 is C attached to either F or ethyl.

In one embodiment p is 2, X^1 is C attached to a CF_3 and X^2 is C attached to F.

- 15 In one embodiment p is 2, X^1 is C attached to a CF_3 and X^2 is C attached to ethyl.

The above 7 embodiments may for example be in the context where X^3 & X^4 are not substituted by $-X^5=X^6-X^7=X^8-$.

In one embodiment n is 0.

In one embodiment n is 1.

- 20 In one embodiment n is 2.

In one embodiment m is 0.

In one embodiment m is 1.

In one embodiment n is 0 and m is 1.

In one embodiment n is 1 and m is 1.

- 25 In one embodiment n is 0 and m is 0.

In one embodiment n is 0, 1 or 2; and m is 1.

In one embodiment n is 1, m is 1 and Q is CH.

In one embodiment n is 1, m is 1 and Q is N.

In one embodiment n is 1, m is 1, Q is CH or N, R^{2a} is H and R^{2b} is H.

- 30 In one embodiment n is 1, m is 1, Q is CH, R^{2a} is H and R^{2b} is H.

In one embodiment n is 0, m is 1, Q is CH, R^{2a} is H and R^{2b} is H

In one embodiment n is 1, m is 0, R^{2a} is H and R^{2b} is C_{1-3} alkyl attached to a C atom other than at Q , where said C atom has an (*R*)-stereochemical configuration.

In one embodiment n is 1, m is 0, R^{2a} is H and R^{2b} is C_{1-3} alkyl attached to a C atom other than at Q , where said C atom has an (*S*)-stereochemical configuration.

- 35 In one embodiment n is 1, m is 1, R^{2a} is H and R^{2b} is C_{1-3} alkyl attached to a C atom other than at Q , where said C atom has an (*R*)-stereochemical configuration.

In one embodiment n is 1, m is 1, R^{2a} is H and R^{2b} is C_{1-3} alkyl attached to a C atom other than at Q , where said C atom has an (*S*)-stereochemical configuration.

- 40 In one embodiment n is 1, m is 1, Q is N, R^{2a} is H and R^{2b} is H.

- In one embodiment **Q** is CH with an (*R*)-stereochemical configuration at said C atom.
- In one embodiment **Q** is CH with an (*S*)-stereochemical configuration at said C atom.
- In one embodiment **n** is 2; **m** is 1; **R^{2a}** & **R^{2b}** are both H; and **Q** is CH.
- In one embodiment **n** is 2; **m** is 1; **R^{2a}** & **R^{2b}** are both H; and **Q** is CH with an (*R*)-stereochemical configuration at said C atom.
- 5 In one embodiment **n** is 2; **m** is 1; **R^{2a}** & **R^{2b}** are both H; and **Q** is CH with an (*S*)-stereochemical configuration at said C atom.
- In one embodiment **R^{2a}** and **R^{2b}** are substituents on the same or different C atoms other than at **Q**, each independently selected from H and C₁₋₃alkyl.
- 10 In one embodiment **R^{2a}** and **R^{2b}** are substituents on the same or different C atoms other than at **Q**, each independently selected from H and Me.
- In one embodiment **R^{2a}** and **R^{2b}** are substituents on the same or different C atoms adjacent **Q** and are otherwise as defined herein.
- In one embodiment **R^{2a}** and **R^{2b}** are substituents on the same or different C atoms adjacent **Q**, each independently selected from H and C₁₋₃alkyl (for example Me).
- 15 In one embodiment **R^{2a}** and **R^{2b}** are substituents on the same or different C atoms and are both H.
- In one embodiment **R^{2a}** and **R^{2b}** are substituents on the same or different C atoms other than at **Q**, each independently selected from H, F and C₁₋₃alkyl.
- In one embodiment **R^{2a}** and **R^{2b}** are substituents on the same or different C atoms other than at **Q**, each independently selected from H and C₁₋₃alkyl, or **R^{2a}** & **R^{2b}** together form a -(CH₂)_r- group where **r** is 1, 2 or 3.
- 20 In one embodiment **r** is 1.
- In one embodiment **r** is 2.
- In one embodiment **r** is 3.
- 25 In one embodiment **R^{2a}** and **R^{2b}** are substituents on the same or different C atoms other than at **Q**, where **R^{2a}** is Me and **R^{2b}** is H.
- In one embodiment **R^{2a}** and **R^{2b}** are substituents on the same C atom other than at **Q**, where **R^{2a}** and **R^{2b}** are both Me.
- In one embodiment **R^{2a}** and **R^{2b}** are substituents on the same C atom adjacent **Q**, where **R^{2a}** and **R^{2b}** are both Me.
- 30 In one embodiment **Y¹**, **Y²**, **Y³** & **Y⁴** are respectively selected from (C, C, C, C), (N, C, C, C), (C, N, C, C) and (N, C, N, C).
- In one embodiment 0 or 1 of **Y¹**, **Y²**, **Y³** & **Y⁴** is N and are otherwise C.
- In one embodiment 1 or 2 of **Y¹**, **Y²**, **Y³** & **Y⁴** is/are N and are otherwise C.
- 35 In one embodiment **Y¹**, **Y²**, **Y³** & **Y⁴** are respectively selected from (N, C, C, C), (C, N, C, C) and (N, C, N, C).
- In one embodiment 1 of **Y¹**, **Y²**, **Y³** & **Y⁴** is N and are otherwise C.
- In one embodiment **Y¹** is N; and **Y²**, **Y³** & **Y⁴** are all C.
- In one embodiment **Y²** is N; and **Y¹**, **Y³** & **Y⁴** are all C.
- In one embodiment 2 of **Y¹**, **Y²**, **Y³** & **Y⁴** are N and are otherwise C.
- 40 In one embodiment **Y¹** & **Y³** are N; and **Y²** and **Y⁴** are C.

- In one embodiment Y^1 , Y^2 , Y^3 & Y^4 are all C.
- In one embodiment q is 0 or 1.
- In one embodiment q is 0.
- In one embodiment q is 1.
- 5 In one embodiment q is 2.
- In one embodiment q is 0, 1 or 2 and R^3 (when present) is a substituent on any C atom at Y^1 , Y^2 , Y^3 & Y^4 selected from F, CN and C_{1-3} alkyl.
- In one embodiment q is 0, 1 or 2 and R^3 (when present) is a substituent on any C atom at Y^1 , Y^2 , Y^3 & Y^4 selected from F and C_{1-3} alkyl.
- 10 In one embodiment q is 0 or 1 and R^3 (when present) is a substituent on any C atom at Y^1 , Y^2 , Y^3 & Y^4 selected from F or C_{1-3} alkyl.
- In one embodiment q is 0 or 1 and R^3 (when present) is a substituent on any C atom at Y^1 , Y^2 , Y^3 & Y^4 selected from F or Me.
- In one embodiment R^3 (when present) is C_{1-3} alkyl.
- 15 In one embodiment R^3 (when present) is Me.
- In one embodiment R^3 (when present) is F.
- In one embodiment R^3 (when present) is CN.
- In one embodiment q is 1 and R^3 is attached to C at Y^1 .
- In one embodiment q is 1 and R^3 is attached to C at Y^1 , and R^3 is selected from F, CN and Me.
- 20 In one embodiment q is 2 and both R^3 groups are F.
- In one embodiment q is 2 and the R^3 groups are attached to C at Y^1 and Y^3 .
- In one embodiment q is 2 and each R^3 group is F, which are attached to C at Y^1 and Y^3 .
- In one embodiment **Linker** is a saturated or a partially or fully unsaturated framework comprising C and H atoms and at least one heteroatom, wherein said framework has end points of attachment 'a' and 'b' and a minimum length of from 6 to 26 atoms between 'a' and 'b'; wherein said framework may include one or more straight and/or branched chains and/or rings and is optionally substituted on any available C atom(s) by one or more F.
- 25
- In one embodiment the framework of the **Linker** is a saturated or partially unsaturated framework.
- In one embodiment the framework of the **Linker** is a saturated framework.
- 30 In one embodiment the framework of the **Linker** comprises C and H atoms and at least two heteroatoms.
- In one embodiment the framework of the **Linker** comprises C and H atoms and at least two heteroatoms selected from O and N.
- In one embodiment the framework of the **Linker** comprises C and H atoms and at least one nitrogen heteroatom.
- 35 In one embodiment the framework of the **Linker** comprises C and H atoms and at least two heteroatoms including at least one nitrogen heteroatom.
- In one embodiment the framework of the **Linker** comprises C and H atoms and at least one nitrogen heteroatom in the form of a secondary or tertiary amine.
- In one embodiment the framework of the **Linker** comprises C and H atoms and at least one nitrogen
- 40 heteroatom in the form of a tertiary amine.

- In one embodiment the framework of the **Linker** comprises C and H atoms and at least two heteroatoms including at least one nitrogen heteroatom in the form of a secondary or tertiary amine.
- In one embodiment the framework of the **Linker** comprises C and H atoms and at least two heteroatoms including at least one nitrogen heteroatom in the form of a tertiary amine.
- 5 In one embodiment the **Linker** has a minimum length of from 6 to 20 atoms between 'a' and 'b'.
- In one embodiment the **Linker** has a minimum length of from 6 to 15 atoms between 'a' and 'b'.
- In one embodiment the **Linker** has a minimum length of from 7 to 14 atoms between 'a' and 'b'.
- In one embodiment the total number of C and hetero atoms in the **Linker** framework is from 6 to 26.
- In one embodiment the total number of C and hetero atoms in the **Linker** framework is from 7 to 24.
- 10 In one embodiment the total number of C and hetero atoms in the **Linker** framework is from 8 to 22.
- In one embodiment the total number of C and hetero atoms in the **Linker** framework is from 9 to 20.
- In one embodiment when **W** is $-\text{Z}-\text{R}^{\text{A}}$, the **Linker** is attached at any available C atom at X^{B} or X^{C} of **Z**.
- In one embodiment the framework of the **Linker** may include one or more straight chains and/or rings and is optionally substituted on any available C atom(s) by one or more F.
- 15 In one embodiment the framework of the **Linker** consists of one or more straight chains and/or rings that are optionally substituted on any available C atom(s) by one or more F.
- In one embodiment the framework of the **Linker** may include (or consist of) one or more straight and/or branched chains and/or rings (wherein the total number of branches is from 0 to 5) that are optionally substituted on any available C atom(s) by one or more F.
- 20 In one embodiment the framework of the **Linker** may include (or consist of) one or more straight and/or branched chains and/or rings (wherein the total number of branches is from 0 to 3) that are optionally substituted on any available C atom(s) by one or more F.
- In one embodiment the framework of the **Linker** may include (or consist of) one or more straight and/or branched chains and/or rings (wherein the total number of branches is 0 or 1) that are optionally
- 25 substituted on any available C atom(s) by one or more F.
- In one embodiment the total number of branches is 0.
- In one embodiment the total number of branches is 1.
- In one embodiment the total number of branches is 2.
- In one embodiment the total number of branches is 3.
- 30 In one embodiment any/each branch in the framework of a **Linker** has from 1 to 5 C and/or hetero atoms.
- In one embodiment any/each branch in the framework of a **Linker** has 1 or 2 C and/or hetero atoms.
- In one embodiment any/each branch in the framework of a **Linker** has 1 C and/or hetero atom.
- In one embodiment any/each branch in the framework of a **Linker** has 1 C atom.
- In one embodiment the total number of C and/or heteroatoms in the branch(es) (where present) of the
- 35 framework of the **Linker** is from 1 to 5.
- In one embodiment the total number of C and/or heteroatoms in the branch(es) (where present) of the framework of the **Linker** is from 1 to 3.
- In one embodiment the total number of C and/or heteroatoms in the branch(es) (where present) of the framework of the **Linker** is 1.
- 40 In one embodiment any the framework of the **Linker** is either unbranched or has one branch that is Me.

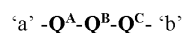
- In one embodiment the framework of the **Linker** is optionally substituted on any available C atom(s) by 1 or 2 F (for example by 2 F, for example where said 2 F are substituted on the same carbon atom).
- In one embodiment the framework of the **Linker** is not substituted by any F.
- In one embodiment the **Linker** is a saturated or a partially unsaturated framework comprising C and H atoms
- 5 and at least one heteroatom, wherein said framework has end points of attachment 'a' and 'b' and:
a minimum length of from 7 to 14 atoms between 'a' and 'b';
wherein the total number of C and hetero atoms in the **Linker** framework is from 9 to 20;
where said framework comprises one or more straight and/or branched chains and/or rings that are
optionally substituted on any available C atom(s) by 1 or 2 F (for example by 2 F);
- 10 wherein the total number of branches is 0 or 1 and when present said branch is Me.
- In one embodiment the framework of the **Linker** includes at least one nitrogen-containing saturated or
partially unsaturated heterocyclic group (e.g. having from 4 to 12 ring atoms) or a $A^1-CH_2-CH_2-A^2$ unit
where A^1 and A^2 are each independently selected from N and O.
- In one embodiment the framework of the **Linker** includes at least one nitrogen-containing saturated
- 15 heterocyclic group (e.g. having from 4 to 12 ring atoms) or a $A^1-CH_2-CH_2-A^2$ unit where A^1 and A^2 are
each independently selected from N and O.
- In one embodiment the framework of the **Linker** includes a $A^1-CH_2-CH_2-A^2$ unit where A^1 and A^2 are each
independently selected from N and O.
- In one embodiment the framework of the **Linker** includes at least one nitrogen-containing saturated or
- 20 partially unsaturated heterocyclic group (e.g. having from 4 to 12 ring atoms) or a $A^1-CH_2-CH_2-A^2$ unit
where one of A^1 & A^2 is N and the other of A^1 & A^2 is selected from N or O.
- In one embodiment the framework of the **Linker** includes at least one nitrogen-containing saturated
heterocyclic group (e.g. having from 4 to 12 ring atoms) or a $A^1-CH_2-CH_2-A^2$ unit where one of A^1 &
 A^2 is N and the other of A^1 & A^2 is selected from N or O.
- 25 In one embodiment the framework of the **Linker** includes a $A^1-CH_2-CH_2-A^2$ unit where one of A^1 & A^2 is N
and the other of A^1 & A^2 is selected from N or O.
- In one embodiment the framework of the **Linker** includes at least one nitrogen-containing saturated or
partially unsaturated heterocyclic group (e.g. having from 4 to 12 ring atoms) or a $A^1-CH_2-CH_2-A^2$ unit
where one of A^1 & A^2 is N in the form of a secondary or tertiary amine, and the other of A^1 & A^2 is
- 30 selected from N or O.
- In one embodiment the framework of the **Linker** includes a $A^1-CH_2-CH_2-A^2$ unit where one of A^1 & A^2 is N
in the form of a secondary or tertiary amine, and the other of A^1 & A^2 is selected from N or O.
- In one embodiment the framework of the **Linker** includes at least one saturated or partially unsaturated
heterocyclic group.
- 35 In one embodiment the framework of the **Linker** includes at least one saturated heterocyclic group.
- In one embodiment the framework of the **Linker** includes at least one nitrogen-containing saturated or
partially unsaturated heterocyclic group.
- In one embodiment the framework of the **Linker** includes at least one nitrogen-containing saturated
heterocyclic group.

- In one embodiment the framework of the **Linker** includes at least one nitrogen-containing saturated or partially unsaturated heterocyclic group having from 4 to 12 ring atoms.
- In one embodiment the framework of the **Linker** includes at least one nitrogen-containing saturated heterocyclic group having from 4 to 12 ring atoms.
- 5 In one embodiment the framework of the **Linker** includes:
- (1) a $A^1-CH_2-CH_2-A^2$ unit where A^1 and A^2 are each independently selected from N and O; and/or
 - (2) at least one nitrogen-containing saturated or partially unsaturated heterocyclic group selected from piperazine, azetidine, piperidine, 1,4-diazepane, 12-oxa-3,9-diazaspiro[5.6]dodecane, pyrrolidine, 3,9-diazaspiro-[5.5]undecane, 2,5-diazabicyclo[2.2.1]heptane, 1,2,3,3a,4,5,6,6a-
- 10 octahydropyrrolo[3,4-*c*]pyrrole, 1,2,3,6-tetrahydropyridine and 9-azaspiro[5.5]undecane.
- In one embodiment the framework of the **Linker** includes:
- (1) a $A^1-CH_2-CH_2-A^2$ unit where one of A^1 & A^2 is N in the form of a secondary or tertiary amine, and the other of A^1 & A^2 is selected from N or O; and/or
 - (2) at least one nitrogen-containing saturated or partially unsaturated heterocyclic group selected from
- 15 piperazine, azetidine, piperidine, 1,4-diazepane, 12-oxa-3,9-diazaspiro[5.6]dodecane, pyrrolidine, 3,9-diazaspiro-[5.5]undecane, 2,5-diazabicyclo[2.2.1]heptane, 1,2,3,3a,4,5,6,6a-octahydropyrrolo[3,4-*c*]pyrrole, 1,2,3,6-tetrahydropyridine and 9-azaspiro[5.5]undecane.
- In one embodiment the framework of the **Linker** includes at least one nitrogen-containing saturated or partially unsaturated heterocyclic group selected from piperazine, azetidine, piperidine, 1,4-diazepane,
- 20 12-oxa-3,9-diazaspiro[5.6]dodecane, pyrrolidine, 3,9-diazaspiro[5.5]undecane, 2,5-diazabicyclo[2.2.1]heptane, 1,2,3,3a,4,5,6,6a-octahydropyrrolo[3,4-*c*]pyrrole, 1,2,3,6-tetrahydropyridine and 9-azaspiro[5.5]undecane.
- In one embodiment the framework of the **Linker** includes an O-CH₂-CH₂-N unit.
- In one embodiment the framework of the **Linker** includes an O-CH₂CH₂-O-CH₂CH₂-N unit.
- 25 In one embodiment the framework of the **Linker** includes a piperazine group.
- In one embodiment the framework of the **Linker** includes an azetidine group.
- In one embodiment the framework of the **Linker** includes a piperidine group.
- In one embodiment the framework of the **Linker** includes a 1,4-diazepane group.
- In one embodiment the framework of the **Linker** includes a 12-oxa-3,9-diazaspiro[5.6]dodecane group.
- 30 In one embodiment the framework of the **Linker** includes a pyrrolidine group.
- In one embodiment the framework of the **Linker** includes a 3,9-diazaspiro[5.5]undecane group.
- In one embodiment the framework of the **Linker** includes a 2,5-diazabicyclo[2.2.1]heptane group.
- In one embodiment the framework of the **Linker** includes a 1,2,3,3a,4,5,6,6a-octahydropyrrolo[3,4-*c*]pyrrole group.
- 35 In one embodiment the framework of the **Linker** includes a 1,2,3,6-tetrahydropyridine group.
- In one embodiment the framework of the **Linker** includes a 9-azaspiro[5.5]undecane group.
- In one embodiment the framework of the **Linker** includes at least two nitrogen-containing saturated or partially unsaturated heterocyclic groups.
- In one embodiment the framework of the **Linker** includes at least two nitrogen-containing saturated
- 40 heterocyclic groups.

- In one embodiment the framework of the **Linker** includes a C, N or O atom at the 'a' point of attachment.
- In one embodiment the framework of the **Linker** includes an N or O atom at the 'a' point of attachment.
- In one embodiment the framework of the **Linker** includes an N or O atom at the 'b' point of attachment.
- In one embodiment the framework of the **Linker** includes a C atom at the 'a' point of attachment.
- 5 In one embodiment the framework of the **Linker** includes an N atom at the 'a' point of attachment.
- In one embodiment the framework of the **Linker** includes a C or N atom at the 'b' point of attachment.
- In one embodiment the framework of the **Linker** includes an N atom at the 'b' point of attachment.
- In one embodiment the framework of the **Linker** includes a C atom at the 'b' point of attachment.
- In one embodiment the framework of the **Linker** includes an O atom at the 'a' point of attachment.
- 10 In one embodiment the framework of the **Linker** includes an O atom at the 'b' point of attachment.
- In one embodiment the framework of the **Linker** includes an N or O atom at both the 'a' and 'b' points of attachment.
- In one embodiment the framework of the **Linker** includes a C, N or O atom at the 'a' point of attachment and a C or N atom at the 'b' point of attachment.
- 15 In one embodiment the framework of the **Linker** includes:
- (1) a $A^1-CH_2-CH_2-A^2$ unit where one of A^1 & A^2 is N in the form of a secondary or tertiary amine, and the other of A^1 & A^2 is selected from N or O; and/or
 - (2) at least one nitrogen-containing saturated or partially saturated heterocyclic group selected from
- 20 piperazin-1,4-diyl, azetidin-1,3-diyl, piperidin-1,4-diyl, 1,4-diazepan-1,4-diyl, 12-oxa-3,9-diazaspiro[5.6]dodecan-3,9-diyl, pyrrolidin-1,3-diyl, 3,9-diazaspiro[5.5]undecan-3,9-diyl, 2,5-diazabicyclo[2.2.1]heptan-2,5-diyl, 1,3,3a,4,6,6a-hexahydropyrrolo[3,4-*c*]pyrrol-2,5-diyl, 3,6-dihydro-2*H*-pyridin-1,4-diyl, and 9-azaspiro[5.5]undecan-3,9-diyl.
- In one embodiment the framework of the **Linker** includes at least one nitrogen-containing saturated or partially saturated heterocyclic group selected from piperazin-1,4-diyl, azetidin-1,3-diyl, piperidin-1,4-diyl, 1,4-diazepan-1,4-diyl, 12-oxa-3,9-diazaspiro[5.6]dodecan-3,9-diyl, pyrrolidin-1,3-diyl, 3,9-diazaspiro[5.5]undecan-3,9-diyl, 2,5-diazabicyclo[2.2.1]heptan-2,5-diyl, 1,3,3a,4,6,6a-hexahydropyrrolo[3,4-*c*]pyrrol-2,5-diyl, 3,6-dihydro-2*H*-pyridin-1,4-diyl, and 9-azaspiro[5.5]undecan-3,9-diyl.
- 25 In one embodiment the framework of the **Linker** includes a piperazin-1,4-diyl group.
- 30 In one embodiment the framework of the **Linker** includes an azetidin-1,3-diyl group.
- In one embodiment the framework of the **Linker** includes a piperidin-1,4-diyl group.
- In one embodiment the framework of the **Linker** includes a 1,4-diazepan-1,4-diyl group.
- In one embodiment the framework of the **Linker** includes a 12-oxa-3,9-diazaspiro[5.6]dodecan-3,9-diyl group.
- 35 In one embodiment the framework of the **Linker** includes a pyrrolidin-1,3-diyl group.
- In one embodiment the framework of the **Linker** includes a 3,9-diazaspiro[5.5]undecan-3,9-diyl group.
- In one embodiment the framework of the **Linker** includes a 2,5-diazabicyclo[2.2.1]heptan-2,5-diyl group.
- In one embodiment the framework of the **Linker** includes a 1,3,3a,4,6,6a-hexahydropyrrolo[3,4-*c*]pyrrol-2,5-diyl group.
- 40 In one embodiment the framework of the **Linker** includes a 3,6-dihydro-2*H*-pyridin-1,4-diyl group.

In one embodiment the framework of the **Linker** includes a 9-azaspiro[5.5]undecan-3,9-diyl group.

In one embodiment the **Linker** has the **Formula**:



wherein:

5 'a' and 'b' represent the end points of attachment;

$\mathbf{Q}^{\mathbf{A}}$ is $-\mathbf{G}-\mathbf{Q}^{\mathbf{H}}-$ or $-\mathbf{G}-(\text{C}_{1-5}\text{alkylene})-$;

$\mathbf{Q}^{\mathbf{B}}$ is a direct bond, $-\mathbf{Q}^{\mathbf{B1}}-\mathbf{Q}^{\mathbf{B2}}-\mathbf{Q}^{\mathbf{B3}}-$ or $\text{C}_{1-3}\text{alkylene}$ optionally substituted by one or more F (for example 1 or 2 F, for example 2 F); where:

$\mathbf{Q}^{\mathbf{B1}}$ & $\mathbf{Q}^{\mathbf{B3}}$ each independently represent a direct bond or $\text{C}_{1-2}\text{alkylene}$;

10 $\mathbf{Q}^{\mathbf{B2}}$ is $\mathbf{Q}^{\mathbf{H}}$, $-\text{O}-\text{CH}_2\text{CH}_2-\text{O}-$, $-\text{O}-$ or $-\text{N}(\mathbf{R}^{\mathbf{J}})-$ where $\mathbf{R}^{\mathbf{J}}$ is H or $\text{C}_{1-3}\text{alkyl}$;

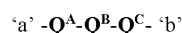
$\mathbf{Q}^{\mathbf{C}}$ is $-\mathbf{Q}^{\mathbf{H}}-\mathbf{G}-$ or $-(\text{C}_{1-5}\text{alkylene})-\mathbf{G}-$;

each $\mathbf{G}$ is independently a direct bond, $-\text{CH}_2-$, $-\text{O}-$, or $-\text{N}(\mathbf{R}^{\mathbf{G}})-$ where each $\mathbf{R}^{\mathbf{G}}$ is independently H or $\text{C}_{1-3}\text{alkyl}$;

each $\mathbf{Q}^{\mathbf{H}}$ is independently a 4-12-membered nitrogen-containing saturated or partially unsaturated heterocyclic group;

15 where the values of $\mathbf{Q}^{\mathbf{A}}$, $\mathbf{Q}^{\mathbf{B}}$ and $\mathbf{Q}^{\mathbf{C}}$ are selected so that the **Linker** does not contain any N-N or N-O bonds.

In one embodiment the **Linker** has the **Formula**:



20 wherein:

'a' and 'b' represent the end points of attachment;

$\mathbf{Q}^{\mathbf{A}}$ is $-\mathbf{G}-\mathbf{Q}^{\mathbf{H}}-$ or $-\mathbf{G}-(\text{C}_{1-5}\text{alkylene})-$;

$\mathbf{Q}^{\mathbf{B}}$ is a direct bond, $-\mathbf{Q}^{\mathbf{B1}}-\mathbf{Q}^{\mathbf{B2}}-\mathbf{Q}^{\mathbf{B3}}-$ or $\text{C}_{1-3}\text{alkylene}$ optionally substituted by one or more F (e.g. 1 or 2); where:

25 $\mathbf{Q}^{\mathbf{B1}}$ & $\mathbf{Q}^{\mathbf{B3}}$ each independently represent a direct bond or $\text{C}_{1-2}\text{alkylene}$;

$\mathbf{Q}^{\mathbf{B2}}$ is $\mathbf{Q}^{\mathbf{H}}$, $-\text{O}-\text{CH}_2\text{CH}_2-\text{O}-$ or $-\text{N}(\mathbf{R}^{\mathbf{J}})-$ where $\mathbf{R}^{\mathbf{J}}$ is $\text{C}_{1-3}\text{alkyl}$;

$\mathbf{Q}^{\mathbf{C}}$ is $-\mathbf{Q}^{\mathbf{H}}-\mathbf{G}-$ or $-(\text{C}_{1-5}\text{alkylene})-\mathbf{G}-$;

each $\mathbf{G}$ is independently a direct bond, $-\text{CH}_2-$, $-\text{O}-$, or $-\text{N}(\mathbf{R}^{\mathbf{G}})-$ where each $\mathbf{R}^{\mathbf{G}}$ is independently H or $\text{C}_{1-3}\text{alkyl}$;

30 each $\mathbf{Q}^{\mathbf{H}}$ is independently a 4-12-membered nitrogen-containing saturated or partially unsaturated heterocyclic group;

where the values of $\mathbf{Q}^{\mathbf{A}}$, $\mathbf{Q}^{\mathbf{B}}$ and $\mathbf{Q}^{\mathbf{C}}$ are selected so that the **Linker** does not contain any N-N or N-O bonds.

In one embodiment the **Linker** has the **Formula**:



wherein:

'a' and 'b' represent the end points of attachment;

$\mathbf{Q}^{\mathbf{A}}$ is $-\mathbf{G}^{\mathbf{A}}-\mathbf{Q}^{\mathbf{HA}}-$ or $-\mathbf{G}^{\mathbf{A}}-(\text{C}_{1-5}\text{alkylene})-$; where $\mathbf{G}^{\mathbf{A}}$ is a direct bond, $-\text{CH}_2-$, $-\text{O}-$, $-\text{NH}-$ or $-\text{N}(\text{Me})-$;

$\mathbf{Q}^{\mathbf{HA}}$ is a 4 to 11-membered nitrogen-containing saturated heterocyclic group;

Q^B is a direct bond, $-Q^{B1}-Q^{B2}-Q^{B3}-$ or C_{1-3} alkylene optionally substituted by one or more F (e.g. 1 or 2);
where:

Q^{B1} & Q^{B3} each independently represent a direct bond or C_{1-2} alkylene;

Q^{B2} is piperazin-1,4-diyl, $-O-CH_2CH_2-O-$ or $-N(R^J)-$ where R^J is C_{1-3} alkyl;

5 Q^C is $-Q^{HC}-G^C-$ or $-(C_{1-2}alkylene)-G^C-$; where G^C is a direct bond, $-O-$ or $-NH-$;

Q^{HC} is a 6 to 12-membered nitrogen-containing saturated or partially unsaturated heterocyclic group;

where the values of Q^A , Q^B and Q^C are selected so that the **Linker** does not contain any N-N or N-O bonds.

10 In one embodiment Q^A is $-G^A-Q^{HA}-$ or $-G^A-(C_{1-5}alkylene)-$ where:

G^A is selected from a direct bond, $-CH_2-$, $-O-$ or $-N(R^G)-$;

each R^G is independently H or C_{1-3} alkyl; and

Q^{HA} is a 4 to 11-membered nitrogen-containing saturated heterocyclic group.

In one embodiment Q^A is $-G^A-Q^{HA}-$ or $-G^A-(C_{1-5}alkylene)-$ where:

15 G^A is selected from a direct bond, $-CH_2-$, $-O-$ or $-N(R^G)-$;

each R^G is independently H or C_{1-3} alkyl; and

Q^{HA} is selected from azetidin-1,3-diyl, pyrrolidin-1,3-diyl, piperidin-1,4-diyl, piperazin-1,4-diyl, 3,9-diazaspiro[5.5]undecan-3,9-diyl and 9-azaspiro[5.5]undecan-3,9-diyl.

In one embodiment Q^A is $-G^A-Q^{HA}-$ or $-G^A-(C_{1-5}alkylene)-$ where:

20 G^A is selected from a direct bond, $-CH_2-$, $-O-$ or $-NH-$ or $-N(Me)-$;

Q^{HA} is selected from azetidin-1,3-diyl, pyrrolidin-1,3-diyl, piperidin-1,4-diyl, piperazin-1,4-diyl, 3,9-diazaspiro[5.5]undecan-3,9-diyl and 9-azaspiro[5.5]undecan-3,9-diyl; and

the $C_{1-5}alkylene$ within said $-G^A-(C_{1-5}alkylene)-$ is selected from $-(CH_2)_f-$ where f is an integer from 1 to 5, cyclobut-1,3-diyl and $-CH_2(cyclobut-1,3-diyl)-$.

25 In one embodiment Q^A is selected from azetidin-1,3-diyl, pyrrolidin-1,3-diyl, piperidin-1,4-diyl, $-O(piperidin-1,4-diyl)-$, $-CH_2(piperidin-1,4-diyl)-$, piperazin-1,4-diyl, 3,9-diazaspiro[5.5]undecan-3,9-diyl, $-O(9-azaspiro[5.5]undecan-3,9-diyl)-$, $-O(cyclobut-1,3-diyl)-$, $-OCH_2(cyclobut-1,3-diyl)-$, $-(CH_2)_f-$, $-O-(CH_2)_f-$, $-NH-(CH_2)_f-$ and $-N(Me)-(CH_2)_f-$, where f is an integer from 1 to 5.

In one embodiment Q^A is azetidin-1,3-diyl.

30 In one embodiment Q^A is pyrrolidin-1,3-diyl.

In one embodiment Q^A is piperidin-1,4-diyl.

In one embodiment Q^A is $-O(piperidin-1,4-diyl)-$.

In one embodiment Q^A is $-CH_2(piperidin-1,4-diyl)-$.

In one embodiment Q^A is piperazin-1,4-diyl.

35 In one embodiment Q^A is 3,9-diazaspiro[5.5]undecan-3,9-diyl.

In one embodiment Q^A is $-O(9-azaspiro[5.5]undecan-3,9-diyl)-$.

In one embodiment Q^A is $-G-(C_{1-5}alkylene)-$.

In one embodiment Q^A is selected from $-O(cyclobut-1,3-diyl)-$, $-OCH_2(cyclobut-1,3-diyl)-$, $-(CH_2)_f-$,

$-O(CH_2)_f-$, $-NH-(CH_2)_f-$ and $-N(Me)-(CH_2)_f-$, where f is an integer from 1 to 5.

40 In one embodiment Q^A is $-O(cyclobut-1,3-diyl)-$.

- In one embodiment Q^A is $-OCH_2(\text{cyclobut-1,3-diyl})-$.
- In one embodiment Q^A is $-(CH_2)_f-$ where f is an integer from 1 to 4 (for example, f is 4).
- In one embodiment Q^A is $-O-(CH_2)_f-$ where f is an integer from 1 to 5 (for example, f is 1 or 2).
- In one embodiment Q^A is $-NH-(CH_2)_f-$ where f is an integer from 1 to 5.
- 5 In one embodiment Q^A is $-N(Me)-(CH_2)_f-$, where f is an integer from 1 to 4.
- In one embodiment Q^B is a direct bond, $-Q^{B1}-Q^{B2}-Q^{B3}-$ or a straight chain C_{1-3} alkylene optionally substituted by one or more F (for example 1 or 2 F, for example by 2 F).
- In one embodiment Q^B is a direct bond.
- In one embodiment Q^B is $-Q^{B1}-Q^{B2}-Q^{B3}-$.
- 10 In one embodiment Q^B is C_{1-3} alkylene optionally substituted by one or more F.
- In one embodiment Q^B is C_{1-3} alkylene optionally substituted by one or two F (for example by 2 F).
- In one embodiment Q^B is a straight chain C_{1-3} alkylene optionally substituted by 1 or 2 F (for example by 2 F).
- In one embodiment Q^B is C_{1-3} alkylene.
- In one embodiment Q^B is a straight chain C_{1-3} alkylene.
- 15 In one embodiment Q^B is $-CF_2-CH_2-CH_2-$ or $-(CH_2)_w-$ where w is 1 to 3.
- In one embodiment Q^{B1} and Q^{B3} each independently represent a direct bond, $-CH_2-$ or $-CH_2CH_2-$.
- In one embodiment Q^{B1} is a direct bond or $-CH_2-$.
- In one embodiment Q^{B1} is a direct bond.
- In one embodiment Q^{B1} is $-CH_2-$.
- 20 In one embodiment Q^{B3} is a direct bond, $-CH_2-$ or $-CH_2CH_2-$.
- In one embodiment Q^{B3} is a direct bond.
- In one embodiment Q^{B3} is $-CH_2-$.
- In one embodiment Q^{B3} is $-CH_2CH_2-$.
- In one embodiment Q^{B2} is Q^H , $-O-CH_2CH_2-O-$ or $-N(R^J)-$ where R^J is C_{1-3} alkyl.
- 25 In one embodiment Q^{B2} is Q^H , $-O-CH_2CH_2-O-$ or $-N(Me)-$.
- In one embodiment Q^{B2} is piperazin-1,4-diyl, azetidin-1,3-diyl, $-O-CH_2CH_2-O-$ or $-N(Me)-$.
- In one embodiment Q^{B2} is piperazin-1,4-diyl, $-O-CH_2CH_2-O-$ or $-N(Me)-$.
- In one embodiment Q^{B2} is Q^H .
- In one embodiment Q^{B2} is piperazin-1,4-diyl.
- 30 In one embodiment Q^{B2} is azetidin-1,3-diyl.
- In one embodiment Q^{B2} is $-O-CH_2CH_2-O-$.
- In one embodiment Q^{B2} is $-N(R^J)-$ where R^J is C_{1-3} alkyl.
- In one embodiment Q^{B2} is $-N(Me)-$.
- In one embodiment Q^C is $-Q^H-G-$ or $-(C_{1-4}\text{alkylene})-G-$.
- 35 In one embodiment Q^C is $-Q^H-G-$ or $-(C_{1-3}\text{alkylene})-G-$.
- In one embodiment Q^C is $-Q^H-G-$ or $-(C_{1-2}\text{alkylene})-G-$.
- In one embodiment Q^C is $-Q^{HC}-G^C-$ or $-(C_{1-5}\text{alkylene})-G^C-$ where:
- G^C is selected from a direct bond, $-O-$ or $-NH-$; and
- Q^{HC} is a 6 to 12-membered nitrogen-containing saturated or partially unsaturated heterocyclic group.
- 40 In one embodiment Q^C is $-Q^{HC}-G^C-$ or $-(C_{1-2}\text{alkylene})-G^C-$ where:

G^C is selected from a direct bond, -O- or -NH-; and

Q^{HC} is a 6 to 12-membered nitrogen-containing saturated or partially unsaturated heterocyclic group.

In one embodiment Q^C is $-Q^{HC}-G^C-$ or $-(C_{1-2}alkylene)-G^C-$ where:

G^C is selected from a direct bond, -O- or -NH-; and

- 5 Q^{HC} is selected from piperazin-1,4-diyl, piperidin-1,4-diyl, 2,5-diazabicyclo[2.2.1]heptan-2,5-diyl, 1,4-diazepan-1,4-diyl, 3,9-diazaspiro[5.5]undecan-3,9-diyl, 12-oxa-3,9-diazaspiro[5.6]dodecan-3,9-diyl, 1,3,3a,4,6,6a-hexahydropyrrolo[3,4-*c*]pyrrol-2,5-diyl and 3,6-dihydro-2*H*-pyridin-1,4-diyl.

In one embodiment Q^C is selected from piperazin-1,4-diyl, piperidin-1,4-diyl, $-(piperidin-1,4-diyl)O-$, 2,5-diazabicyclo[2.2.1]heptan-2,5-diyl, 1,4-diazepan-1,4-diyl, 3,9-diazaspiro[5.5]undecan-3,9-diyl, 12-oxa-3,9-diazaspiro[5.6]dodecan-3,9-diyl, 1,3,3a,4,6,6a-hexahydropyrrolo[3,4-*c*]pyrrol-2,5-diyl, 3,6-dihydro-2*H*-pyridin-1,4-diyl, and $-CH_2CH_2-NH-$ and $-(CH_2)_g-O-$ where g is an integer from 1 to 4.

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In one embodiment Q^C is piperazin-1,4-diyl.

In one embodiment Q^C is piperidin-1,4-diyl.

In one embodiment Q^C is $-(piperidin-1,4-diyl)O-$.

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In one embodiment Q^C is 2,5-diazabicyclo[2.2.1]heptan-2,5-diyl.

In one embodiment Q^C is 1,4-diazepan-1,4-diyl.

In one embodiment Q^C is 3,9-diazaspiro[5.5]undecan-3,9-diyl.

In one embodiment Q^C is 12-oxa-3,9-diazaspiro[5.6]dodecan-3,9-diyl.

In one embodiment Q^C is 1,3,3a,4,6,6a-hexahydropyrrolo[3,4-*c*]pyrrol-2,5-diyl.

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In one embodiment Q^C is 3,6-dihydro-2*H*-pyridin-1,4-diyl.

In one embodiment Q^C is $-(C_{1-5}alkylene)-G-$ [for example, $-(CH_2)_g-O-$ where g is an integer from 1 to 5].

In one embodiment Q^C is $-(C_{1-4}alkylene)-G-$ [for example, $-(CH_2)_g-O-$ where g is an integer from 1 to 4].

In one embodiment Q^C is $-(C_{1-3}alkylene)-G-$ [for example, $-(CH_2)_g-O-$ where g is 1, 2 or 3].

In one embodiment Q^C is $-(C_{1-2}alkylene)-G-$ [for example, $-(CH_2)_g-O-$ where g is 1 or 2].

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In one embodiment Q^C is $-(CH_2)_g-G^C-$ where g is an integer from 1 to 5 and G^C is -O- or -NH-.

In one embodiment Q^C is $-(CH_2)_g-G^C-$ where g is 1 or 2 and G^C is -O- or -NH-.

In one embodiment Q^C is $-CH_2CH_2NH-$.

In one embodiment each Q^H is independently selected from piperazin-1,4-diyl, azetidin-1,3-diyl, piperidin-

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1,4-diyl, 1,4-diazepan-1,4-diyl, 12-oxa-3,9-diazaspiro[5.6]dodecan-3,9-diyl, pyrrolidin-1,3-diyl, 3,9-diazaspiro[5.5]undecan-3,9-diyl, 2,5-diazabicyclo[2.2.1]heptan-2,5-diyl, 1,3,3a,4,6,6a-hexahydropyrrolo[3,4-*c*]pyrrol-2,5-diyl, 3,6-dihydro-2*H*-pyridin-1,4-diyl and 9-azaspiro[5.5]undecan-3,9-diyl.

In one embodiment each Q^H is independently selected from piperazin-1,4-diyl, azetidin-1,3-diyl, piperidin-

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1,4-diyl, 1,4-diazepan-1,4-diyl, 12-oxa-3,9-diazaspiro[5.6]dodecan-3,9-diyl, pyrrolidin-1,3-diyl, 3,9-diazaspiro[5.5]undecan-3,9-diyl, 2,5-diazabicyclo[2.2.1]heptan-2,5-diyl, 1,3,3a,4,6,6a-hexahydropyrrolo[3,4-*c*]pyrrol-2,5-diyl and 9-azaspiro[5.5]undecan-3,9-diyl.

In one embodiment Q^H is piperazin-1,4-diyl.

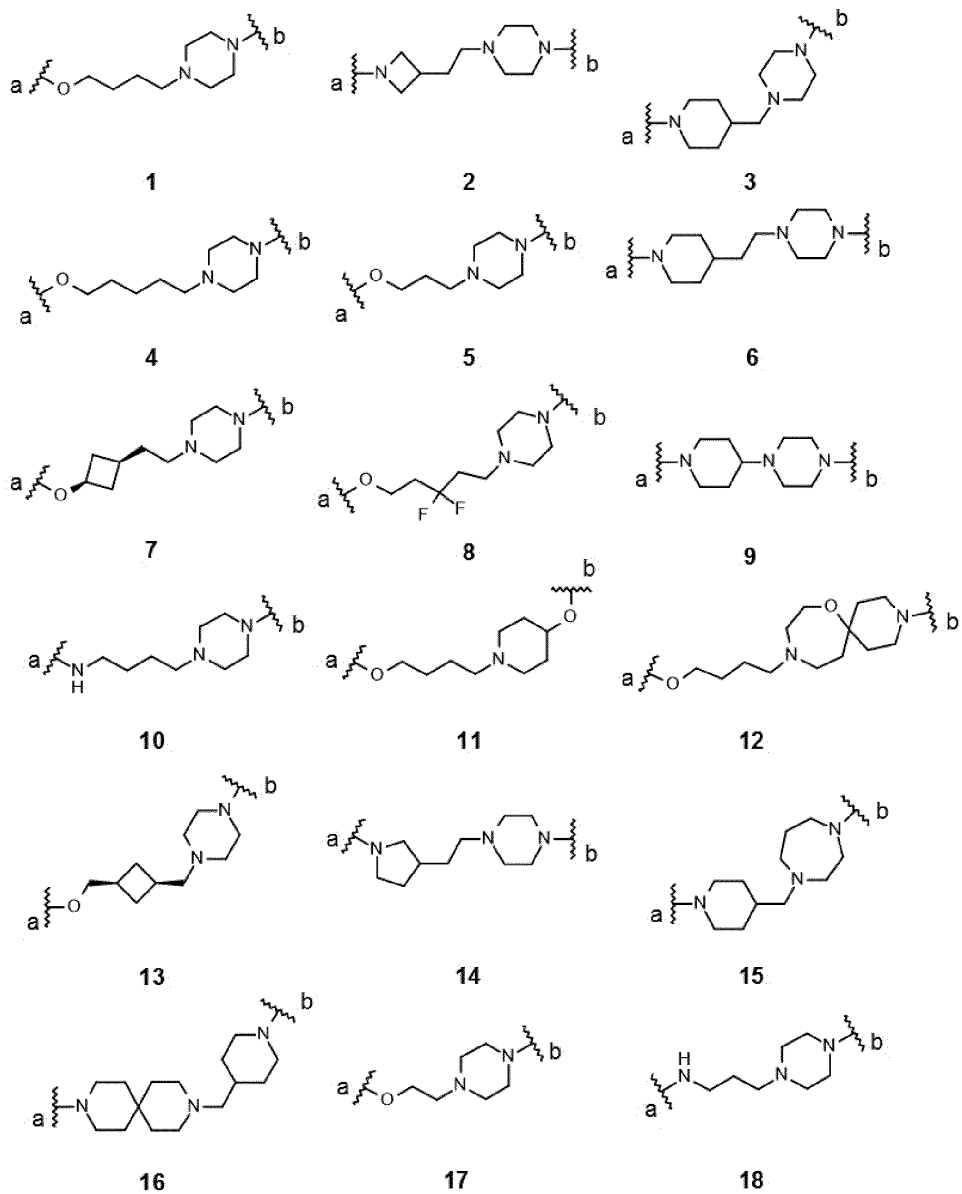
In one embodiment Q^H is azetidin-1,3-diyl.

In one embodiment Q^H is piperidin-1,4-diyl.

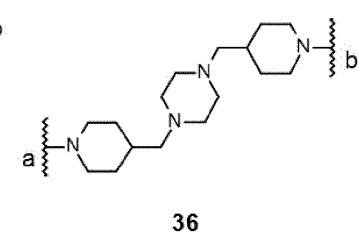
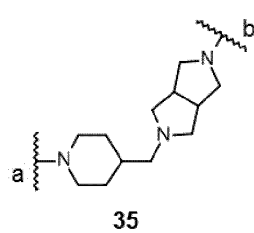
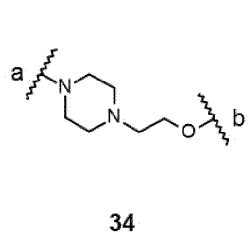
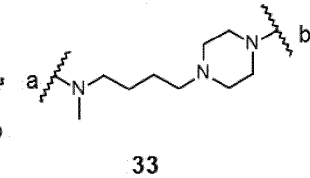
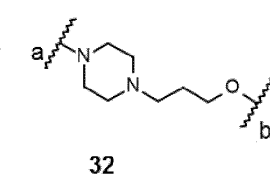
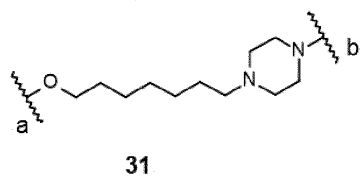
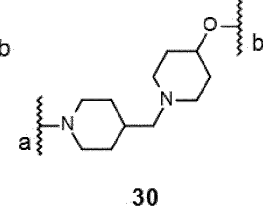
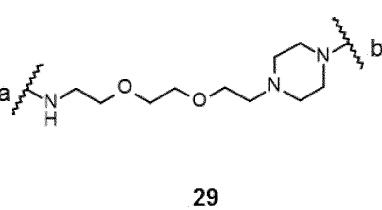
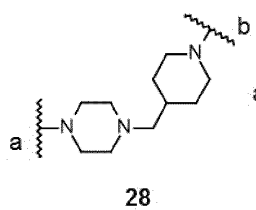
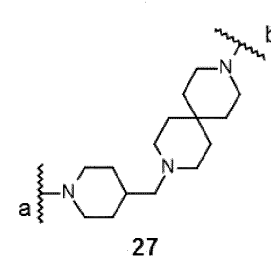
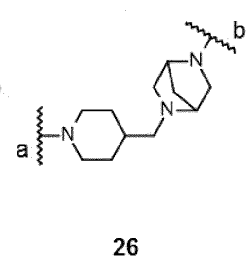
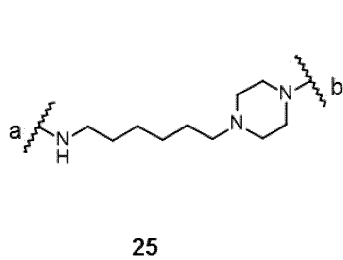
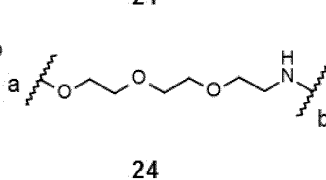
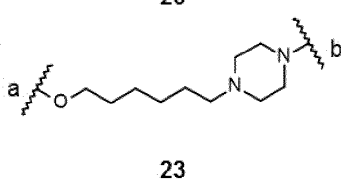
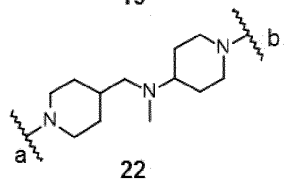
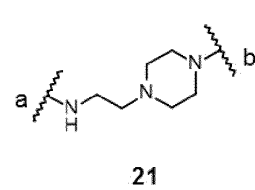
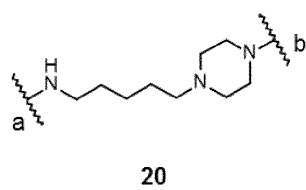
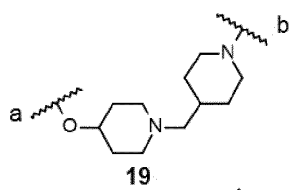
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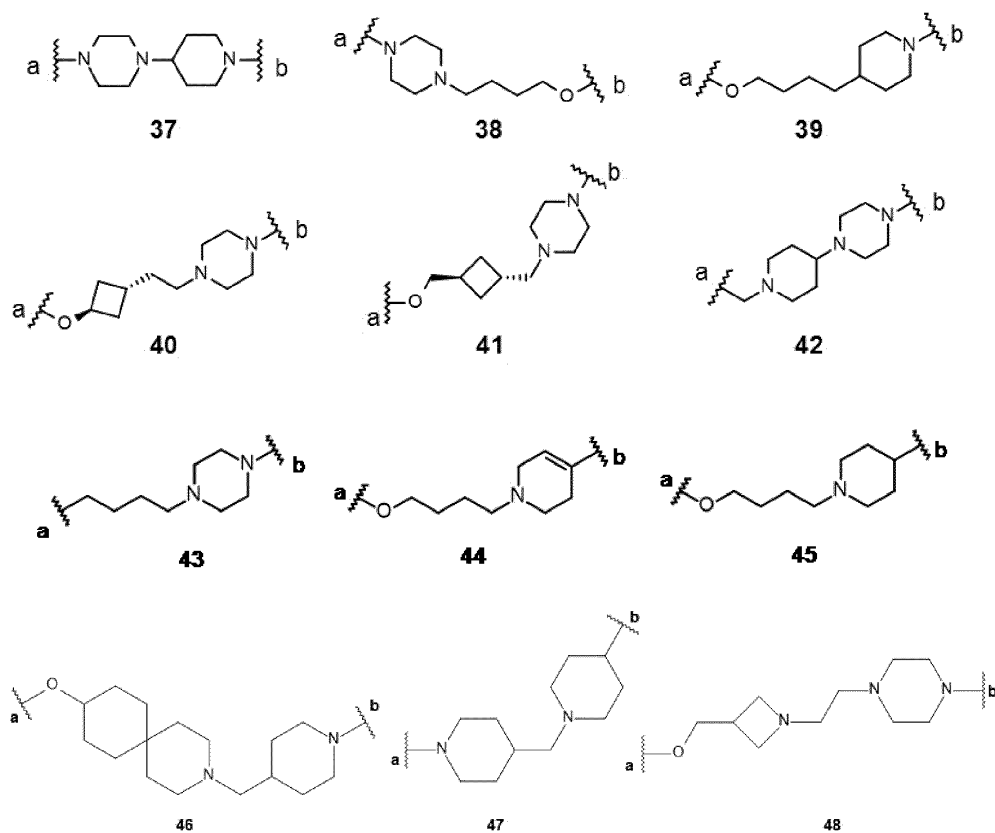
In one embodiment Q^H is 1,4-diazepan-1,4-diyl.

- In one embodiment $\mathbf{Q}^{\mathbf{H}}$ is 12-oxa-3,9-diazaspiro[5.6]dodecan-3,9-diyl.
- In one embodiment $\mathbf{Q}^{\mathbf{H}}$ is pyrrolidin-1,3-diyl.
- In one embodiment $\mathbf{Q}^{\mathbf{H}}$ is 3,9-diazaspiro[5.5]undecan-3,9-diyl.
- In one embodiment $\mathbf{Q}^{\mathbf{H}}$ is 2,5-diazabicyclo[2.2.1]heptan-2,5-diyl.
- 5 In one embodiment $\mathbf{Q}^{\mathbf{H}}$ is 1,3,3a,4,6,6a-hexahydropyrrolo[3,4-*c*]pyrrol-2,5-diyl.
- In one embodiment $\mathbf{Q}^{\mathbf{H}}$ is 3,6-dihydro-2*H*-pyridin-1,4-diyl.
- In one embodiment $\mathbf{Q}^{\mathbf{H}}$ is 9-azaspiro[5.5]undecan-3,9-diyl.
- In one embodiment $\mathbf{R}^{\mathbf{J}}$ is C₁₋₃alkyl.
- In one embodiment $\mathbf{R}^{\mathbf{J}}$ is Me.
- 10 In one embodiment $\mathbf{R}^{\mathbf{G}}$ is C₁₋₃alkyl.
- In one embodiment $\mathbf{R}^{\mathbf{G}}$ is H or Me.
- In one embodiment $\mathbf{R}^{\mathbf{G}}$ is Me.
- In one embodiment $\mathbf{R}^{\mathbf{G}}$ is H.
- In one embodiment the **Linker** (for example 'a' - $\mathbf{Q}^{\mathbf{A}}$ - $\mathbf{Q}^{\mathbf{B}}$ - $\mathbf{Q}^{\mathbf{C}}$ - 'b') is selected from any of **Linkers** 1 to 46 or 1
- 15 to 48 shown below:



25

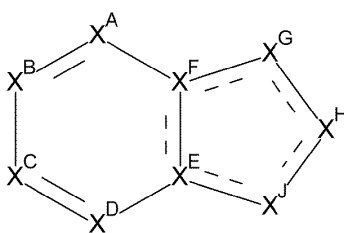




- 5 In one embodiment **W** is an E3 ubiquitin ligase cereblon binder unit attached to the 'b' end of the **Linker** via an available C atom within said E3 ubiquitin ligase cereblon binder unit.

In one embodiment **W** is **W1** which is: $-\text{Z}-(\text{R}^A)_n$

where **Z** is:



10

wherein:



0, 1 or 2 of X^A , X^B , X^C , X^D , X^E & X^F

1 of X^G , X^H & X^J

15

1 of X^G , X^H & X^J

represents a single covalent bond or a double covalent bond;

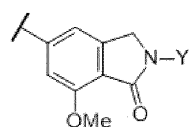
is/are N, where X^E & X^F are not both N, and are otherwise C;

is C(O);

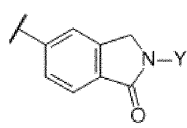
is N-(2,6-dioxopiperidin-3-yl) (**Y**); and

- 1 of X^G , X^H & X^J is selected from $C(R^T)_2$, $-CH_2CH_2-$, $C(O)$, $N(C_{1-3}alkyl)$, $-O-$ and $-N=$, wherein each R^T is selected from H, F, Me or together with the carbon of $C(R^T)_2$ forms a cycloprop-1,1-diyl group; where X^G , X^H & X^J are selected such that there are not two $C(O)$ groups present at adjacent positions, and that the N-(2,6-dioxopiperidin-3-yl) is not at an adjacent position to either $N(C_{1-3}alkyl)$ or O;
- 5 each R^A is independently a substituent on any available C atom at X^A , X^B , X^C or X^D selected from F, Cl, $C_{1-3}alkyl$, $C_{1-3}alkoxy$ wherein said $C_{1-3}alkyl$ and $C_{1-3}alkoxy$ is independently optionally substituted by one or more F;
- 10 h is 0, 1 or 2; and wherein the **Linker** is attached to any C atom at X^A , X^B , X^C or X^D .
- 15 In one embodiment 0 or 1 of X^A , X^B , X^C , X^D , X^E & X^F is N and are otherwise C.
In one embodiment 1 or 2 of X^A , X^B , X^C , X^D , X^E & X^F is/are N and are otherwise C.
In one embodiment X^A , X^B , X^C , X^D , X^E & X^F are all C.
In one embodiment 1 of X^A , X^B , X^C , X^D , X^E & X^F is N and are otherwise C.
In one embodiment 2 of X^A , X^B , X^C , X^D , X^E & X^F are N where X^E & X^F are not both N, and are otherwise C.
- 20 In one embodiment X^B , X^D & X^F are all C, and 0, 1 or 2 of X^A , X^C & X^E is/are N, and are otherwise C.
In one embodiment X^B , X^D & X^F are all C, and 0, 1 or 2 of X^A , X^C & X^E is/are N, and are otherwise C; where the **Linker** is attached to X^B or to X^A when X^A is C.
In one embodiment X^B , X^D & X^F are all C, and 0, 1 or 2 of X^A , X^C & X^E is/are N, and are otherwise C; where the **Linker** is attached to X^B .
- 25 In one embodiment X^G - X^H - X^J is:
(i) X^G - NY - $C(O)$ where X^G is $-CH_2-$, $-CH_2CH_2-$, $=N-$ or $C(O)$;
(ii) X^G - $C(O)$ - NY where X^G is $-O-$ or $N(C_{1-3}alkyl)$ [for example $N(Me)$]; or
(iii) $C(O)$ - NY - CH_2 .
In one embodiment the **Linker** is attached to a C atom at X^A or X^B and X^G - X^H - X^J is:
- 30 (i) X^G - NY - $C(O)$ where X^G is $-CH_2-$, $-CH_2CH_2-$, $=N-$ or $C(O)$;
(ii) X^G - $C(O)$ - NY where X^G is $-O-$ or $N(C_{1-3}alkyl)$ [for example $N(Me)$]; or
(iii) $C(O)$ - NY - CH_2 .
In one embodiment the **Linker** is attached to a C atom at X^B and X^G - X^H - X^J is:
- 35 (i) X^G - NY - $C(O)$ where X^G is $-CH_2-$, $-CH_2CH_2-$, $=N-$ or $C(O)$;
(ii) X^G - $C(O)$ - NY where X^G is $-O-$ or $N(C_{1-3}alkyl)$ [for example $N(Me)$]; or
(iii) $C(O)$ - NY - CH_2 .
In one embodiment X^G - X^H - X^J is CH_2 - NY - $C(O)$.
In one embodiment X^G - X^H - X^J is CH_2CH_2 - NY - $C(O)$.
In one embodiment X^G - X^H - X^J is $=N$ - NY - $C(O)$.
- 40 In one embodiment X^G - X^H - X^J is $C(O)$ - NY - $C(O)$.

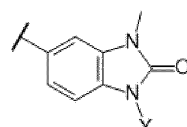
- In one embodiment $X^G-X^H-X^J$ is $O-C(O)-NY$.
- In one embodiment $X^G-X^H-X^J$ is $N(C_{1-3}alkyl)-C(O)-NY$ [for example $N(Me)-C(O)-NY$].
- In one embodiment $X^G-X^H-X^J$ is $C(O)-NY-CH_2$.
- In one embodiment each R^A is a substituent on any available C at X^A , X^B , X^C or X^D selected from F, Cl and
- 5 $C_{1-3}alkoxy$ optionally substituted by one or more F.
- In one embodiment each R^A is a substituent on any available C at X^A , X^B , X^C or X^D selected from F, Cl, OMe and $-OCHF_2$.
- In one embodiment h is 0.
- In one embodiment h is 1.
- 10 In one embodiment h is 2.
- In one embodiment the **Linker** is attached to X^C , where X^C is C; and X^A is C attached to R^A where R^A is OMe where said methyl is optionally substituted by one or more F (e.g. $-OCHF_2$).
- In one embodiment the **Linker** is attached to X^C , where X^C is C; and X^A is C attached to R^A where R^A is OMe or $-OCHF_2$.
- 15 In one embodiment $-Z-(R^A)_h$ together represent any one of groups 1, 4, 16, 17 and 19 (referring to the specific $-Z-(R^A)_h$ groups 1 to 21 whose structures are drawn out below).
- In one embodiment h is 1 and R^A is $C_{1-3}alkoxy$ [for example OMe].
- In one embodiment h is 1 or 2, one R^A is OMe and the other R^A (when present, i.e. when h is 2) is Cl.
- In one embodiment h is 1 or 2, one R^A is Cl and the other R^A (when present, i.e. when h is 2) is OMe.
- 20 In one embodiment h is 1 and R^A is F.
- In one embodiment h is 1 and R^A is Cl.
- In one embodiment h is 1 and R^A is $-OCHF_2$.
- In one embodiment the **Linker** is attached to a C at X^A or X^B , and h is 0.
- In one embodiment the **Linker** is attached to a C at X^A or X^B , h is 1 and R^A is a substituent on X^C where X^C is
- 25 C and R^A is F.
- In one embodiment the **Linker** is attached to a C at X^A or X^B , h is 1 and R^A is a substituent on X^D where X^D is C and R^A is OMe or $-OCHF_2$.
- In one embodiment the **Linker** is attached to a C at X^B , h is 0, 1 or 2; the first R^A (when present, i.e. when h is 1 or 2) is a substituent on an available C at X^D and the second R^A (when present, i.e. when h is 2) is on
- 30 an available C at X^A .
- In one embodiment the **Linker** is attached to a C at X^B , h is 0, 1 or 2; the first R^A (when present, i.e. when h is 1 or 2) is a substituent on an available C at X^D selected from Cl, OMe and $-OCHF_2$; and the second R^A (when present, i.e. when h is 2) is on an available C at X^A and is selected from Cl and OMe.
- In one embodiment $-Z-(R^A)_h$ together represent any of the groups 1 to 21 shown below:



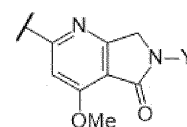
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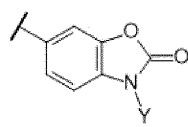
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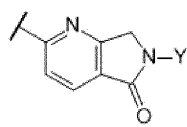
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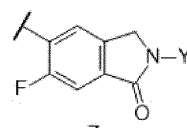
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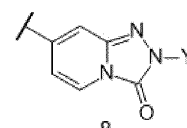
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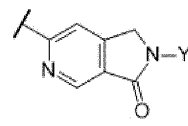
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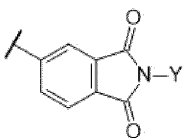
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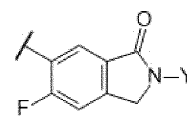
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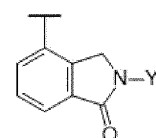
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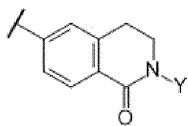
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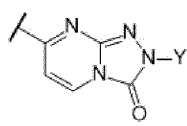
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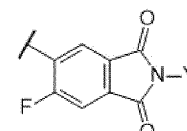
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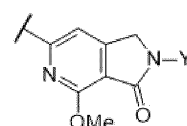
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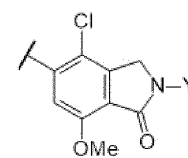
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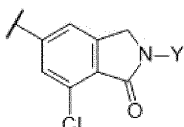
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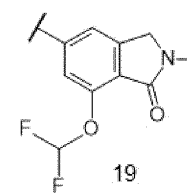
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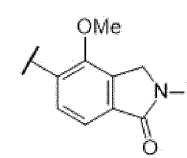
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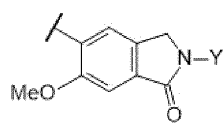
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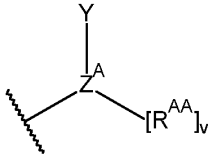
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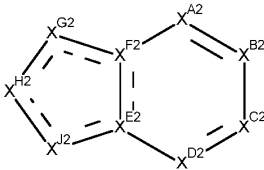
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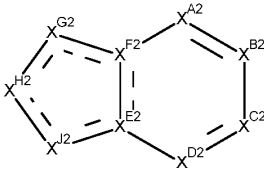
In one embodiment **W** is **W2** which is **Z^A** is:



- 5 wherein:

1 of **X^{A2}**, **X^{B2}**, **X^{C2}** & **X^{D2}**
0, 1 or 2 of **X^{A2}**, **X^{B2}**, **X^{C2}**, **X^{D2}**, **X^{E2}** & **X^{F2}**
10 1 or 2 of **X^{G2}**, **X^{H2}** & **X^{J2}**
each **R^{AA}**
15 each **R^{AA1}**
each **R^{AA2}**
20 **v**
Y
- represents a single covalent bond or a double covalent bond;
is C and covalently bound to **Y**;
is/are N (where **X^{E2}** & **X^{F2}** are not both N) and are otherwise C;
is/are N; and are otherwise C;
is a substituent on any available C or N atom of **Z** – in each case independently selected from **R^{AA1}** optionally substituted by one or more **R^{AA2}**, where **R^{AA}** is further selected from **R^{AA2}** when **R^{AA}** is a substituent on an available C atom of **Z^A**;
is independently C₁₋₄alkyl, C₂₋₃alkenyl, C₂₋₃alkynyl, C₁₋₃alkoxyC₁₋₃alkyl, carboxyC₁₋₃alkyl, C₅₋₇carbocyclyl or a 4-6 membered heterocyclyl;
is independently selected from F, Cl, Br, CN, NH₂, C₁₋₃alkyl, O(C₁₋₃alkyl), NH(C₁₋₃alkyl) and N(C₁₋₃alkyl)₂; wherein said C₁₋₃alkyls are optionally substituted by one or more F;
is 0, 1 or 2;
is N-(2,6-dioxopiperidin-3-yl).

In one embodiment **Z^A** is:

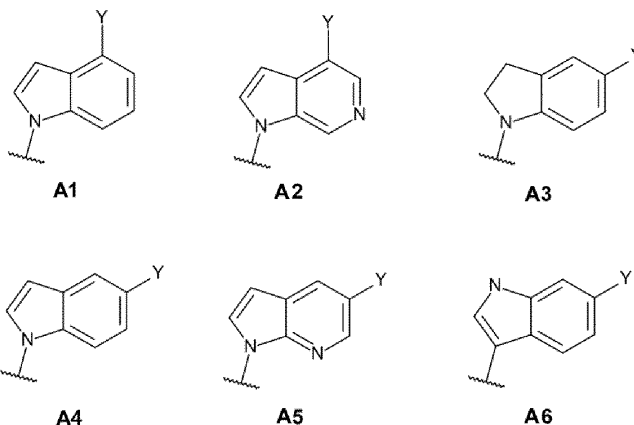


- 25 wherein:

represents a single covalent bond or a double covalent bond;

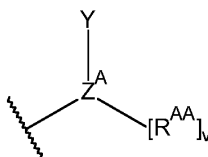
1 of X^{A2} & X^{B2} is C and covalently bound to Y and the other of X^{A2} & X^{B2} is C;
 0 or 1 of X^{C2} & X^{D2} is N and is/are otherwise C;
 1 of X^{G2} & X^{J2} is N and the other of X^{G2} & X^{J2} is C; and
 X^{H2} , X^{E2} & X^{F2} are all C.

- 5 In one embodiment - Z^A -Y together represent any one or more of the groups A1 to A6 shown below, where in each case said Z^A group is optionally substituted on available C and/or N atom(s) by $-(R^{AA})_v$ as further defined herein.

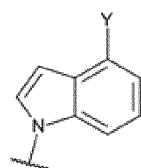
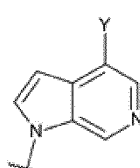
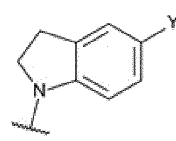
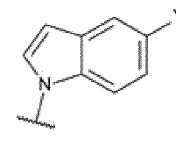
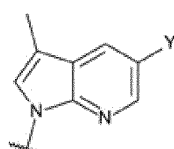
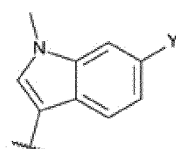
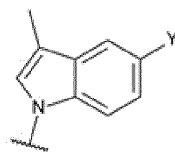
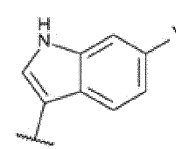
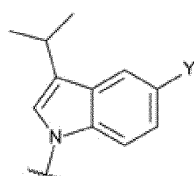
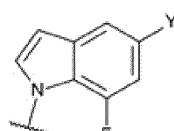
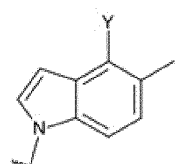
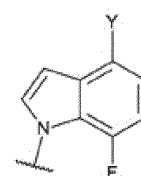
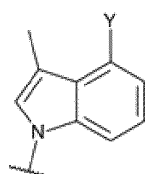
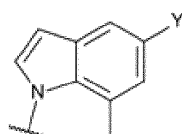
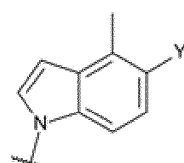
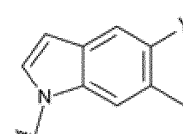
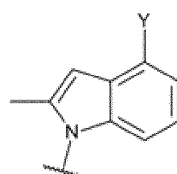
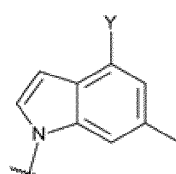
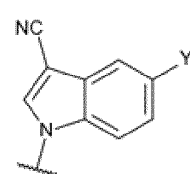
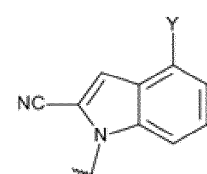
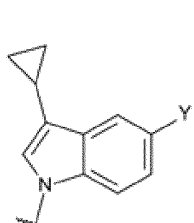
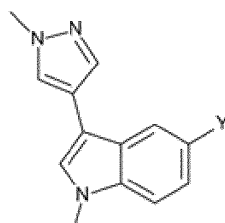
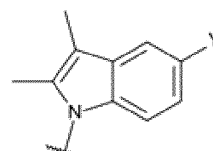
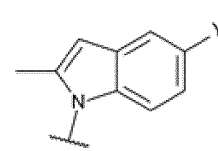


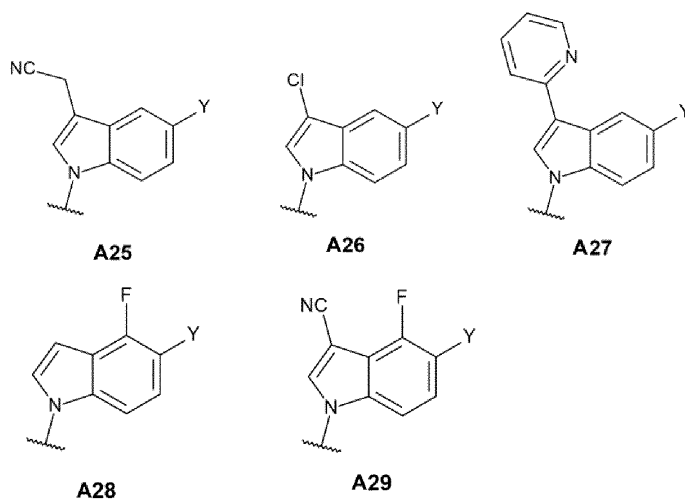
- 10 In one embodiment each R^{AA} is a substituent on any available C or N atom of Z^A – in each case independently selected from R^{AA1} optionally substituted by one or more R^{AA2} ; where R^{AA} is further selected from R^{AA2} when R^{AA} is a substituent on an available C atom of Z ; wherein each R^{AA1} is independently C_{1-4} alkyl or a 4-6 membered heterocyclyl; and each R^{AA2} is independently selected from F, Cl, CN and C_{1-3} alkyl.
- 15 In one embodiment each R^{AA} is a substituent on any available C or N atom of Z^A – in each case independently selected from R^{AA1} optionally substituted by one or more R^{AA2} ; where R^{AA} is further selected from R^{AA2} when R^{AA} is a substituent on an available C atom of Z^A ; wherein each R^{AA1} is independently methyl, isopropyl, cyclopropyl, pyridinyl or pyrazolyl; and each R^{AA2} is independently F, Cl, CN or methyl.
- 20 In one embodiment each R^{AA} is a substituent on an available C atom of Z^A , each independently selected from methyl, isopropyl, cyclopropyl, pyridin-2-yl, 1-methylpyrazol-4-yl, $-CH_2CN$, F, Cl, CN; and/or a methyl substituent on an available N atom of Z^A .
- In one embodiment v is 0.
- In one embodiment v is 1.
- In one embodiment v is 2.
- 25 In one embodiment v is 1 or 2.
- In one embodiment v is 0 or 1.
- In one embodiment v is 1; X^{A1} is a C atom; and R^{AA} is a substituent on X^{A1} .
- In one embodiment v is 1; X^{A1} is a C atom; and R^{AA} is a C_{1-4} alkyl substituent on X^{A1} .
- In one embodiment v is 1; X^{B1} is a C atom; and R^{AA} is a substituent on X^{B1} .

- In one embodiment v is 1; X^{B1} is a C atom; and R^{AA} is a C_{1-4} alkyl (e.g. methyl) substituent on X^{B1} .
- In one embodiment v is 1; X^{C1} is a C atom; and R^{AA} is a substituent on X^{C1} .
- In one embodiment v is 1; X^{C1} is a C atom; and R^{AA} is a C_{1-4} alkyl (e.g. methyl) substituent on X^{C1} .
- In one embodiment v is 1; X^{D1} is a C atom; and R^{AA} is a substituent on X^{D1} .
- 5 In one embodiment v is 1; X^{D1} is a C atom; and R^{AA} is a C_{1-4} alkyl (e.g. methyl) or F substituent on X^{D1} .
- In one embodiment v is 1; X^{G1} is a C atom; and R^{AA} is a substituent on X^{G1} .
- In one embodiment v is 1; X^{G1} is a C atom; and R^{AA} is a substituent on X^{G1} ; where R^{AA} is selected from R^{AA1} optionally substituted by one or more R^{AA2} ; or R^{AA} is selected from R^{AA2} ; wherein R^{AA1} is C_{1-4} alkyl or a 4-6 membered heterocyclyl; and R^{AA2} is selected from F, Cl, CN and C_{1-3} alkyl.
- 10 In one embodiment v is 1; X^{G1} is a C atom; and R^{AA} is a substituent on X^{G1} ; where R^{AA} is selected from methyl, isopropyl, cyclopropyl, pyridine-2-yl, 1-methylpyrazol-4-yl, $-CH_2CN$, F, Cl and CN.
- In one embodiment v is 1 or 2; X^{G1} is a C atom; and one/the R^{AA} is a substituent on X^{G1} ; where R^{AA} is selected from R^{AA1} optionally substituted by one or more R^{AA2} ; or R^{AA} is selected from R^{AA2} ; wherein R^{AA1} is C_{1-4} alkyl or a 4-6 membered heterocyclyl; and R^{AA2} is selected from F, Cl, CN and C_{1-3} alkyl;
- 15 and when v is 2, the additional R^{AA} is a fluoro substituted on an available C atom of Z^A .
- In one embodiment v is 1; X^{G1} is a N atom; and R^{AA} is a substituent on X^{G1} .
- In one embodiment v is 1; X^{G1} is a N atom; and R^{AA} is a C_{1-4} alkyl (e.g. methyl) substituent on X^{G1} .
- In one embodiment v is 1; X^{H1} is a C atom; and R^{AA} is a substituent on X^{H1} .
- In one embodiment v is 1; X^{H1} is a C atom; and R^{AA} is a substituent on X^{H1} that is CN or C_{1-4} alkyl (e.g. methyl).
- 20 In one embodiment v is 1 or 2; X^{H1} and X^{G1} are both C atoms, one or both of which are substituted by R^{AA} where each R^{AA} is independently selected from CN or C_{1-4} alkyl (e.g. methyl).
- In one embodiment the group:

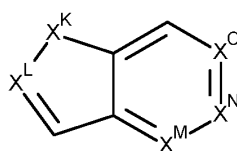


- 25 together represents one or more of the groups A1 to A29, shown below:

**A1****A2****A3****A4****A5****A6****A7****A8****A9****A10****A11****A12****A13****A14****A15****A16****A17****A18****A19****A20****A21****A22****A23****A24**



In some of these embodiments **W** is **W2-1**



5

wherein:

X^K and X^L are either N-linker and CH or NMe and C-linker respectively;

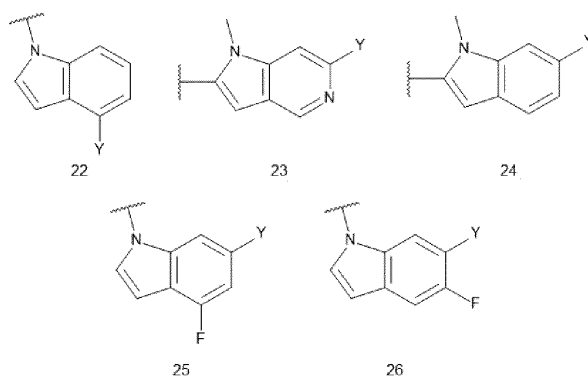
1 of X^M and X^O is N-(2,6-dioxopiperidin-3-yl) (**Y**);

0 or 1 of X^M and X^N is C-F;

10 X^N may be N if X^M is not C-F;

the remainder of X^N , X^M and X^O are CH.

In one embodiment **W** represents any of the groups 22 to 26 shown below:



15

In a further aspect of the specification **Formula (Ia)** is selected from any one or more of the following groups

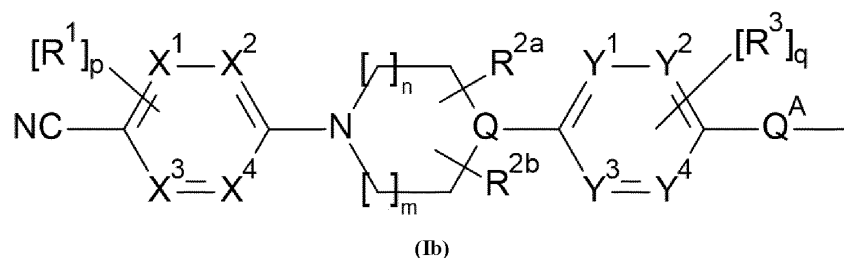
(1) to (28) or (1) to (39):

- 5 (1) 4-[1-[4-cyano-3-(trifluoromethyl)phenyl]-4-piperidyl]phenyl,
(2) 4-[1-(4-cyano-3-cyclopropyl-phenyl)-4-piperidyl]phenyl,
(3) 4-[1-[4-cyano-2-fluoro-3-(trifluoromethyl)phenyl]-4-piperidyl]phenyl,
(4) 2-[1-[4-cyano-3-(trifluoromethyl)phenyl]-4-piperidyl]pyrimidin-5-yl,
(5) 6-[1-[4-cyano-3-(trifluoromethyl)phenyl]-4-piperidyl]pyridin-3-yl,
(6) 4-[1-[6-cyano-5-(trifluoromethyl)-3-pyridyl]-4-piperidyl]phenyl,
10 (7) 4-[1-(3-chloro-4-cyano-phenyl)-4-piperidyl]phenyl,
(8) 4-[1-(4-cyano-3-methoxy-phenyl)-4-piperidyl]phenyl,
(9) 4-[1-(5-cyano-6-methyl-2-pyridyl)-4-piperidyl]phenyl,
(10) 4-[1-(5-cyano-8-quinolyl)-4-piperidyl]phenyl,
(11) 4-[(4*S*)-1-[4-cyano-3-(trifluoromethyl)phenyl]-3,3-dimethyl-4-piperidyl]phenyl
15 (12) 4-[(4*R*)-1-[4-cyano-3-(trifluoromethyl)phenyl]-3,3-dimethyl-4-piperidyl]phenyl
(13) 4-[1-[4-cyano-3-(trifluoromethyl)phenyl]-3,3-dimethyl-4-piperidyl]phenyl,
(14) 4-[1-[4-cyano-3-(trifluoromethyl)phenyl]-4-piperidyl]-2-fluorophenyl,
(15) 4-[1-[4-cyano-3-(trifluoromethyl)phenyl]-4-piperidyl]-3-fluorophenyl,
(16) 4-[1-[4-cyano-3-(trifluoromethyl)phenyl]-4-piperidyl]-3-methylphenyl,
20 (17) 4-[(2*S*)-4-[4-cyano-3-(trifluoromethyl)phenyl]-2-methyl-piperazin-1-yl]phenyl,
(18) 4-[(2*R*)-4-[4-cyano-3-(trifluoromethyl)phenyl]-2-methyl-piperazin-1-yl]phenyl,
(19) 4-[4-[4-cyano-3-(trifluoromethyl)phenyl]-2-methyl-piperazin-1-yl]phenyl,
(20) 5-[1-[4-cyano-3-(trifluoromethyl)phenyl]-4-piperidyl]pyridin-2-yl,
(21) 4-[4-[4-cyano-3-(trifluoromethyl)phenyl]piperazin-1-yl]phenyl,
25 (22) 4-[(3*R*)-1-[4-cyano-3-(trifluoromethyl)phenyl]pyrrolidin-3-yl]phenyl,
(23) 4-[(3*S*)-1-[4-cyano-3-(trifluoromethyl)phenyl]pyrrolidin-3-yl]phenyl,
(24) 4-[1-[4-cyano-3-(trifluoromethyl)phenyl]pyrrolidin-3-yl]phenyl,
(25) 4-[1-[4-cyano-3-(difluoromethyl)phenyl]-4-piperidyl]phenyl,
(26) 4-[(4*R*)-1-[4-cyano-3-(trifluoromethyl)phenyl]azepan-4-yl]phenyl,
30 (27) 4-[(4*R*)-1-[4-cyano-3-(trifluoromethyl)phenyl]azepan-4-yl]phenyl,
(28) 4-[1-[4-cyano-3-(trifluoromethyl)phenyl]azepan-4-yl]phenyl,
(29) 4-[1-[4-cyano-3-(trifluoromethyl)phenyl]-4-piperidyl]-3,5-difluoro-phenyl,
(30) 4-[(2*S*)-4-[4-cyano-2-fluoro-3-(trifluoromethyl)phenyl]-2-methyl-piperazin-1-yl]phenyl,
(31) 4-[(3*R*)-4-[4-cyano-3-(trifluoromethyl)phenyl]-3-methyl-piperazin-1-yl]phenyl,
35 (32) 4-[(3*S*)-4-[4-cyano-3-(trifluoromethyl)phenyl]-3-methyl-piperazin-1-yl]phenyl,
(33) (3*S*,4*R*)-1-[4-cyano-2-fluoro-3-(trifluoromethyl)phenyl]-3-methyl-4-piperidyl,
(34) (3*R*,4*S*)-1-[4-cyano-2-fluoro-3-(trifluoromethyl)phenyl]-3-methyl-4-piperidyl,
(35) 4-[1-[4-cyano-2-ethyl-3-(trifluoromethyl)phenyl]-4-piperidyl]phenyl,
(36) 4-[1-[4-cyano-2-fluoro-3-(trifluoromethyl)phenyl]-4-piperidyl]-3,5-difluoro-phenyl,
40 (37) 4-[1-[4-cyano-2-fluoro-3-(trifluoromethyl)phenyl]-4-piperidyl]-3-fluoro-phenyl,

- (38) 4-[1-(4-cyano-3-cyclopropyl-phenyl)-4-piperidyl]-3-fluoro-phenyl and
 (39) 4-[1-[4-cyano-2-fluoro-3-(trifluoromethyl)phenyl]-4-piperidyl]-3-methyl-phenyl.

In a further aspect of the specification there is provided a PROTAC compound or a pharmaceutically acceptable salt thereof, containing an E3 ubiquitin ligase cereblon binder unit and an AR binding unit of

Formula (Ia) or **Formula (Ib)**:



where:

Q^A is $-G-Q^H-$ or $-G-(C_{1-3}alkylene)-$;

G is a direct bond, $-CH_2-$, $-O-$, or $-N(R^G)-$ where each R^G is independently H or $C_{1-3}alkyl$;

Q^H is a 4-12-membered nitrogen-containing saturated or partially unsaturated heterocyclic group;

and where R^1 , p , X^1 , X^2 , X^3 , X^4 , n , m , R^{2a} , R^{2b} , Q , Y^1 , Y^2 , Y^3 , Y^4 , R^3 and q may take any of the values defined herein for each of these groups/variables respectively.

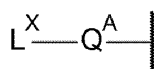
In one embodiment Q^H is a 4-12-membered nitrogen-containing saturated heterocyclic group.



For avoidance of doubt in **Formula (Ib)** indicates a point of connection via a single covalent bond to the remainder of the PROTAC compound.

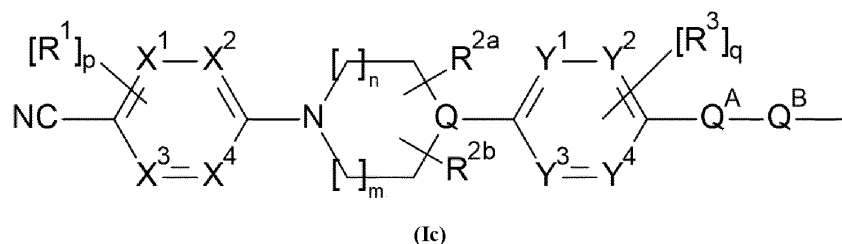
In a further aspect of the specification there is provided a PROTAC compound or a pharmaceutically acceptable salt thereof, containing an E3 ubiquitin ligase cereblon binder unit linked to an AR binding unit of **Formula (Ia)** of **Formula (Ib)**, as defined herein.

In further embodiments of this specification **Formula (Ib)** may be:



where L^X may be any of the groups (1) to (28) or (1) to (39) listed hereinabove in connection with **Formula (Ia)**; and where Q^A may take any value(s) disclosed herein for Q^A .

In a further aspect of the specification there is provided a PROTAC compound or a pharmaceutically acceptable salt thereof, containing an E3 ubiquitin ligase cereblon binder unit and an AR binding unit of **Formula (Ia)** of **Formula (Ic)**:



where:

Q^A is $-G-Q^H-$ or $-G-(C_{1-5}alkylene)-$;

5 G is a direct bond, $-CH_2-$, $-O-$, or $-N(R^G)-$ where R^G is H or $C_{1-3}alkyl$;

Q^B is a direct bond, $-Q^{B1}-Q^{B2}-Q^{B3}-$ or $C_{1-3}alkylene$ optionally substituted by one or more F (e.g. 1 or 2);

where:

Q^{B1} & Q^{B3} each independently represent a direct bond or $C_{1-2}alkylene$;

Q^{B2} is Q^H , $-O-CH_2CH_2-O-$, $-O-$ or $-N(R^J)-$ where R^J is H or $C_{1-3}alkyl$;

10 and each Q^H is independently a 4-12-membered nitrogen-containing saturated or partially unsaturated heterocyclic group;

where the values of Q^A and Q^B are selected so that **Formula (Ic)** does not contain any N-N or N-O bonds;

and where R^1 , p , X^1 , X^2 , X^3 , X^4 , n , m , R^{2a} , R^{2b} , Q , Y^1 , Y^2 , Y^3 , Y^4 , R^3 and q may otherwise take any of the values defined herein for each of these groups/variables respectively.

15 In one embodiment Q^H is a 4-12-membered nitrogen-containing saturated heterocyclic group. For avoidance of

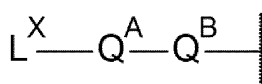


doubt in **Formula (Ic)** indicates a point of connection via a single covalent bond to the remainder of the PROTAC compound.

In a further aspect of the specification there is provided a PROTAC compound or a pharmaceutically acceptable salt thereof, containing an E3 ubiquitin ligase cereblon binder unit linked to an AR binding unit of

20 **Formula (Ia)** of **Formula (Ic)**, as defined herein.

In further embodiments of this specification **Formula (Ib)** may be:



where L^X may be any of the groups (1) to (28) listed hereinabove in connection with **Formula (Ia)**; and where

Q^A and Q^B may take any value(s) disclosed herein for Q^A and Q^B .

25 In further embodiments there is/are provided compound(s) or pharmaceutically acceptable salt thereof wherein said compound(s) is/are selected from one or more of the "Examples" listed hereinafter.

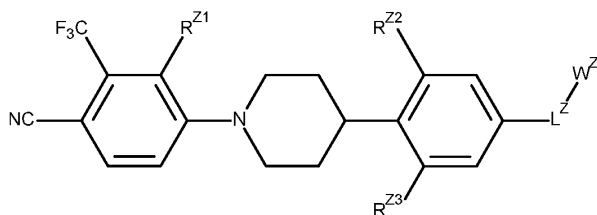
Thus, these embodiments include one or more specific **Examples** (for instance one **Example**, or two or three specific **Examples**) selected from the group consisting of **Examples** 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14,

30 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123,

124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 153, 164, 165, 166 and 167.

- 5 It is to be understood that the compound of an **Example** listed hereinafter relates to the title compound name, and is not limited in any way by the method of preparation nor whether a given compound was isolated in the form of a salt rather than as a neutral molecule.

In some embodiments there is provided a compound of Formula (VI):



or a pharmaceutically acceptable salt thereof,

- 10 wherein:

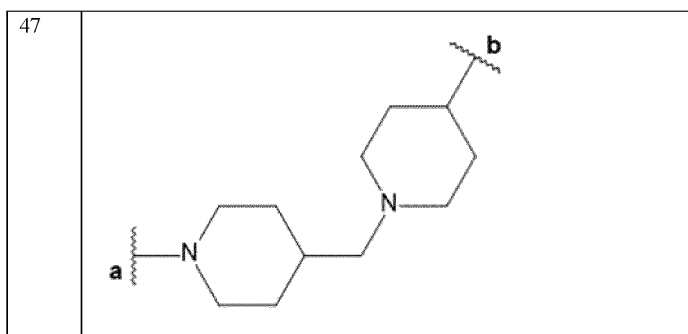
R^{Z1} is H or F;

R^{Z2} is H or F;

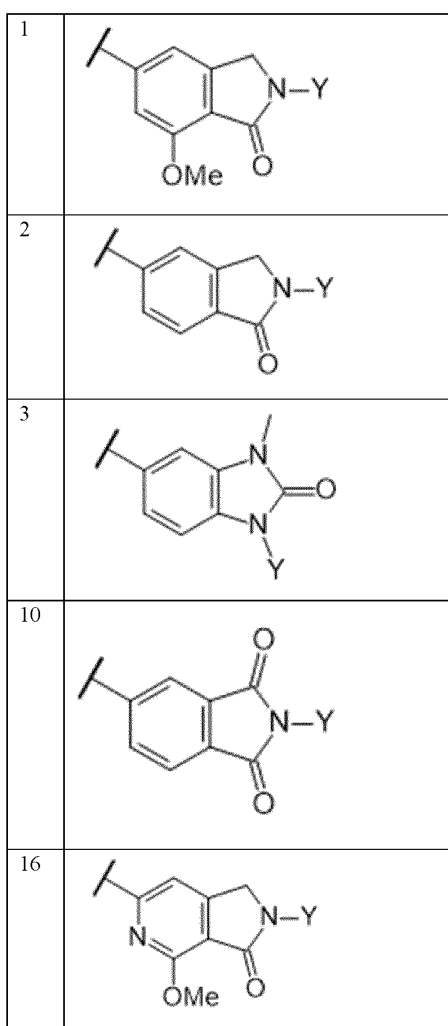
R^{Z3} is H or F;

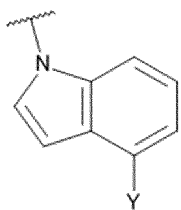
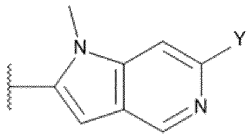
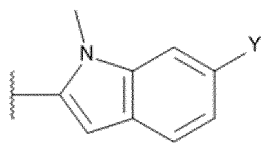
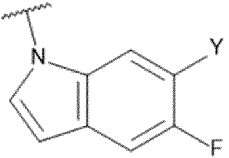
L^Z is a linker selected from 1, 3, 45 and 47:

1	Chemical structure 1: A linker consisting of a piperidine ring connected to a 4-((4-oxo-4H-pyran-2-yl)methoxy)butyl group. The piperidine ring is substituted with a wavy line 'a' and a wavy line 'b'.
3	Chemical structure 3: A linker consisting of a piperidine ring connected to a 4-((4-oxo-4H-pyran-2-yl)methoxy)butyl group. The piperidine ring is substituted with a wavy line 'a' and a wavy line 'b'.
45	Chemical structure 45: A linker consisting of a piperidine ring connected to a 4-((4-oxo-4H-pyran-2-yl)methoxy)butyl group. The piperidine ring is substituted with a wavy line 'a' and a wavy line 'b'.



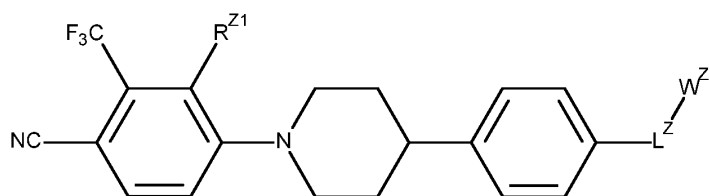
and W^Z is selected from 1, 2, 3, 10, 16, 22, 23, 24 and 26:



22	
23	
24	
26	

where Y is N-(2,6-dioxopiperidin-3-yl).

In some embodiments there is provided a compound of Formula (VI-1):

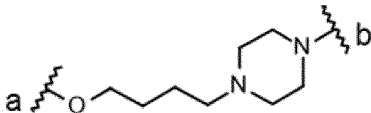


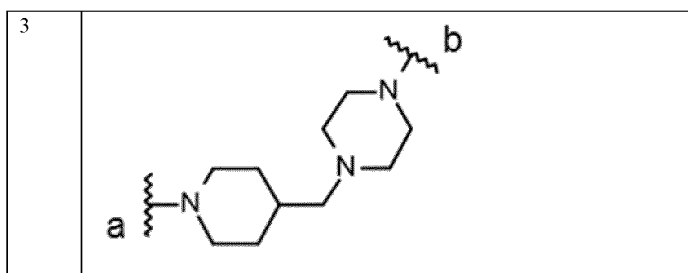
or a pharmaceutically acceptable salt thereof,

5 wherein:

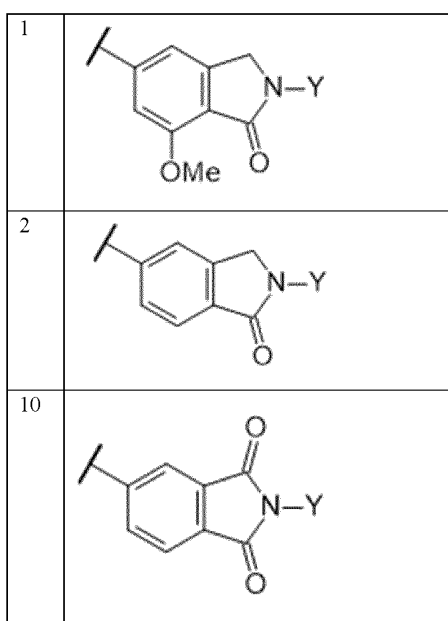
R^{Z1} is H or F;

L^Z is a linker selected from 1 and 3:

1	
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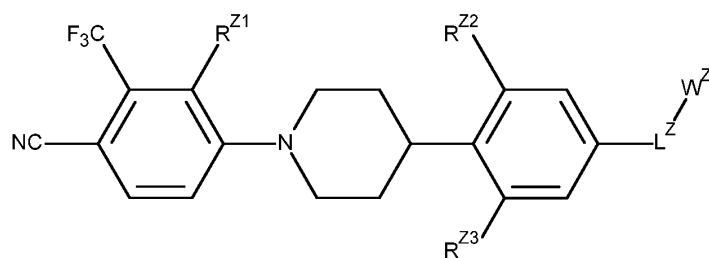


and W^Z is selected from 1, 2 and 10:



where Y is N-(2,6-dioxopiperidin-3-yl).

In some embodiments there is provided a compound of Formula (VI-2):



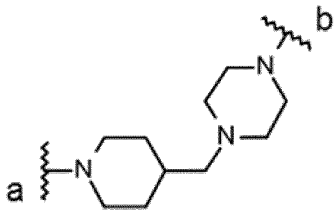
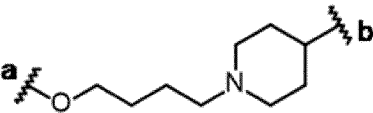
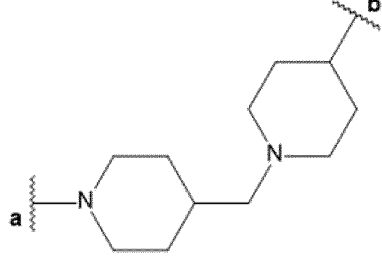
- 5 or a pharmaceutically acceptable salt thereof,
wherein:

R^{Z1} is H or F;

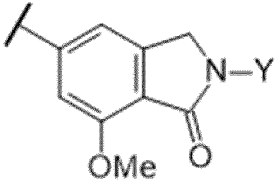
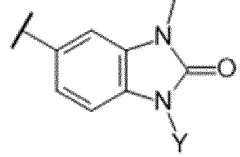
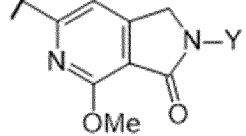
R^{Z2} is H or F;

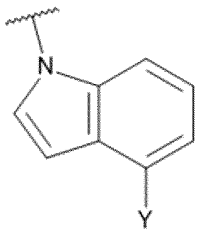
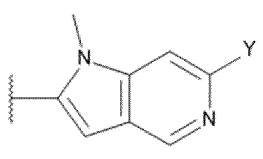
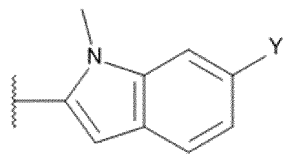
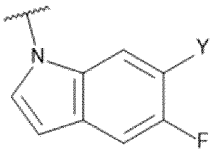
R^{Z3} is H or F;

- 10 L^Z is a linker selected from 3, 45 and 47:

3	
45	
47	

and W^Z is selected from 1, 3, 16, 22, 23, 24 and 26:

1	
3	
16	

22	
23	
24	
26	

where Y is N-(2,6-dioxopiperidin-3-yl).

A further embodiment provides any of the embodiments, claims or aspects defined herein with the proviso that one or more specific **Examples** (for instance one **Example**, or two or three specific **Examples**) selected from the group consisting of **Examples** 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135 and 136 is individually disclaimed.

A further embodiment provides any of the embodiments, claims or aspects defined herein with the proviso that one or more specific **Examples** (for instance one **Example**, or two or three specific **Examples**) selected from the group consisting of **Examples** 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166 and 167 is individually disclaimed.

The compounds of **Formula (I)** and PROTAC compounds containing binding units of **Formula (Ia)** may have one or more chiral centres and it will be recognised that such compounds may be prepared, isolated and/or supplied with or without the presence of one or more of the other possible enantiomeric and/or diastereomeric isomers of said compounds or that such isomers may be provided in any relative proportions.

5 The preparation of enantioenriched/ enantiopure and/or diastereoenriched/ diastereopure compounds may be carried out by standard techniques of organic chemistry that are well known in the art, for example by synthesis from enantioenriched or enantiopure starting materials, and/or by use of an appropriately enantioenriched or enantiopure catalyst during synthesis, and/or by resolution of a racemic or partially enriched mixture of stereoisomers, for example via chiral chromatography.

10 For use in a pharmaceutical context it may be preferable to provide such compounds (or a pharmaceutically acceptable salt thereof) without large amounts of the other stereoisomeric forms being present.

Accordingly, in one embodiment there is provided a composition comprising a compound of **Formula (I)** [or PROTAC compound containing a unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, optionally together with one or more of the other stereoisomeric forms of the compound of **Formula (I)** [or PROTAC compound containing a unit of **Formula (Ia)**] or pharmaceutically acceptable salt thereof, wherein the compound of **Formula (I)** [or PROTAC compound containing a unit of **Formula (Ia)**] or pharmaceutically acceptable salt thereof is present within the composition with a diastereomeric excess (%de) of $\geq 90\%$.

20 In a further embodiment the %de in the above-mentioned composition is $\geq 95\%$.

In a further embodiment the %de in the above-mentioned composition is $\geq 98\%$.

In a further embodiment the %de in the above-mentioned composition is $\geq 99\%$.

In a further embodiment there is provided a composition comprising a compound of **Formula (I)** [or PROTAC compound containing a unit of **Formula (Ia)** as defined herein] or a pharmaceutically acceptable salt thereof, optionally together with one or more of the other stereoisomeric forms of the compound of **Formula (I)** [or PROTAC compound containing a unit of **Formula (Ia)** as defined herein] or pharmaceutically acceptable salt thereof, wherein the compound of **Formula (I)** [or PROTAC compound containing a unit of **Formula (Ia)** as defined herein] or pharmaceutically acceptable salt thereof is present within the composition with an enantiomeric excess (%ee) of $\geq 90\%$.

30 In a further embodiment the %ee in the above-mentioned composition is $\geq 95\%$.

In a further embodiment the %ee in the above-mentioned composition is $\geq 98\%$.

In a further embodiment the %ee in the above-mentioned composition is $\geq 99\%$.

In a further embodiment there is provided a composition comprising a compound of **Formula (I)** [or PROTAC compound containing a unit of **Formula (Ia)** as defined herein] or a pharmaceutically acceptable salt thereof, optionally together with one or more of the other stereoisomeric forms of the compound of **Formula (I)** [or PROTAC compound containing a unit of **Formula (Ia)** as defined herein], or pharmaceutically acceptable salt thereof, wherein the compound of **Formula (I)** [or PROTAC compound containing a unit of **Formula (Ia)** as defined herein], or pharmaceutically acceptable salt thereof is present

within the composition with an enantiomeric excess (%ee) of $\geq 90\%$ and a diastereomeric excess (%de) of $\geq 90\%$.

In further embodiments of the above-mentioned composition the %ee and %de may take any combination of values as listed below:

- 5
- The %ee is $\leq 5\%$ and the %de is $\geq 80\%$.
 - The %ee is $\leq 5\%$ and the %de is $\geq 90\%$.
 - The %ee is $\leq 5\%$ and the %de is $\geq 95\%$.
 - The %ee is $\leq 5\%$ and the %de is $\geq 98\%$.
 - The %ee is $\geq 95\%$ and the %de is $\geq 95\%$.
- 10
- The %ee is $\geq 98\%$ and the %de is $\geq 98\%$.
 - The %ee is $\geq 99\%$ and the %de is $\geq 99\%$.

In a further embodiment there is provided a pharmaceutical composition which comprises a compound of the **Formula (I)** [or PROTAC compound containing a unit of **Formula (Ia)** as defined herein], or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient.

- 15
- In one embodiment there is provided a pharmaceutical composition which comprises a compound of the **Formula (I)** [or PROTAC compound containing a unit of **Formula (Ia)** as defined herein], or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient, optionally further comprising one or more of the other stereoisomeric forms of the compound of **Formula (I)** [or PROTAC compound containing a unit of **Formula (Ia)** as defined herein], or pharmaceutically acceptable
- 20
- salt thereof, wherein the compound of **Formula (I)** [or PROTAC compound containing a unit of **Formula (Ia)** as defined herein], or pharmaceutically acceptable salt thereof is present within the composition with an enantiomeric excess (%ee) of $\geq 90\%$.

In a further embodiment the %ee in the above-mentioned composition is $\geq 95\%$.

In a further embodiment the %ee in the above-mentioned composition is $\geq 98\%$.

- 25
- In a further embodiment the %ee in the above-mentioned composition is $\geq 99\%$.

- In one embodiment there is provided a pharmaceutical composition which comprises a compound of the **Formula (I)** [or PROTAC compound containing a unit of **Formula (Ia)** as defined herein], or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient, optionally further comprising one or more of the other stereoisomeric forms of the compound of **Formula (I)**
- 30
- [or PROTAC compound containing a unit of **Formula (Ia)** as defined herein], or pharmaceutically acceptable salt thereof, wherein the compound of **Formula (I)** [or PROTAC compound containing a unit of **Formula (Ia)** as defined herein], or pharmaceutically acceptable salt thereof is present within the composition with a diastereomeric excess (%de) of $\geq 90\%$.

In a further embodiment the %de in the above-mentioned composition is $\geq 95\%$.

- 35
- In a further embodiment the %de in the above-mentioned composition is $\geq 98\%$.

In a further embodiment the %de in the above-mentioned composition is $\geq 99\%$.

In one embodiment there is provided a pharmaceutical composition which comprises a compound of the **Formula (I)** [or PROTAC compound containing a unit of **Formula (Ia)** as defined herein], or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient,

- optionally further comprising one or more of the other stereoisomeric forms of the compound of **Formula (I)** [or PROTAC compound containing a unit of **Formula (Ia)** as defined herein], or pharmaceutically acceptable salt thereof, wherein the compound of **Formula (I)** [or PROTAC compound containing a unit of **Formula (Ia)** as defined herein], or pharmaceutically acceptable salt thereof is present within the composition with an
- 5 enantiomeric excess (%ee) of $\geq 90\%$ and a diastereomeric excess (%de) of $\geq 90\%$.

In further embodiments of the above-mentioned pharmaceutical composition the %ee and %de may take any combination of values as listed below:

- The %ee is $\geq 95\%$ and the %de is $\geq 95\%$.
- The %ee is $\geq 98\%$ and the %de is $\geq 98\%$.
- 10 • The %ee is $\geq 99\%$ and the %de is $\geq 99\%$.

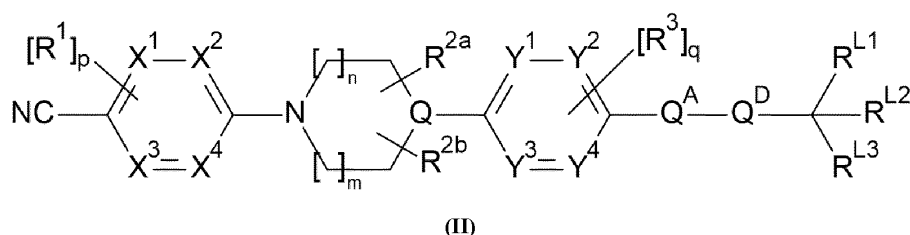
- The compounds of **Formula (I)** [or PROTAC compound containing a unit of **Formula (Ia)** as defined herein], and pharmaceutically acceptable salts thereof may be prepared, used or supplied in amorphous form, crystalline form, or semicrystalline form and any given compound of **Formula (I)** [or PROTAC compound containing a unit of **Formula (Ia)** as defined herein], or pharmaceutically acceptable salt thereof may be capable of being formed into more than one crystalline / polymorphic form, including hydrated (e.g. hemi-hydrate, a mono-hydrate, a di-hydrate, a tri-hydrate or other stoichiometry of hydrate) and/or solvated forms. It is to be understood that the present specification encompasses any and all such solid forms of the compound of **Formula (I)** [or PROTAC compound containing a unit of **Formula (Ia)** as defined herein], and pharmaceutically acceptable salts thereof.

- 20 In further embodiments there is provided a compound of **Formula (I)** [or PROTAC compound containing a unit of **Formula (Ia)** as defined herein] which is obtainable by the methods described in the 'Examples' section hereinafter.

Intermediate Compounds

- 25 As demonstrated in the experimental section hereinafter, the compounds of **Formula (I)** or PROTACs of **Formula (Ia)** may be prepared, for example, by the following methods.

A compound of **Formula (I)** [or salt thereof] or a PROTAC compound of **Formula (Ia)** [or a salt thereof] may be prepared from a compound of **Formula (II)**:



- 30 or a salt thereof, where:

Q^A is $-G-Q^H-$ or $-G-(C_{1-3}alkylene)-$;

G is a direct bond, $-CH_2-$, $-O-$, or $-N(R^G)-$ where R^G is H or $C_{1-3}alkyl$;

Q^H is a 4 to 12-membered nitrogen-containing saturated or partially unsaturated heterocyclic group;

- 35 Q^D is a direct bond or $C_{1-2}alkylene$ optionally substituted by one or more F;

R^{L1} and R^{L2} together form “=O”, R^{L3} is H;

where when Q^D is a direct bond and Q^A is $-G-Q^H$ -, the value of Q^H is selected so that Q^D connects to a C atom of Q^H ; and

R^1 , p , X^1 , X^2 , X^3 , X^4 , n , m , Q , R^{2a} , R^{2b} , Y^1 , Y^2 , Y^3 , Y^4 , R^3 and q may take any of the values disclosed herein for each of those groups/variables respectively.

In one embodiment Q^H is a 4-12-membered nitrogen-containing saturated heterocyclic group.

Accordingly such compound of **Formula (II)** as described above is an aldehyde which may be reacted with a suitable molecule containing an amine group (for example a secondary amine group) to form the compound of **Formula (I)** or PROTAC compound of **Formula (Ia)** – either directly, or after one or more additional reaction steps. Such reaction of said aldehyde with said amine can be carried out under reductive amination conditions, using for example $NaBH(OAc)_3$ or another reductive amination protocol known to the skilled person.

Such aldehyde may in turn be prepared from the corresponding acetal, for example a compound of **Formula (II)**, or salt thereof, as defined above, except that: R^{L1} and R^{L2} are each independently C_{1-6} alkoxy (for example C_{1-3} alkoxy) or R^{L1} & R^{L2} together form $-O-(CH_2)_k-O-$ where k is 2 or 3. Such acetal may be converted to the corresponding aldehyde under acidic conditions, for example using formic acid under conditions well known to the skilled person.

Alternatively, as shown in the experimental section hereinafter, the above-mentioned aldehyde may be prepared by oxidation of the corresponding primary alcohol, i.e. a compound of **Formula (II)**, or salt thereof, as defined above except that R^{L1} is OH and R^{L2} is H. Such oxidation may be carried out using mild oxidising conditions, for example Dess-Martin periodinane or some other mild oxidation protocol known to the skilled person.

As shown in the experimental section hereinafter, a compound of **Formula (I)** [or salt thereof] or a PROTAC compound of **Formula (Ia)** [or a salt thereof] may be prepared from a compound of **Formula (II)** or a salt thereof, as described above except that R^{L1} is a leaving group and R^{L2} is H. Accordingly, such compound of **Formula (II)** is an electrophile that may be reacted with a molecule containing an amine group (for example a secondary amine group) via an alkylation reaction to form the compound of **Formula (I)** or PROTAC compound of **Formula (Ia)** – either directly, or after one or more additional reaction steps. Suitable leaving groups for alkylation reactions are well known to the skilled person and include Cl, Br, I, trifluoromethanesulfonate, mesylate and tosylate. Alkylation reaction conditions are well known to the skilled person and generally involve a non-nucleophilic base (e.g. DIPEA) and a polar aprotic solvent (e.g. MeCN). As demonstrated in the experimental section hereinafter, in cases where the leaving group is not I, a metal iodide salt may be used in the reaction mixture to form the corresponding iodide *in-situ* (i.e. where R^{L1} is I) to facilitate the overall alkylation process. As shown in the experimental section hereinafter, a compound of **Formula (II)** where R^{L1} is a bromo leaving group may be prepared from the corresponding primary alcohol (i.e. as already described above where R^{L1} is OH, and R^{L2} & R^{L3} are both H).

In turn, the above-mentioned primary alcohol compound of **Formula (II)** may be prepared by the reduction of the corresponding ester compound, i.e. a compound of **Formula (II)**, or salt thereof, as defined above, except that: R^{L1} and R^{L2} together form “=O” and R^{L3} is C_{1-6} alkoxy (for example C_{1-3} alkoxy). Such

reduction may be carried out using strong reduction conditions, for example using DIBAL or other stronger reducing conditions which are well known to the skilled person.

- Alternatively, as demonstrated in the experimental section hereinafter, it may be convenient to form the above-mentioned primary alcohol compound of **Formula (II)** via deprotection of a protected form of the alcohol. For example, deprotection of a compound where the alcohol is protected by a silicon-based protecting group, using a source of fluoride in order to achieve the deprotection, for example TBAF or other deprotection methods well-known to the skilled person.

- Therefore, as described above, various compounds of **Formula (II)**, and salts thereof, may be useful as intermediates in the synthesis of the compounds of **Formula (I)** or PROTAC compounds of **Formula (Ia)**, and accordingly such intermediate compounds provide a further aspect of the specification.

Therefore, in a further aspect there is provided a compound of **Formula (II)**, as shown above, or a salt thereof, wherein:

Q^A is $-G-Q^H-$ or $-G-(C_{1-5}alkylene)-$;

G is a direct bond, $-CH_2-$, $-O-$, or $-N(R^G)-$ where R^G is H or $C_{1-3}alkyl$;

- Q^H is a 4-12-membered nitrogen-containing saturated or partially unsaturated heterocyclic group;

Q^D is a direct bond or $C_{1-2}alkylene$ optionally substituted by one or more F (for example 1 or 2 F); and

- (i) R^{L1} & R^{L2} together form “=O” and R^{L3} is H or $C_{1-6}alkoxy$ (for example OMe);
- (ii) R^{L1} & R^{L2} are each independently $C_{1-6}alkoxy$ (for example OMe), and R^{L3} is H;
- (iii) R^{L1} & R^{L2} together form $-O-(CH_2)_k-O-$ where k is 2 or 3, and R^{L3} is H; or
- (iv) R^{L1} is OH, OPG^1 (where PG^1 is a protecting group), or LG^1 (where LG^1 is a leaving group), and R^{L2} & R^{L3} are both H;

where when Q^D is a direct bond and Q^A is $-G-Q^H-$, the value of Q^H is selected so that Q^D connects to a C atom of Q^H ,

and R^1 , p , X^1 , X^2 , X^3 , X^4 , n , m , Q , R^{2a} , R^{2b} , Y^1 , Y^2 , Y^3 , Y^4 , R^3 and q may take any of the values disclosed

- herein for each of those groups/variables respectively.

In one embodiment Q^H is a 4-12-membered nitrogen-containing saturated heterocyclic group.

The skilled person is aware of suitable protecting groups for alcohol groups and therefore is aware of suitable values of PG^1 . For example PG^1 is an alcohol protecting group.

In one embodiment PG^1 is a silicon-based alcohol protecting group.

- In one embodiment PG^1 is $Si(R^{Si})_3$ where each R^{Si} is independently a $C_{1-6}hydrocarbyl$ group.

In one embodiment PG^1 is *tert*-butyldimethylsilyl or *tert*-butyldiphenylsilyl.

In one embodiment the LG^1 is selected from Cl, Br, I, trifluoromethanesulfonate and $C_{1-7}hydrocarbylsulfonate$ (for example mesylate or *p*-toluenesulfonate).

In one embodiment LG^1 is Br or I.

- In one embodiment LG^1 is Br.

In one embodiment LG^1 is Cl.

In one embodiment LG^1 is I.

In one embodiment LG^1 is trifluoromethanesulfonate.

In one embodiment LG^1 is $C_{1-7}hydrocarbylsulfonate$.

- In one embodiment LG^1 is mesylate.

In one embodiment LG^1 is *p*-toluenesulfonate.

In one embodiment Q^{D} is a direct bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$ or $-\text{CF}_2\text{CH}_2-$.

In one embodiment Q^{D} is a direct bond.

In one embodiment Q^{D} is CH_2 .

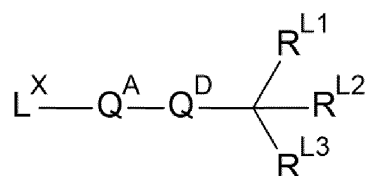
5 In one embodiment Q^{D} is C_{1-2} alkylene optionally substituted by 1 or 2 F.

In one embodiment Q^{D} is C_{1-2} alkylene.

In one embodiment Q^{D} is $-\text{CH}_2\text{CH}_2-$.

In one embodiment Q^{D} is $-\text{CF}_2\text{CH}_2-$.

In further embodiments of this specification **Formula (II)** may be **Formula (IIa)**:

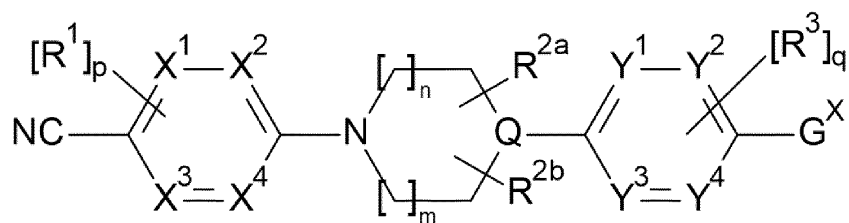


10

(IIa)

where L^{X} may be any of the groups (1) to (28) or (1) to (39) listed hereinabove in connection with **Formula (Ia)**; and where Q^{A} , Q^{D} , R^{L1} , R^{L2} and R^{L3} may take any of the values disclosed herein for each of said groups respectively.

15 As demonstrated in the experimental section hereinafter, certain compounds of **Formula (I)** and certain PROTACS of **Formula (Ia)** and certain intermediate compounds of **Formula (II)** may be prepared using a compound of **Formula (III)**:



(III)

20 or a salt thereof, where G^{X} is OH, where the oxygen atom of said OH is alkylated by a suitable molecule to form certain compounds of **Formula (I)** or PROTACs of **Formula (Ia)** - either directly, or after one or more further reaction steps (for example via **Formula (II)** as described hereinabove). Such alkylation reactions may be carried out under conditions well known to the skilled person, for example using a primary alkyl bromide (or using some other leaving group in place of Br) using a non-nucleophilic base such as a metal carbonate

25 (e.g. K_2CO_3) in a polar aprotic solvent such as MeCN, optionally in the presence of a metal iodide salt such as KI.

Alternatively, as shown in the experimental section hereinafter, a compound of **Formula (III)** where G^{X} is $-\text{NH}(\text{R}^{\text{G}})$ [where R^{G} is H or C_{1-3} alkyl (for example Me)] may be used as an intermediate to prepare compounds of **Formula (I)** or PROTACs of **Formula (Ia)** via reductive amination chemistry with an

30 appropriate aldehyde-containing compound.

Alternatively, as shown in the experimental section hereinafter, a compound of **Formula (III)** where G^X is bromo may be coupled with a secondary amine compound to give certain compounds of **Formula (I)** or PROTACs of **Formula (Ia)** - either directly, or after one or more further reaction steps (for example via **Formula (II)** as described hereinabove). Similarly, compounds of **Formula (III)** where G^X is chloro or trifluoromethanesulfonate may also be used in a coupling reaction with the relevant secondary amine to give certain compounds of **Formula (I)** or PROTACs of **Formula (Ia)**. Such coupling may be carried out under palladium-based coupling conditions (e.g. using 'Ruphos Pd G3' and 'Ruphos') in the presence of a base and an anhydrous solvent such as 1,4-dioxane under an inert atmosphere, or by heating with CuI in the presence of a base such as K_3PO_4 in a polar solvent such as DMSO. Alternatively, also as shown in the experimental section herein, a compound of **Formula (III)** where G^X is bromo may be coupled with a suitable alcohol to form certain compounds of **Formula (I)** or PROTACs of **Formula (Ia)** - either directly, or after one or more further reaction steps (for example via **Formula (II)** as described hereinabove). Such coupling may be carried out using a palladium-based reagent such as 'Rockphos Pd G3' in the presence of a base such as Cs_2CO_3 in a solvent such as toluene.

Accordingly, compounds of **Formula (III)**, and salts thereof, may be useful as intermediates in the synthesis of certain compounds of **Formula (I)** or PROTAC compounds of **Formula (Ia)** or compounds of **Formula (II)**, and accordingly such intermediate compounds provide a further aspect of the specification.

Therefore, in a further aspect there is provided a compound of **Formula (III)**, as shown above, or a salt thereof, wherein:

G^X is OH, Cl, Br, trifluoromethanesulfonate or $-NH(R^G)$ where R^G is H or $C_{1-3}alkyl$; and R^1 , p, X^1 , X^2 , X^3 , X^4 , n, m, Q, R^{2a} , R^{2b} , Y^1 , Y^2 , Y^3 , Y^4 , R^3 and q may take any of the values disclosed herein for each of those groups/variables respectively.

G^X is OH, Cl, Br, trifluoromethanesulfonate or $-NH(R^G)$ where R^G is $C_{1-3}alkyl$ (for example Me).

In one embodiment G^X is OH, Br, trifluoromethanesulfonate or $-NH(R^G)$ where R^G is $C_{1-3}alkyl$ (for example Me).

In one embodiment G^X is OH, Br or $-NH(R^G)$ where R^G is $C_{1-3}alkyl$ (for example Me).

In one embodiment G^X is OH or Br.

In one embodiment G^X is OH.

In one embodiment G^X is Br.

In one embodiment G^X is Cl.

In one embodiment G^X is trifluoromethanesulfonate.

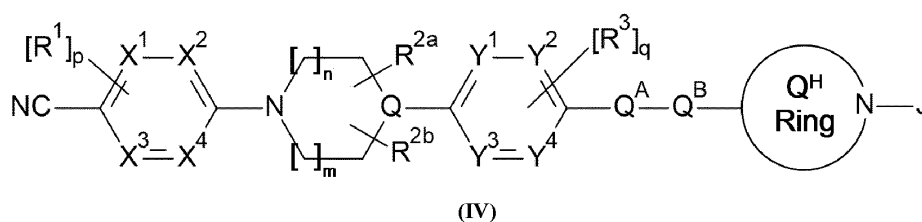
In one embodiment G^X is $-NH(R^G)$ where R^G is H or $C_{1-3}alkyl$.

In one embodiment G^X is $-NH(R^G)$ where R^G is $C_{1-3}alkyl$.

In one embodiment G^X is $-NH(Me)$.

In further embodiments of this specification, **Formula (III)** may be L^X-G^X wherein L^X may be any of the groups (1) to (28) or (1) to (39) listed hereinabove in connection with **Formula (Ia)**; and where G^X may take any value(s) disclosed herein for G^X .

As demonstrated in the experimental section hereinafter, certain compounds of **Formula (I)** and PROTACs of **Formula (Ia)** may be prepared using an intermediate compound of **Formula (IV)**:



or a salt thereof, as further defined below. For example, a compound of **Formula (IV)**, or salt thereof, where **J** is H (i.e. a secondary amine compound) may be coupled to a further chemical fragment, using chemistry well known to the skilled person and exemplified in the experimental section hereinafter, to provide a compound of **Formula (I)** or PROTAC of **Formula (Ia)**, either directly, or after one or more further reaction steps.

In turn, such a compound of **Formula (IV)** where **J** is H may conveniently be prepared via deprotection of an *N*-protected form of the aforementioned amine compound. Accordingly compounds of **Formula (IV)** where **J** is H may be conveniently be prepared using a compound of **Formula (IV)** where **J** is **PG²** where **PG²** is a nitrogen protecting group (for example a C₁₋₆alkoxycarbonyl group such as *tert*-butoxycarbonyl). Therefore, compounds of **Formula (IV)** where **J** is **PG²** are useful intermediates in the preparation of the compound of **Formula (I)** and PROTAC of **Formula (Ia)** and provide a further aspect of the specification.

Therefore in a further aspect of the specification there is provided a compound of **Formula (IV)** as depicted above, or a salt thereof, wherein:

J is H or **PG²** where **PG²** is a nitrogen protecting group (for example a *tert*-butoxycarbonyl group);

Q^A is -**G-Q^H**- or -**G-(C₁₋₅alkylene)**-;

G is a direct bond, -CH₂-, -O-, or -N(**R^G**)- where **R^G** is H or C₁₋₃alkyl;

Q^B is a direct bond, -**Q^{B1}-Q^{B2}-Q^{B3}**- or C₁₋₃alkylene optionally substituted by one or more F (e.g. 1 or 2);

where:

Q^{B1} & **Q^{B3}** each independently represent a direct bond or C₁₋₂alkylene;

Q^{B2} is **Q^H**, -O-CH₂CH₂-O-, -O- or -N(**R^J**)- where **R^J** is H or C₁₋₃alkyl;

and each **Q^H** (including the “**Q^H Ring**” attached to **J**) is independently a 4-12-membered nitrogen-containing saturated or partially unsaturated heterocyclic group;

where the values of **Q^A**, **Q^B** and **Q^H Ring** are selected so that **Formula (IV)** does not contain any N-N or N-O bonds;

and where **R¹**, **p**, **X¹**, **X²**, **X³**, **X⁴**, **n**, **m**, **R^{2a}**, **R^{2b}**, **Q**, **Y¹**, **Y²**, **Y³**, **Y⁴**, **R³** and **q** may take any of the values defined herein for each of these groups/variables respectively.

In one embodiment each **Q^H** (including the “**Q^H Ring**” attached to **J**) is independently a 4-12-membered nitrogen-containing saturated heterocyclic group.

In one embodiment the **Q^H Ring** is piperidin-1,4-diyl or piperazin-1,4-diyl.

In one embodiment **J** is H.

In one embodiment **J** is **PG²**.

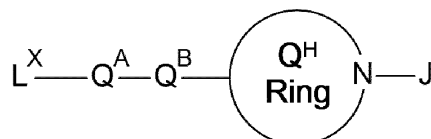
In one embodiment **PG²** is C₁₋₆alkoxycarbonyl.

In one embodiment **PG²** is *tert*-butoxycarbonyl.

In one embodiment where **PG**² is C₁₋₆alkoxycarbonyl (e.g. *tert*-butoxycarbonyl) the ‘and salts thereof’ element of the claim is excluded.

In further embodiments the compound of **Formula (IV)** may take any combination of alternative values mentioned in relation to **Q**^A, **Q**^B and **Q**^H in any other context, embodiment, aspect or claim found herein.

- 5 In further embodiments of this specification **Formula (IV)** may be **Formula (IVa)**:

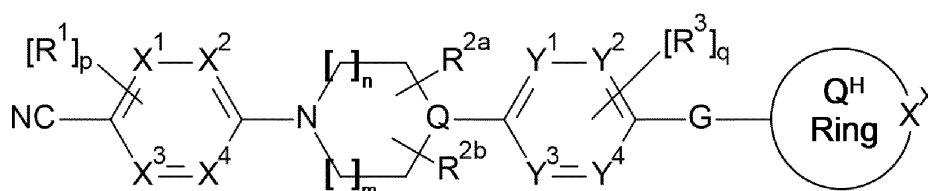


(IVa)

where **L**^X may be any of the groups (1) to (28) or (1) to (39) listed hereinabove in connection with **Formula (Ia)**; and where **Q**^A, **Q**^B, **Q**^H and **J** may take any of the values disclosed herein for each of said groups respectively.

10

As also demonstrated in the experimental section hereinafter, certain compounds of **Formula (I)** and PROTACs of **Formula (Ia)** may be prepared using an intermediate compound of **Formula (V)**:



(V)

15

or a salt thereof, wherein:

X^X is N substituted by **J** where **J** is H;

G is a direct bond, -CH₂-, -O-, or -N(**R**^G)- where **R**^G is H or C₁₋₃alkyl;

Q^H **Ring** is a 4-12-membered nitrogen-containing saturated or partially unsaturated heterocyclic group;

where the values of **G** and **Q**^H **Ring** are selected so that **Formula (V)** does not contain any N-N or N-O bonds;

20

and where **R**¹, **p**, **X**¹, **X**², **X**³, **X**⁴, **n**, **m**, **R**^{2a}, **R**^{2b}, **Q**, **Y**¹, **Y**², **Y**³, **Y**⁴, **R**³ and **q** may take any of the values defined herein for each of these groups/variables respectively.

Such a compound of **Formula (V)** may be converted to a compound of **Formula (I)** or PROTAC of **Formula (Ia)** via reductive amination or alkylation or other coupling chemistry known to the skilled person – to provide the compound of **Formula (I)** or PROTAC of **Formula (Ia)** either directly, or after one or more additional steps.

25

In turn, as shown in the experimental section hereinafter, such a compound of **Formula (V)**, or a salt thereof, may be conveniently prepared by deprotection of the corresponding *N*-protected compound. Such *N*-protected form may be a BOC-protected form (i.e. *tert*-butoxycarbonyl) or may use another *N*-protecting group known to the skilled person. Accordingly, such *N*-protected compounds are also useful intermediates in the preparation of the compounds of **Formula (I)** and PROTACs of **Formula (Ia)** and provide a further aspect of the specification.

30

Accordingly one aspect of the specification provides a compound of **Formula (V)**, or a salt thereof, as described above except that **X^X** is N substituted by **J** where **J** is **PG³** and **PG³** is a protecting group. In one embodiment **PG³** is C₁₋₆alkoxycarbonyl. In one embodiment **PG³** is *tert*-butoxycarbonyl. In one embodiment where **PG³** is C₁₋₆alkoxycarbonyl (e.g. *tert*-butoxycarbonyl) the 'and salts thereof' element of the claim is excluded.

Other compounds of **Formula (I)** and PROTACs of **Formula (Ia)** – and salts thereof – may be prepared from an intermediate compound of **Formula (V)**, or a salt thereof, as described above except that **X^X** is C=O. Such an intermediate may be converted to a compound of **Formula (I)** or PROTAC of **Formula (Ia)** by reductive amination chemistry using an appropriate amine-containing compound, using reductive amination conditions that well-known to the skilled person – either directly or via one or more additional synthetic steps.

In turn, as demonstrated in the experimental section hereinafter, such compounds of **Formula (V)** where **X^X** is C=O may be conveniently prepared from the corresponding compound where the ketone is protected/masked as a ketal. Accordingly such ketal compounds, and salts thereof are useful intermediates in the preparation of a compound of **Formula (I)** or a PROTAC of **Formula (Ia)** and provide a further aspect of the specification.

Accordingly such ketal compound may be represented as a compound of **Formula (V)**, or a salt thereof, as described above except that **X^X** is C substituted by **R^{U1}** and **R^{U2}**, where **R^{U1}** and **R^{U2}** are each C₁₋₆alkoxy; or **R^{U1}** and **R^{U2}** together represent –O-(CH₂)_u-O- where **u** is 2 or 3.

Therefore, in a further aspect of the specification there is provided compound of **Formula (V)**, as depicted above, or a salt thereof, wherein:

X^X is selected from:

- (i) N substituted by **J** where **J** is H or **PG³** where **PG³** is a protecting group; and
- (ii) C substituted by oxo, or by **R^{U1}** and **R^{U2}**, where **R^{U1}** and **R^{U2}** are each C₁₋₆alkoxy; or **R^{U1}** and **R^{U2}** together represent –O-(CH₂)_u-O- where **u** is 2 or 3;

G is a direct bond, -CH₂-, -O-, or -N(**R^G**)- where **R^G** is H or C₁₋₃alkyl;

Q^H Ring is a 4-12-membered nitrogen-containing saturated or partially unsaturated heterocyclic group;

and the values of **G** and **Q^H Ring** are selected so that **Formula (V)** does not contain any N-N or N-O bonds;

and where **R¹**, **p**, **X¹**, **X²**, **X³**, **X⁴**, **n**, **m**, **R^{2a}**, **R^{2b}**, **Q**, **Y¹**, **Y²**, **Y³**, **Y⁴**, **R³** and **q** may take any of the values

defined herein for each of these groups/variables respectively.

In one embodiment **J** is H.

In one embodiment **J** is **PG³**.

In one embodiment **PG³** is C₁₋₆alkoxycarbonyl.

In one embodiment **PG³** is *tert*-butoxycarbonyl.

In one embodiment **X^X** is C=O.

In one embodiment **X^X** is C substituted by **R^{U1}** and **R^{U2}**, where **R^{U1}** and **R^{U2}** are each C₁₋₆alkoxy.

In one embodiment **X^X** is C substituted by **R^{U1}** and **R^{U2}**, where **R^{U1}** and **R^{U2}** together represent –O-(CH₂)_u-O- where **u** is 2 or 3 (for example **u** = 2).

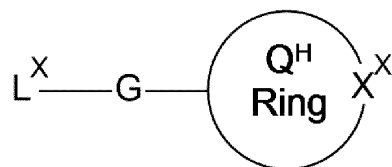
In one embodiment **G** is a direct bond or –O–.

In one embodiment **Q^H Ring** is a 4-12-membered nitrogen-containing saturated heterocyclic group.

The values of **Q^H Ring** may take any of the values mentioned herein for **Q^H**.

In one embodiment **Q^H Ring** is a piperidine ring, a piperazine ring, a 9-azaspiro[5.5]undecane ring or a 3,9-diazaspiro[5.5]undecane ring.

In further embodiments of this specification **Formula (V)** may be **Formula (Va)**:



5

(Va)

where **L^X** may be any of the groups (1) to (28) or (1) to (39) listed hereinabove in connection with **Formula (Ia)**; and where **G**, **Q^H Ring** and **X^X** may take any of the values disclosed herein for each of said groups respectively.

10 In addition to the methods described above, the compounds of **Formulae (I), (II), (III), (IV) & (V)** and PROTAC compounds including **Formula (Ia)** may be prepared according to the general procedures and chemical transformations demonstrated in the experimental section hereinafter and using standard procedures and knowledge known to the skilled chemist.

15 In further embodiments of this specification there is/are provided compound(s), or a salt thereof, wherein said compound(s) is/are selected from one or more of the “**Intermediates**” listed hereinafter in the experimental section.

20 It is to be understood that the compound of an **Intermediate** listed hereinafter relates to the title chemical name listed in the experimental section, and is not limited in any way by the method of preparation nor whether a given intermediate compound was isolated in the form of a salt rather than as a neutral molecule.

According to a further aspect of the specification there is provided a pharmaceutical composition, which comprises a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein, in association with a pharmaceutically acceptable excipient.

25 According to a further aspect of the specification there is provided a pharmaceutical composition, which comprises a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein, for use in the treatment of cancer.

30 According to a further aspect of the specification there is provided a pharmaceutical composition, which comprises a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein, for use in the treatment of a solid tumour.

35 According to a further aspect of the specification there is provided a pharmaceutical composition, which comprises a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein, for use in the treatment of an AR-sensitive tumour type.

According to a further aspect of the specification there is provided a pharmaceutical composition, which comprises a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein, for use in the treatment of tumour types that harbour one or more mutated forms of the androgen receptor.

According to a further aspect of the specification there is provided a pharmaceutical composition, which comprises a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein, for use in the treatment of prostate cancer (for example CRPC, for example metastatic CRPC).

According to a further aspect of the specification there is provided a pharmaceutical composition, which comprises a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein, for use in the treatment of AR-mutated cancer.

In any embodiment, aspect or claim herein that mentions “cancer” without further specificity, further embodiments, aspects or claims may be provided where said cancer is (or includes) AR+ breast cancer.

The compositions may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous or intramuscular dosing). The compositions may be obtained by conventional procedures using conventional pharmaceutical excipients that are well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

For further information on formulations the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host being treated and the particular route of administration.

The size of the dose for therapeutic or prophylactic purposes of compounds of the present specification will naturally vary according to the nature and severity of the disease state, the age and sex of the animal or patient and the route of administration, according to well-known principles of medicine.

As explained hereinabove, the compounds of the present specification may be of value as anti-tumour agents, in particular as selective inhibitors of the proliferation, survival, motility, dissemination and invasiveness of mammalian cancer cells leading to inhibition of tumour growth and survival and to inhibition of metastatic tumour growth. Particularly, the compounds of the present specification may be of value as anti-proliferative and anti-invasive agents in the containment and/or treatment of solid tumour disease.

Accordingly, the compounds of the present specification may be useful in the prevention or treatment of those tumours which are sensitive to degradation of the androgen receptor and that are involved in the signal transduction steps which lead to the proliferation and survival of tumour cells and the migratory ability and invasiveness of metastasising tumour cells. Further, the compounds of the present specification may be useful in the prevention or treatment of those tumours which are treatable by degradation of androgen

receptors, *i.e.* the compounds may be used to produce an androgen receptor degradation effect in a warm-blooded animal in need of such treatment.

According to a further aspect of the specification, there is provided a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein, for use as a medicament.

According to a further aspect of the specification, there is provided a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein, for use in therapy.

According to a further aspect of the specification, there is provided a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein, for use in a method of treatment of the human or animal body by therapy.

According to a further aspect of the specification, there is provided a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein for use in the production of an anti-proliferative effect (for example, in a warm-blooded animal such as man).

According to a further aspect of the specification, there is provided the use of a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein, for the manufacture of a medicament for the production of an anti-proliferative effect (for example, in a warm-blooded animal such as man).

According to a further aspect of the specification, there is provided a method for producing an anti-proliferative effect in a warm-blooded animal, such as man, in need of such effect, which comprises administering to said animal an effective amount of a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein.

According to a further aspect of the specification, there is provided a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein, for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease (for example: in a warm-blooded animal such as man).

According to a further aspect of the specification, there is provided the use of a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein, for the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease (for example: in a warm-blooded animal such as man).

According to a further aspect of the specification, there is provided a method for producing an anti-invasive effect by the containment and/or treatment of solid tumour disease, in a warm-blooded animal, such as man, in need of such effect, which comprises administering to said animal an effective amount of a

compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein.

5 According to a further aspect of the specification, there is provided a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein, for use in the prevention or treatment of cancer (for example: in a warm-blooded animal such as man).

10 According to a further aspect of the specification there is provided the use of a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein, for the manufacture of a medicament for the prevention or treatment of cancer (for example: in a warm-blooded animal such as man).

15 According to a further aspect of the specification there is provided a method for the prevention or treatment of cancer in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein.

20 According to a further aspect of the specification, there is provided a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein, for use in the prevention or treatment of solid tumour(s) (for example, in a warm-blooded animal such as man).

25 According to a further aspect of the specification, there is provided the use of a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein, for the manufacture of a medicament for the prevention or treatment of solid tumour(s) (for example, in a warm-blooded animal such as man).

30 According to a further aspect of the specification, there is provided a method for the prevention or treatment of solid tumour(s) in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein.

35 According to a further aspect of the specification, there is provided a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein, for use in the prevention or treatment of tumour types that are sensitive to degradation of androgen receptors.

40 According to a further aspect of the specification, there is provided the use of a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein, for the manufacture of a medicament for the prevention or treatment of those tumour types that are sensitive to degradation of androgen receptors.

According to a further aspect of the specification, there is provided a method for the prevention or treatment of those tumour types that are sensitive to degradation of androgen receptors in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein.

As explained hereinabove, tumour types that are sensitive to degradation of androgen receptors include prostate cancer (for example castrate-resistant prostate cancer (CRPC), for example metastatic CRPC).

According to a further aspect of the specification, there is provided a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein, for use in providing a degrading effect on androgen receptors (for example in a warm-blooded animal such as man).

According to a further aspect of the specification, there is provided the use of a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein, for the manufacture of a medicament for providing a degrading effect on androgen receptors (for example in a warm-blooded animal such as man).

According to a further aspect of the specification, there is provided a method for providing a degrading effect on androgen receptors in a warm-blooded animal, such as man, in need of such effect, which comprises administering to said animal an effective amount of a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein.

According to a further aspect of the specification, there is provided a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein, for use in providing a selective degrading effect on androgen receptors (for example in a warm-blooded animal such as man).

According to a further aspect of the specification, there is provided the use of a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein, for the manufacture of a medicament for providing a selective degrading effect on androgen receptors (for example in a warm-blooded animal such as man).

According to a further aspect of the specification, there is provided a method for providing a selective degrading effect on androgen receptors in a warm-blooded animal, such as man, in need of such effect, which comprises administering an effective amount of a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein.

According to a further aspect of the specification, there is provided a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein, for use in the treatment of tumour types that harbour androgen receptor mutations.

According to a further aspect of the specification, there is provided the use of a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein, for the manufacture of a medicament for the prevention or treatment of those tumour types that harbour androgen receptor mutations.

According to a further aspect of the specification, there is provided a method for the prevention or treatment of those tumour types that harbour androgen receptor mutations in a warm-blooded animal, such as man, in need of such prevention or treatment, which comprises administering to said animal an effective amount of a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein.

As mentioned above, tumour types known to harbour androgen receptor mutations include prostate tumours and therefore prostate cancer, castrate-resistant prostate cancer (CRPC), and metastatic (CRPC).

According to a further aspect of the specification, there is provided a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein, for use in the treatment of prostate cancer (for example castrate-resistant prostate cancer (CRPC), for example metastatic CRPC).

According to a further aspect of the specification, there is provided the use of a compound of the **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein, for the manufacture of a medicament for the treatment of prostate cancer (for example castrate-resistant prostate cancer (CRPC), for example metastatic CRPC).

According to a further aspect of the specification, there is provided a method for treating prostate cancer (for example castrate-resistant prostate cancer (CRPC), for example metastatic CRPC) in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of **Formula (I)**, [or a PROTAC compound containing an E3 ubiquitin ligase cereblon binder unit and (e.g. linked to) an AR binding unit of **Formula (Ia)**] or a pharmaceutically acceptable salt thereof, as defined herein.

In one embodiment where cancer is mentioned herein, said cancer is prostate cancer.

In one embodiment where cancer is mentioned herein, said cancer is CRPC.

In one embodiment where cancer is mentioned herein, said cancer is metastatic CRPC.

General Experimental Conditions and Abbreviations

The following abbreviations are used: AcOH = acetic acid; AIBN = 2,2'-azobis(2-methylpropionitrile); aq. = aqueous; Boc = butoxycarbonyl; Brettphos = 2-(Dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl; Brettphos Pd G3 = [(2-Di-cyclohexylphosphino-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate; CDI = 1,1'-Carbonyldiimidazole; Dave-phos-Pd G3 = Methanesulfonato 2-dicyclohexylphosphino-2-(*N,N*-dimethylamino)biphenyl(2'-amino-1,1'-biphenyl-2-yl) palladium(II); DCM = dichloromethane; DIAD = Diisopropyl azodicarboxylate; DIPEA = *N,N*-diisopropylethylamine; Cbz = carboxybenzyl; Dess-Martin periodinane = 3-Oxo-115-

- benzo[d][1,2]iodaoxole-1,1,1(3*H*)-triyl triacetate; DMF = *N,N*-dimethylformamide; DMSO = dimethylsulfoxide; Et₂O = diethyl ether; EtOAc = ethyl acetate; EtOH = ethanol; FSC = flash silica chromatography; h = hour(s); HPLC = high-performance liquid chromatography; IPA = isopropyl alcohol; MeCN = acetonitrile; MeOH = methanol; mins. = minutes; *m/z* = mass to charge ratio observed for major mass spectrometry peak(s); MTBE = methyl-*tert*-butyl-ether; NBS = *N*-bromosuccinimide; NMP = *N*-methyl-2-pyrrolidone; NMR = nuclear magnetic resonance; Pd₂dba₃ = tris(dibenzylideneacetone)dipalladium; Pd-PEPPSI-IHept^{Cl} = dichloro[1,3-bis(2,6-di-4-heptylphenyl)imidazol-2-ylidene(3-chloropyridyl)palladium(II); Pd-PEPPSI-IPent = dichloro[1,3-bis(2,6-Di-3-pentylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II), Pd(dppf)₂Cl₂-DCM = 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex; RockPhos Pd G3 = [(2-di-*tert*-butylphosphino-3-methoxy-6-methyl-2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2-aminobiphenyl)]-palladium(II) methanesulfonate; RT = room temperature (~17-25°C); RuPhos = 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl; RuPhos Pd G3 = methanesulfonato(2-dicyclohexylphosphino-2',6'-di-iso-propoxy-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)-palladium(II); TFA = trifluoroacetic acid; THF = tetrahydrofuran; sat. = saturated; SFC = supercritical fluid chromatography; S Phos = 2-dicyclohexylphosphino-2,6-di-methyloxy-1,1-biphenyl; XPhos = 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl.

NMR was carried out at 400 MHz in deuterated DMSO and at a temperature of 20-30°C unless otherwise stated. The following standard abbreviations are used for NMR data: s = singlet, d = doublet, m = multiplet, br = broad, dd = doublet of doublets, q = quartet, dt = doublet of triplets, etc.

- Preparative reverse phase HPLC** (RP HPLC) using decreasingly polar mixture of eluents (e.g. water and MeCN) may typically involve a gradient over 10-20 minutes, at 40-50mL per minute, from a 95:5 mixture of solvents a 5:95 mixture. The following Column and Eluent conditions are used herein:

Column A: Waters XSelect CSH C18 ODB column, 5µm silica, 30 mm diameter, 100 mm length

Column B: Waters XSelect CSH C18 ODB column, 5µm silica, 19 mm diameter, 150 mm length

- Eluent A:** Decreasingly polar mixtures of water (containing 0.1% formic acid) and MeCN

Eluent B: Decreasingly polar mixtures of water (containing 0.3% formic acid aq) and MeCN

Eluent C: Decreasingly polar mixtures of water (containing 0.1% TFA) and MeCN

Eluent D: Decreasingly polar mixtures of water (containing 0.1% NH₃) and MeCN

- After HPLC (which often involves the presence of formic acid or trifluoroacetic acid in the eluent), the fractions containing desired product were in some cases treated with a suitable base as part of a further work-up step in order to ensure delivery of the title compound as a neutral molecule rather than a salt. Accordingly where “**Basic Work-Up A**” is mentioned: fractions containing the desired compound were concentrated to remove MeCN. The resulting, mainly-aqueous fractions were basified with NaHCO₃ solution (e.g. 50 mL) and extracted into DCM (e.g. 3 × 100 mL). The combined organic solutions were washed with brine (e.g. 100 mL), dried (e.g. with Na₂SO₄ or MgSO₄) and concentrated to give the title compound.

Concentration: where solutions or mixtures are described as being concentrated, this is generally performed on a rotary evaporator under reduced pressure using a warm or hot water bath.

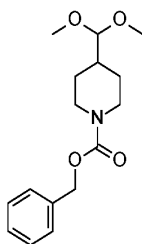
Salts: Where certain compounds were obtained as an acid-addition salt, for example a mono-hydrochloride salt or a bis-hydrochloride salt, the stoichiometry of the salt is assumed, based on the number

and nature of the basic groups in the compound, and may not have been determined experimentally e.g. by means of elemental analysis data.

Chemical naming: In general Examples and Intermediate compounds were named using ACD Name, "Structure to Name" part of ChemDraw Ultra (CambridgeSoft) or Biovia Draw 2016.

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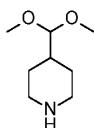
Intermediate 1a: Benzyl 4-(dimethoxymethyl)piperidine-1-carboxylate



4-Formyl-*N*-Cbz-piperidine (5.00 g, 20.22 mmol) was dissolved in MeOH (11 mL) at 0°C under N₂. A solution of TiCl₄ (0.11 mL, 1.01 mmol) in DCM (1.1 mL) was then added, followed after 15 mins by NEt₃ (0.338 mL, 2.43 mmol) and the resulting solution was stirred at RT for 0.5h. The mixture was then diluted with DCM (50 mL) and water (20 mL) and stirred at RT for 0.5h. The layers were then separated, the organic portion was dried over a hydrophobic frit and then concentrated. Purification by FSC (gradient: 0-50% EtOAc in heptane) gave the title compound (5.16 g, 87%) as a colourless oil; ¹H NMR: (CDCl₃) 1.14-1.33 (2H, m), 1.63-1.82 (3H, m), 2.63-2.84 (2H, m), 3.35 (6H, s), 4.02 (1H, d), 4.13-4.3 (2H, m), 5.12 (2H, s), 7.3-7.44 (5H, m).

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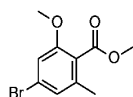
Intermediate 1b: 4-(Dimethoxymethyl)piperidine



Pd(OH)₂ (10wt%, 0.73 g, 0.52 mmol) was added to benzyl 4-(dimethoxymethyl)piperidine-1-carboxylate (7.60 g, 25.9 mmol) in MeOH (60 mL) at RT under N₂ in a steel pressured reactor. The resulting suspension was purged with N₂ followed by H₂ and was then stirred at RT at a pressure of 4 atmospheres of H₂ for 2 days. The mixture was then filtered through celite and washed through with MeOH (500 mL). The filtrate was concentrated to give the title compound (4.00 g, 97%) as a colourless oil; ¹H NMR: (CDCl₃) 1.19-1.41 (2H, m), 1.69-1.86 (3H, m), 2.61 (2H, td), 3.15 (2H, d), 3.35 (6H, s), 4.03 (1H, d), 4.47 (1H, s).

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Intermediate 1c: Methyl 4-bromo-2-methoxy-6-methylbenzoate

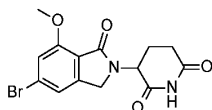


A 25% methanolic solution of NaOMe (512 µL, 2.24 mmol) was added dropwise to a stirred solution of methyl 4-bromo-2-fluoro-6-methylbenzoate (527 mg, 2.13 mmol) in DMF (10 mL) at RT under N₂. The

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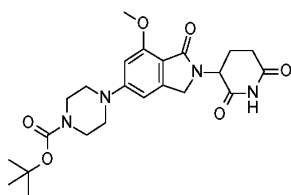
- resulting mixture was stirred at RT for 18h (reaction complete within 1h). The mixture was then cooled to 0°C and quenched with EtOAc (20 mL) and 1N HCl (10 mL). The phases were separated and the aqueous portion was extracted with EtOAc (2 × 30 mL). The combined organic solutions were dried (MgSO₄) and concentrated. Purification by FSC (gradient 0-25% EtOAc in heptane) gave the title compound (0.410 g, 74%) as a colourless oil which solidified on standing; ¹H NMR: (CDCl₃) 2.25 (3H, s), 3.81 (3H, s), 3.90 (3H, s), 6.91 (1H, d), 6.98 (1H, dd).

Intermediate 1d: 3-(5-Bromo-7-methoxy-1-oxo-1,3-dihydro-2H-isoindol-2-yl)piperidine-2,6-dione



- 10 NBS (1.574 g, 8.84 mmol) was added to a stirred solution of methyl 4-bromo-2-methoxy-6-methylbenzoate (1.432 g, 5.53 mmol) and AIBN (0.182 g, 1.11 mmol) in *tert*-butyl acetate (20 mL) and the mixture was stirred at 100°C for 3h. The mixture was then cooled to RT, diluted with EtOAc (50 mL) and washed with water (50 mL). The organic layer was passed through a phase separator cartridge and concentrated. Purification by FSC (gradient: 0-15% EtOAc in heptane) gave 4-bromo-2-(bromomethyl)-6-methoxybenzoate (1.495 g, 80 %) as a
- 15 yellow gum, that was 70% pure. DIPEA (1.654 mL, 9.29 mmol) was added in one portion to a stirred solution of methyl 4-bromo-2-(bromomethyl)-6-methoxybenzoate (1.495 g, 3.10 mmol) and 3-aminopiperidine-2,6-dione hydrochloride (0.510 g, 3.10 mmol) in MeCN (20 mL) at RT under air. The resulting solution was stirred at 80°C for 16h. The mixture was then cooled to 0°C and a solid was collected by filtration. The solid was washed with MeCN (50 mL) and Et₂O (50 mL) and dried under vacuum to give the title compound (0.761
- 20 g, 39% over 2 steps) as a mauve solid; ¹H NMR: 1.97 (1H, dtd), 2.34 (1H, qd), 2.54-2.63 (1H, m), 2.90 (1H, ddd), 3.90 (3H, s), 4.25 (1H, d), 4.38 (1H, d), 5.02 (1H, dd), 7.26 (1H, d), 7.39 (1H, d), 10.94 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 355.0.

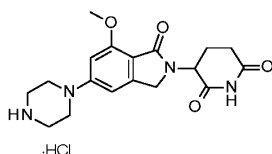
Intermediate 1e: *tert*-Butyl 4-[2-(2,6-dioxopiperidin-3-yl)-7-methoxy-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazine-1-carboxylate



- 25 Pd-PEPPSI-IHept^{Cl} (0.380 g, 0.39 mmol) was added to *tert*-butyl piperazine-1-carboxylate (2.183 g, 11.72 mmol), Cs₂CO₃ (3.82 g, 11.72 mmol) and 3-(5-bromo-7-methoxy-1-oxo-1,3-dihydro-2H-isoindol-2-yl)-piperidine-2,6-dione (1.38 g, 3.91 mmol) in degassed 1,4-dioxane (39 mL) at RT under N₂. The resulting
- 30 suspension was stirred at 100°C for 6h. The mixture was then diluted with DCM (100 mL) and washed sequentially with 5% AcOH in water (100 mL), water (100 mL), sat. NaHCO₃ (100 mL) and sat. brine (100 mL). The organic layer was dried (MgSO₄) and concentrated. Trituration with EtOAc (40 mL) and washing with Et₂O (50 mL) gave a solid which was collected by filtration and dried under vacuum to give the title

compound (1.154 g, 64%) as a dark grey powder; ^1H NMR: 1.43 (9H, s), 1.79-1.97 (1H, m), 2.28 (1H, dd), 2.53-2.62 (1H, m), 2.76-2.94 (1H, m), 3.32 (4H, s), 3.41-3.54 (4H, m), 3.85 (3H, s), 4.12 (1H, d), 4.24 (1H, d), 4.95 (1H, dd), 6.51 (1H, d), 6.62 (1H, s), 10.87 (1H, s); m/z : ES^+ $[\text{M}+\text{H}]^+ = 459.2$.

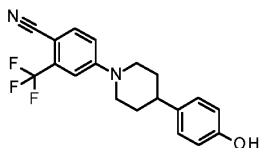
5 Intermediate 1f: 3-[7-Methoxy-1-oxo-5-(piperazin-1-yl)-1,3-dihydro-2H-isoindol-2-yl]piperidine-2,6-dione



4M HCl in 1,4-dioxane (2 mL, 8.00 mmol) was added in one portion to *tert*-butyl 4-[2-(2,6-dioxopiperidin-3-yl)-7-methoxy-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazine-1-carboxylate (107 mg, 0.19 mmol) at RT under air. The resulting mixture was stirred at RT for 1 day, then diluted with Et_2O (20 mL). The resulting mixture was filtered and the solid was washed with Et_2O (20 mL) to give the title compound as a hydrochloride salt (0.080 g, 100%) as a white solid; ^1H NMR: 1.93 (1H, dd), 2.25-2.4 (1H, m), 2.57 (1H, d), 2.89 (1H, s), 3.19 (4H, s), 3.59 (4H, s), 3.86 (3H, s), 4.14 (1H, d), 4.26 (1H, d), 4.97 (1H, dd), 6.49-6.6 (1H, m), 6.68 (1H, s), 9.55 (2H, s), 10.89 (1H, s); m/z : ES^+ $[\text{M}+\text{H}]^+ = 359.2$.

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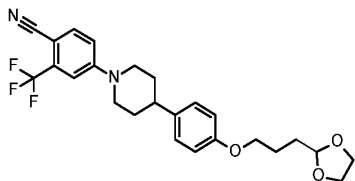
Intermediate 1g: 4-(4-(4-Hydroxyphenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



DIPEA (6.93 mL, 39.66 mmol), 4-fluoro-2-(trifluoromethyl)benzonitrile (5.00 g, 26.44 mmol) and 4-(piperidin-4-yl)phenol (4.69 g, 26.44 mmol) were stirred in DMSO (10 mL) at 50°C for 18h. The mixture was then cooled to RT, diluted with water (150 mL) and then stirred for 18h. A resulting solid was collected by filtration, washed with Et_2O (50 mL) and dried under vacuum to give the title compound (5.65 g, 62%) as a yellow solid; ^1H NMR: (CDCl_3) 1.75 (2H, qd), 1.88-2 (2H, m), 2.73 (1H, tt), 3.06 (2H, td), 3.98-4.1 (2H, m), 4.78 (1H, s), 6.76-6.83 (2H, m), 6.99 (1H, dd), 7.06-7.12 (2H, m), 7.16 (1H, d), 7.62 (1H, d); m/z : ES^+ $[\text{M}+\text{H}]^+ = 347.0$.

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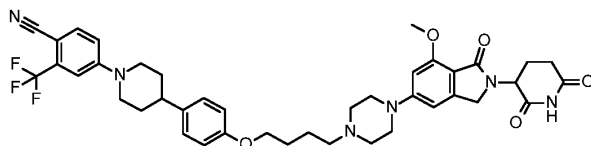
Intermediate 1h: 4-(4-(4-(3-(1,3-Dioxolan-2-yl)propoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



2-(3-Chloropropyl)-1,3-dioxolane (2.57 mL, 19.49 mmol) was added in one portion to 4-(4-(4-hydroxy-

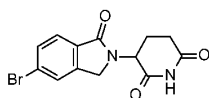
phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (3.75 g, 10.83 mmol), K₂CO₃ (3.74 g, 27.07 mmol) and KI (4.49 g, 27.07 mmol) in MeCN (100 mL) at RT under air. The resulting suspension was stirred at 90°C for 2 days. The mixture was then cooled to RT, filtered and washed with DCM (100 mL). The filtrate was concentrated under reduced pressure. The crude residue was diluted with EtOAc (300 mL), washed with water (100 mL) then sat. brine (100 mL), dried (MgSO₄) and concentrated. Purification by FSC (gradient 0-5% MeOH in DCM) gave the title compound (3.10 g, 62%) as a yellow solid; ¹H NMR: (CDCl₃) 1.56-1.67 (2H, m), 1.71 (2H, ddd), 1.74-1.82 (2H, m), 1.85 (2H, d), 2.77 (1H, ddd), 3-3.1 (2H, m), 3.75-3.82 (2H, m), 3.85-3.92 (2H, m), 3.95 (2H, q), 4.17 (2H, d), 4.85 (1H, t), 6.79-6.9 (2H, m), 7.15 (2H, d), 7.23-7.38 (2H, m), 7.81 (1H, d); *m/z*: ES⁺ [M+H]⁺ = 461.3.

Example 1: 4-{4-[4-(4-{4-[2-(2,6-Dioxopiperidin-3-yl)-7-methoxy-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]-piperazin-1-yl]butoxy]phenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile



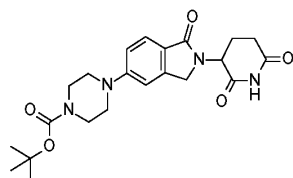
4-(4-(4-(3-(1,3-Dioxolan-2-yl)propoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (178 mg, 0.39 mmol) and *tert*-butyl 4-[2-(2,6-dioxopiperidin-3-yl)-7-methoxy-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazine-1-carboxylate (177 mg, 0.39 mmol) were stirred in formic acid (0.5 mL) and 1,4-dioxane (0.5 mL) at 40 °C for 18h. The mixture was then concentrated and the residue was re-dissolved in IPA (2 mL) and DCM (2 mL) at RT under air. NaBH(OAc)₃ (164 mg, 0.77 mmol) was added in one portion after 10 mins. The resulting dark suspension was stirred at RT for 1h and then concentrated. Purification by preparative HPLC (Column A, Eluent A) gave the title compound in the form of a formate salt (70 mg, 23%) as a dry film; ¹H NMR: (CDCl₃) 1.54-1.68 (4H, m), 1.74 (2H, q), 1.84 (2H, d), 1.92 (1H, dd), 2.28 (1H, dd), 2.39 (2H, t), 2.54-2.62 (2H, m), 2.76 (1H, td), 2.89 (1H, ddd), 3.04 (2H, t), 3.2-3.38 (6H, m), 3.47 (1H, s), 3.84 (3H, s), 3.97 (2H, t), 4.07-4.29 (4H, m), 4.96 (1H, dd), 6.48 (1H, d), 6.60 (1H, s), 6.81-6.94 (2H, m), 7.16 (2H, d), 7.27 (1H, dd), 7.32 (1H, d), 7.81 (1H, d), 8.16 (2H, s), 10.88 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 759.4.

Intermediate 2a: 3-(5-Bromo-1-oxo-1,3-dihydro-2*H*-isoindol-2-yl)piperidine-2,6-dione



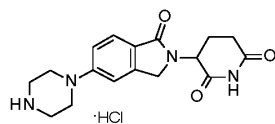
DIPEA (25 mL, 143.52 mmol) was added to methyl 4-bromo-2-(bromomethyl)benzoate (14.65 g, 47.57 mmol) and 3-aminopiperidine-2,6-dione hydrochloride salt (11.74 g, 71.35 mmol) in MeCN (200 mL) under N₂. The resulting suspension was stirred at 80°C for 4h. The mixture was cooled to RT and filtered. The resulting solid was washed with MeCN (60 mL), MeCN:Et₂O (50 mL [2:3]) and Et₂O (2 × 50 mL) to give the title compound (13.10 g, 85%) as a dark blue solid; ¹H NMR: 1.95-2.08 (1H, m), 2.34-2.46 (1H, m), 2.57-2.65 (1H, m), 2.91 (1H, ddd), 4.35 (1H, d), 4.48 (1H, d), 5.11 (1H, dd), 7.67 (1H, d), 7.72 (1H, dd), 7.83-7.96 (1H, m), 10.98 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 323.0.

5 **Intermediate 2b: tert-Butyl 4-[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazine-1-carboxylate**



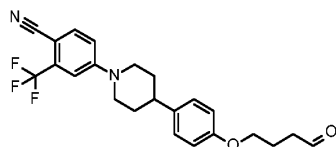
- 10 Cs₂CO₃ (57.40 g, 176 mmol) and Pd-PEPPSI-IPent (2.33 g, 2.94 mmol) were added in one portion to a degassed solution of *tert*-butyl piperazine-1-carboxylate (14.22 g, 76.36 mmol) and 3-(5-bromo-1-oxo-1,3-dihydro-2H-isoindol-2-yl)piperidine-2,6-dione (19.0 g, 58.74 mmol) in 1,4-dioxane (590 mL) under N₂. The resulting mixture was stirred at 90°C for 24h. The mixture was then cooled to RT, diluted with DCM (1L) and washed sequentially with 5% AcOH in water (500 mL) and brine (500 mL). The organic solution was then dried (MgSO₄) and concentrated. Trituration with EtOAc (250 mL) gave a solid that was collected by filtration, washed with Et₂O (100 mL) and dried under vacuum to give the title compound (22.10 g, 88%) as a grey solid; ¹H NMR: 1.43 (9H, s), 1.96 (1H, d), 2.31-2.41 (1H, m), 2.59 (1H, d), 2.87 (1H, s), 3.29 (4H, d), 3.47 (4H, d), 4.22 (1H, d), 4.34 (1H, d), 5.05 (1H, dd), 7.07 (2H, d), 7.54 (1H, d), 10.92 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 429.2.
- 15

Intermediate 2c: 3-[1-Oxo-5-(Piperazin-1-yl)-1,3-dihydro-2H-isoindol-2-yl]piperidine-2,6-dione



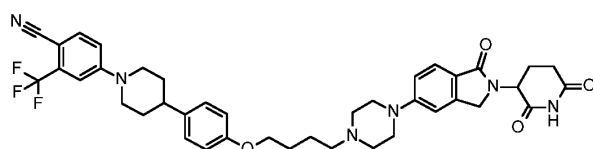
- 20 A solution of 4M HCl in dioxane (8.75 mL, 35.0 mmol) was added to *tert*-butyl 4-[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazine-1-carboxylate (1.50 g, 3.50 mmol) in 1,4-dioxane (2 mL) at RT and the mixture was stirred for 1h. EtOAc (5 mL) was then added and the mixture was stirred for 10 mins. The resulting precipitate was collected by filtration, washed with EtOAc (2 × 5 mL) and dried under vacuum to give the title compound in the form of a hydrochloride salt (1.08 g, 85%) as a dark grey solid; ¹H NMR: 1.97 (1H, dd), 2.36-2.44 (1H, m), 2.60 (1H, d), 2.84-2.99 (1H, m), 3.23 (4H, s), 3.5-3.57 (4H, m), 4.27 (1H, s), 4.34 (1H, s), 5.06 (1H, dd), 7.11-7.18 (2H, m), 7.59 (1H, d), 9.17 (2H, s), 10.93 (1H, s); *m/z*: ES⁺ [M+H]⁺ 329.0.
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30 **Intermediate 2d: 4-(4-(4-(4-Oxobutoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile**



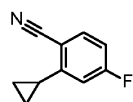
- 4-(4-(4-(3-(1,3-Dioxolan-2-yl)propoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (example 1h) (4.61 g, 10.01 mmol) was dissolved in 1,4-dioxane (100 mL) and formic acid (75 mL) and the mixture was warmed to 50°C for 18h. The solvent was then removed under reduced pressure to give the title compound as a yellow oil (used directly in next step, assumed 100% yield); m/z : ES^+ $[M+H]^+ = 417.0$.

Example 2: 4-{4-[4-(4-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl]butoxy}phenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile

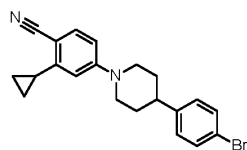


- 10 4-(4-(4-(4-Oxobutoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (4.17 g, 8.71 mmol), 3-[1-oxo-5-(piperazin-1-yl)-1,3-dihydro-2H-isoindol-2-yl]piperidine-2,6-dione hydrochloride salt (3.18 g, 8.71 mmol) and NaOAc (2.144 g, 26.13 mmol) were dissolved in DCM (150 mL) at RT. The resulting suspension was stirred for 1h at RT then $NaBH(OAc)_3$ (3.69 g, 17.42 mmol) was added and the mixture was stirred for 0.5h. The mixture was then diluted with DCM (200 mL) and washed sat. $NaHCO_3$ (2×200 mL) then sat. brine (200 mL). The organic solution was then dried ($MgSO_4$) and concentrated. Purification by preparative HPLC (Column A, Eluent B, Basic Work-Up A) gave the title compound (820 mg, 13%); ^1H NMR: 1.52-1.69 (4H, m), 1.74 (2H, p), 1.84 (2H, d), 1.91-2.03 (1H, m), 2.34-2.42 (3H, m), 2.52-2.54 (4H, m), 2.59 (1H, d), 2.76 (1H, td), 2.83-2.96 (1H, m), 2.96-3.1 (2H, m), 3.27-3.29 (4H, m), 3.97 (2H, t), 4.1-4.28 (3H, m), 4.33 (1H, d), 5.05 (1H, dd), 6.78-6.9 (2H, m), 7.05 (2H, d), 7.15 (2H, d), 7.23-7.36 (2H, m), 7.52 (1H, d), 7.81 (1H, d), 10.92 (1H, s); m/z : ES^+ $[M+H]^+ = 729.5$.

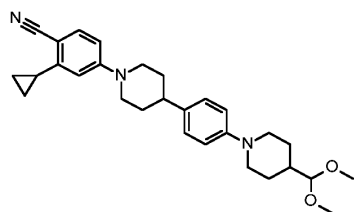
Intermediate 3a: 2-Cyclopropyl-4-fluorobenzonitrile



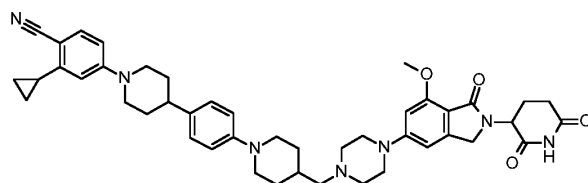
- 25 $Pd(OAc)_2$ (0.168 g, 0.75 mmol) was added to cyclopropylboronic acid (0.834 g, 9.71 mmol), 2-bromo-4-fluorobenzonitrile (1.50 g, 7.50 mmol), tricyclohexylphosphine (0.210 g, 0.75 mmol) and K_3PO_4 (5.57 g, 26.25 mmol) in toluene (20 mL) at RT under N_2 . The resulting mixture was stirred at 100°C for 3h. The mixture was then filtered through Celite and washed through with EtOAc (30 mL). The filtrate was concentrated and purification by FSC (gradient: 0-5% EtOAc in petroleum ether) gave the title compound (0.950 g, 79%) as a green solid; ^1H NMR: 0.85-0.94 (2H, m), 1.07-1.21 (2H, m), 2.13-2.25 (1H, m), 6.95-7.03 (1H, m), 7.15-7.25 (1H, m), 7.81-7.89 (1H, m).

Intermediate 3b: 4-(4-(4-Bromophenyl)piperidin-1-yl)-2-cyclopropylbenzonitrile

- 2-Cyclopropyl-4-fluorobenzonitrile (1.00 g, 6.20 mmol) was added to a mixture of 4-(4-bromophenyl)-piperidine (1.788 g, 7.45 mmol) and Cs_2CO_3 (6.06 g, 18.61 mmol) in DMSO (1.5 mL) at 80°C. The resulting mixture was stirred at 80°C for 16h, then cooled to RT and diluted with water. The mixture was then filtered, diluted with EtOAc (1 L), and washed with water (500 mL) then sat. brine (500 mL). The organic layer was dried (Na_2SO_4) and concentrated. Purification by FSC (gradient: 0-20% EtOAc in petroleum ether) gave the title compound (1.70 g, 72%) as a yellow solid; ^1H NMR: 0.79-0.93 (2H, m), 0.97-1.08 (2H, m), 1.54-1.69 (2H, m), 1.78-1.87 (2H, m), 2.02-2.13 (1H, m), 2.70-2.83 (1H, m), 2.83-2.95 (2H, m), 4.00-4.08 (2H, m), 6.47 (1H, d), 6.82-6.90 (1H, m), 7.18-7.26 (2H, m), 7.45-7.52 (3H, m); m/z : $\text{ES}^+ [\text{M}+\text{H}]^+ = 381.1$.

Intermediate 3c: 2-Cyclopropyl-4-(4-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)piperidin-1-yl)benzonitrile

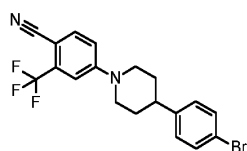
- Ruphos Pd G3 (88 mg, 0.10 mmol) and Ruphos (46 mg, 0.10 mmol) were added to a mixture of Cs_2CO_3 (1.025 g, 3.15 mmol), 4-(dimethoxymethyl)piperidine (334 mg, 2.10 mmol) and 4-(4-(4-bromophenyl)-piperidin-1-yl)-2-cyclopropylbenzonitrile (400 mg, 1.05 mmol) in 1,4-dioxane (6 mL) at RT under N_2 . The resulting mixture was stirred at 100°C for 16h. After cooling, the solvent was removed under reduced pressure. Purification by FSC (gradient: 0-30% EtOAc in petroleum ether) gave the title compound (0.228 g, 47%) as a yellow solid; ^1H NMR: 0.79-0.90 (2H, m), 0.97-1.10 (2H, m), 1.20-1.41 (2H, m), 1.50-1.74 (5H, m), 1.80 (2H, d), 1.97-2.15 (1H, m), 2.52-2.71 (3H, m), 2.81-2.95 (2H, m), 3.27 (6H, s), 3.58-3.68 (2H, m), 3.99-4.11 (3H, m), 6.46 (1H, d), 6.81-6.90 (3H, m), 7.06 (2H, d), 7.47 (1H, d); m/z : $\text{ES}^+ [\text{M}+\text{H}]^+ = 460.3$.

Example 3: 2-Cyclopropyl-4-(4-(4-(4-(4-(2-(2,6-dioxopiperidin-3-yl)-7-methoxy-1-oxo-2,3-dihydro-1H-isoindol-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)phenyl)piperidin-1-yl)benzonitrile

2-Cyclopropyl-4-(4-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)piperidin-1-yl)benzonitrile (150 mg, 0.33

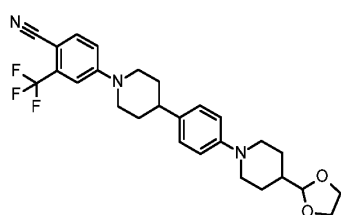
- mmol) and 3-[7-methoxy-1-oxo-5-(piperazin-1-yl)-1,3-dihydro-2H-isoindol-2-yl]piperidine-2,6-dione hydrochloride salt (130 mg, 0.33 mmol) were stirred in formic acid (0.5 mL) and 1,4-dioxane (0.5 mL) at 40°C for 7 days. The resulting mixture was then concentrated, and the residue dissolved in IPA (2 mL) and DCM (2 mL) at RT under air. NaBH(OAc)₃ (138 mg, 0.65 mmol) was then added in one portion after 10 mins and the resulting dark suspension was stirred at RT for 1h. The mixture was then concentrated, dissolved in DMF (3 mL) and filtered. Purification by preparative HPLC (Column A, Eluent A) gave the title compound as a formate salt (59 mg, 24%) as a white solid; ¹H NMR: 0.8-0.88 (2H, m), 0.98-1.07 (2H, m), 1.23 (2H, q), 1.51-1.64 (2H, m), 1.67 (1H, d), 1.79-1.83 (4H, m), 1.88-1.96 (1H, m), 2.09 (1H, s), 2.23 (2H, d), 2.28-2.37 (1H, m), 2.52-2.53 (4H, m), 2.54-2.72 (4H, m), 2.82-2.95 (3H, m), 3.30-3.32 (4H, d), 3.62 (2H, d), 3.84 (3H, s), 4.02 (2H, d), 4.11 (1H, d), 4.24 (1H, d), 4.96 (1H, dd), 6.44-6.52 (2H, m), 6.61 (1H, s), 6.86 (3H, td), 7.07 (2H, d), 7.47 (1H, d), 8.15 (2H, s), 10.88 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 756.7.

Intermediate 4a: 4-(4-(4-Bromophenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



- Cs₂CO₃ (73.6 g, 225.95 mmol) was added portion-wise to 4-fluoro-2-(trifluoromethyl)benzonitrile (20.51 g, 108.46 mmol) and 4-(4-bromophenyl)piperidine hydrochloride salt (25.0 g, 90.38 mmol) in DMSO (260 mL) at RT. The resulting cream suspension was stirred at RT for 18h and was then diluted slowly with water (600 mL). The resulting cream suspension was stirred at RT for 0.5h, then filtered, washed with water (2 × 25 mL) and Et₂O (50 mL). The solid was dried under vacuum to give the title compound (35.0 g, 95%) as a cream solid; ¹H NMR: 1.65 (2H, qd), 1.87 (2H, d), 2.85 (1H, tt), 3.06 (2H, td), 4.19 (2H, d), 7.22-7.26 (2H, m), 7.28 (1H, dd), 7.33 (1H, d), 7.43-7.59 (2H, m), 7.74-7.88 (1H, m).

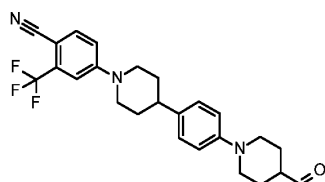
Intermediate 4b: 4-(4-(4-(4-(1,3-Dioxolan-2-yl)piperidin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



- Anhydrous 1,4-dioxane (160 mL) was added to a mixture of 4-(4-(4-bromophenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (10.00 g, 24.43 mmol), 4-(1,3-dioxolan-2-yl)piperidine (4.17 g, 26.51 mmol), RuPhos Pd G3 (1.533 g, 1.83 mmol), RuPhos (0.855 g, 1.83 mmol) and sodium 2-methylpropan-2-olate (7.04 g, 73.30 mmol). The mixture was degassed by bubbling N₂ through the mixture for 5 mins and was then stirred at 100°C for 2h. The mixture was then cooled to RT and water (320 mL) was added. A precipitate formed which was collected by filtration to give an orange solid. The solid was slurried in MTBE (50 mL), heated at 45°C

- for 0.5h then allowed to cool to RT and filtered. The solid was washed with MTBE (2 × 5 mL) and dried to give the title compound (12.0 g, 100%) as a pale orange solid; ¹H NMR: 1.39 (2H, qd), 1.54-1.68 (3H, m), 1.72 (2H, d), 1.84 (2H, d), 2.58 (2H, td), 2.65-2.79 (1H, m), 2.99-3.12 (2H, m), 3.66 (2H, d), 3.76-3.83 (2H, m), 3.83-3.91 (2H, m), 4.17 (2H, d), 4.61 (1H, d), 6.86 (2H, d), 7.08 (2H, d), 7.27 (1H, dd), 7.32 (1H, d), 7.81 (1H, d); *m/z*: ES⁺ [M+H]⁺ = 486.3.

Intermediate 4c: 4-(4-(4-(4-Formylpiperidin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile

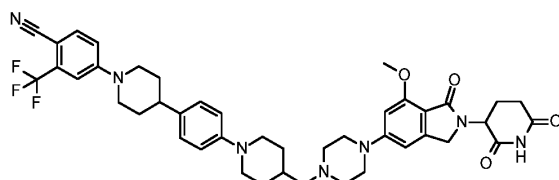


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4-(4-(4-(4-(1,3-Dioxolan-2-yl)piperidin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (10.00 g, 20.60 mmol) was dissolved in toluene (100 mL), formic acid (100 mL) and water (50 mL) and then warmed to 80°C for 1h. The mixture was then cooled to RT, diluted with EtOAc (50 mL) and water (50 mL). The layers were separated. The organic solution was washed with water (50 mL), sat. NaHCO₃ (50 mL) and brine (50 mL), then dried (MgSO₄) and concentrated. Purification by FSC (gradient: 0-100% EtOAc in heptane) gave the title compound (4.60 g, 51%) as a white solid; ¹H NMR: 1.53-1.68 (4H, m), 1.84 (2H, d), 1.92 (2H, dd), 2.45 (1H, dd), 2.73 (1H, d), 2.74-2.85 (2H, m), 2.97-3.11 (2H, m), 3.54 (2H, dt), 4.17 (2H, d), 6.88 (2H, d), 7.09 (2H, d), 7.22-7.4 (2H, m), 7.81 (1H, d), 9.59-9.72 (1H, m); *m/z*: ES⁺ [M+H]⁺ 442.3.

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Example 4: 4-(4-{4-[4-{4-[2-(2,6-Dioxopiperidin-3-yl)-7-methoxy-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]-piperazin-1-yl}methyl]piperidin-1-yl}phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



25

A mixture of 4-(4-(4-(4-formylpiperidin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (4.60 g, 10.42 mmol) and 3-[7-methoxy-1-oxo-5-(piperazin-1-yl)-1,3-dihydro-2*H*-isoindol-2-yl]piperidine-2,6-dione hydrochloride salt (4.11 g, 10.42 mmol) and NaOAc (1.71 g, 20.84 mmol) was stirred in IPA (2 mL) and DCM (250 mL) at RT under air. NaBH(OAc)₃ (4.42 g, 20.84 mmol) was added portion-wise after 1h. The resulting dark suspension was stirred at RT for 1h. The mixture was then diluted with DCM (2 × 250 mL), washed (sat. NaHCO₃ (250 mL), water (250 mL) then sat. brine (250 mL)), dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-100% EtOAc in heptane, then 0-5% IPA in EtOAc) gave a solid which was slurried in MeCN (100 mL) at RT and collected by filtration to give the title compound (2.05 g, 31%) as a white solid; ¹H NMR: 1.18-1.31 (2H, m), 1.55-1.74 (3H, m), 1.80-1.86 (4H, m), 1.88-1.97 (1H, m), 2.23 (2H, d), 2.27-2.34

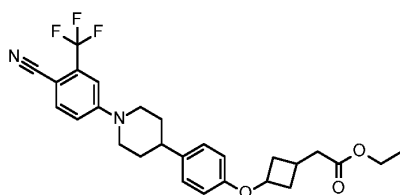
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(1H, m), 2.52-2.53 (4H, m), 2.54-2.67 (3H, m), 2.73 (1H, t), 2.82-2.97 (1H, m), 3.04 (2H, t), 3.32-3.35 (4H, s), 3.62 (2H, d), 3.84 (3H, s), 4.08-4.28 (4H, m), 4.96 (1H, dd), 6.49 (1H, s), 6.61 (1H, s), 6.87 (2H, d), 7.08 (2H, d), 7.27 (1H, dd), 7.32 (1H, d), 7.81 (1H, d), 10.88 (1H, s); m/z : $ES^+ [M+H]^+ = 784.6$.

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Intermediate 5a: Ethyl 2-(3-(4-(1-(4-cyano-3-(trifluoromethyl)phenyl)piperidin-4-yl)phenoxy)-cyclobutyl)acetate

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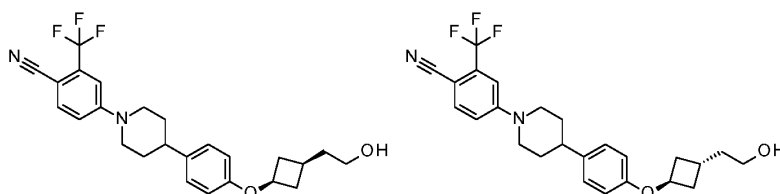


RockPhos Pd G3 (0.103 g, 0.12 mmol) was added in one portion to a degassed mixture of ethyl 2-(3-hydroxy-cyclobutyl)acetate (0.387 g, 2.44 mmol), 4-(4-(4-bromophenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (1.00 g, 2.44 mmol) and CS_2CO_3 (2.79 g, 8.55 mmol) in toluene (20 mL) at RT under N_2 . The resulting mixture was stirred at 90°C for 18h. The mixture was then cooled to RT and diluted with EtOAc (50 mL) and water (15 mL). The organic layer was separated and washed with sat. brine (20 mL), dried ($MgSO_4$) and concentrated. Purification by FSC (gradient: 0-60% EtOAc in heptane) gave the title compound (0.34 g, 29%) as a white solid; ^1H NMR: ($CDCl_3$) 1.25 (3H, td), 1.75 (2H, qd), 1.81-1.91 (1H, m), 1.97 (2H, d), 2.25 (1H, ddd), 2.29-2.45 (1H, m), 2.50 (2H, dd), 2.71 (3H, dddd), 3.05 (2H, td), 4.01 (2H, d), 4.07-4.18 (2H, m), 4.51 (1H, p), 6.7-6.81 (2H, m), 6.98 (1H, dd), 7.05-7.12 (2H, m), 7.15 (1H, d), 7.61 (1H, d); m/z : $ES^+ [M+H]^+ = 487.3$.

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Intermediate 5b and 5c: 4-(4-(4-((1r,3s)-3-(2-Hydroxyethyl)cyclobutoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile and 4-(4-(4-((1s,3r)-3-(2-hydroxyethyl)cyclobutoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile

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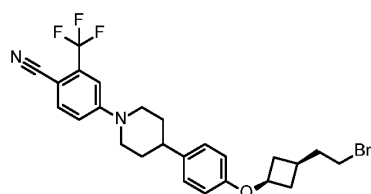


Diisobutylaluminum hydride (1M in toluene, 1.048 mL, 1.05 mmol) was added dropwise to a stirred solution of ethyl 2-(3-(4-(1-(4-cyano-3-(trifluoromethyl)phenyl)piperidin-4-yl)phenoxy)cyclobutyl)acetate (340 mg, 0.70 mmol) in THF (10 mL) at 0°C under N_2 . The resulting mixture was stirred at 0°C for 10 mins. The reaction was then quenched by addition of Rochelle's salt (15 mL). EtOAc (25 mL) was added and the mixture was stirred at RT for 18h. The phases were then separated and the aqueous portion was extracted with EtOAc

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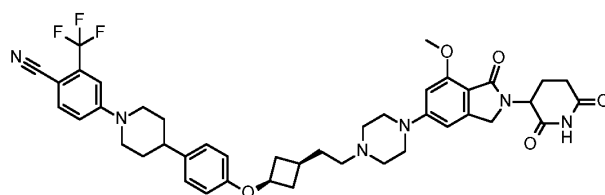
- (3 × 50 mL). The combined organic solutions were washed with brine (50 mL), dried (MgSO₄) and concentrated. Purification by FSC (gradient: 0-100% EtOAc in heptane) gave a ~2:1 mixture of cis/trans isomers (0.280 g, 90%). A sample was purified on Sepiatec SFC system (Column: YMC Chiral Art Cellulose-SJ, 20 × 250 mm, 5µm, Eluent: 70% CO₂, 30% MeOH+0.1%NH₃) to give the title compounds: Intermediate 5b (*cis*, 0.142 g, 53%) and Intermediate 5c (*trans*, 0.054 g, 20%); **Intermediate 5b (*cis*)**: ¹H NMR: 1.52-1.69 (6H, m), 1.85 (2H, d), 1.98 (1H, ddd), 2.53-2.61 (2H, m), 2.7-2.83 (1H, m), 2.97-3.1 (2H, m), 3.36 (2H, td), 4.17 (2H, d), 4.31 (1H, t), 4.49 (1H, p), 6.65-6.83 (2H, m), 7.06-7.19 (2H, m), 7.27 (1H, dd), 7.32 (1H, d), 7.81 (1H, d); **Intermediate 5c (*trans*)**: ¹H NMR: 1.55-1.72 (4H, m), 1.85 (2H, d), 2.14-2.16 (4H, m), 2.34-2.4 (1H, m), 2.7-2.82 (1H, m), 2.96-3.13 (2H, m), 3.34-3.44 (2H, m), 4.17 (2H, d), 4.33 (1H, t), 4.76 (1H, p), 6.64-6.78 (2H, m), 7.14 (2H, d), 7.27 (1H, dd), 7.32 (1H, d), 7.81 (1H, d).

Intermediate 5d: 4-(4-(4-((1*s*,3*s*)-3-(2-Bromoethyl)cyclobutoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



- 15 A solution of PPh₃ (142 mg, 0.54 mmol) in THF (2 mL) was added dropwise to a stirred mixture of 4-(4-((1*s*,3*s*)-3-(2-hydroxyethyl)cyclobutoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (120 mg, 0.27 mmol) and CBr₄ (179 mg, 0.54 mmol) in THF (2 mL) at 0°C. The resulting mixture was stirred at RT for 1h and then filtered. The solid was then washed with EtOAc (20 mL) and the filtrate concentrated under reduced pressure. Purification by FSC (gradient: 0-30% EtOAc in heptane) gave the title compound (0.140 g, 100%) as a colourless oil; ¹H NMR: (500 MHz, CDCl₃) 1.21-1.26 (1H, m), 1.63-1.78 (4H, m), 1.90 (2H, d), 1.95 (1H, d), 2.01-2.15 (1H, m), 2.49-2.73 (3H, m), 2.98 (2H, td), 3.28 (2H, t), 3.9-3.98 (2H, m), 4.44 (1H, p), 6.68-6.75 (2H, m), 6.92 (1H, dd), 6.98-7.07 (2H, m), 7.09 (1H, d), 7.55 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 507.1.

- 25 **Example 5: 4-[4-(4-((1*s*,3*s*)-3-(2-[4-[2-(2,6-Dioxopiperidin-3-yl)-7-methoxy-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazin-1-yl)ethyl)cyclobutyl]oxy}phenyl)piperidin-1-yl]-2-(trifluoromethyl)benzonitrile**



- 30 4-(4-(4-((1*s*,3*s*)-3-(2-Bromoethyl)cyclobutoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (65.0 mg, 0.13 mmol), 3-[7-methoxy-1-oxo-5-(piperazin-1-yl)-1,3-dihydro-2*H*-isoindol-2-yl]piperidine-2,6-dione hydrochloride salt (50.6 mg, 0.13 mmol), KI (63.8 mg, 0.38 mmol) and DIPEA (112 µL, 0.64 mmol) were dissolved in MeCN (2.5 mL) and stirred at 70°C for 18h. The mixture was then diluted with DCM (20 mL),

washed (5% AcOH in water (20 mL), water (20 mL) then sat. NaHCO₃ (20 mL)), dried (Na₂SO₄) and concentrated. Purification by preparative HPLC (Column A, Eluent A, Basic Work-Up A) gave the title compound (8 mg, 8%) as a white solid; ¹H NMR: 1.66-1.75 (3H, m), 1.75-1.84 (3H, m), 1.92-1.99 (3H, m), 2.15 (1H, dtd), 2.28 (1H, td), 2.32-2.4 (2H, m), 2.54-2.61 (4H, m), 2.61-2.69 (2H, m), 2.69-2.78 (1H, m), 2.78-2.85 (1H, m), 2.85-2.91 (1H, m), 3.05 (2H, td), 3.27-3.36 (4H, m), 3.94 (3H, s), 4.02 (2H, d), 4.19 (1H, d), 4.35 (1H, d), 4.49 (1H, p), 5.12 (1H, dd), 6.36 (1H, d), 6.45 (1H, s), 6.7-6.82 (2H, m), 6.98 (1H, dd), 7.10 (2H, dd), 7.15 (1H, d), 7.61 (1H, d), 7.96 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 785.4.

Intermediate 6a: 3,4-Difluoro-2-(trifluoromethyl)benzonitrile



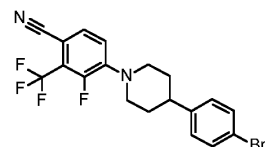
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1-Bromo-3,4-difluoro-2-(trifluoromethyl)benzene (5.00 g, 19.16 mmol) and cyanocopper (1.89 g, 21.07 mmol) were stirred in NMP (48 mL) at 150°C for 3h. The mixture was then cooled to RT, diluted with Et₂O (100 mL), washed with sat. brine (3 × 100 mL) then dilute NH₃ solution (50 mL), dried (MgSO₄) and concentrated to give the title compound (4.27 g) which was used in the next step without further purification;

¹H NMR: (500 MHz, CDCl₃) 7.46 (1H, q), 7.59 (1H, dddd).

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Intermediate 6b: 4-(4-(4-Bromophenyl)piperidin-1-yl)-3-fluoro-2-(trifluoromethyl)benzonitrile

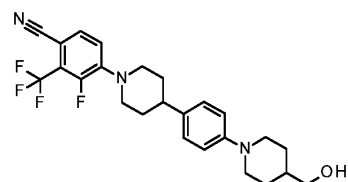


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4-(4-Bromophenyl)piperidine (4.92 g, 20.49 mmol), 3,4-difluoro-2-(trifluoromethyl)benzonitrile (4.287 g, 18.63 mmol) and DIPEA (3.90 mL, 22.36 mmol) were dissolved in NMP (43 mL). The mixture was then heated to 100°C for 0.5h, then cooled to RT and diluted with Et₂O (100 mL). The mixture was washed with brine (2 × 100 mL), 2M aqueous HCl (50 mL) then sat. NaHCO₃ (50 mL) and brine (50 mL). The organic solution was dried (MgSO₄) and concentrated to give the title compound (6.16 g, 77%) as a pale brown solid which was used without further purification; ¹H NMR: (500 MHz, CDCl₃) 1.82 (2H, qd), 1.87-1.94 (2H, m), 2.63 (1H, tt), 2.91 (2H, td), 3.63-3.73 (2H, m), 7.01-7.08 (3H, m), 7.36-7.4 (2H, m), 7.42 (1H, d); *m/z*: ES⁺ [M+H]⁺ = 427.1.

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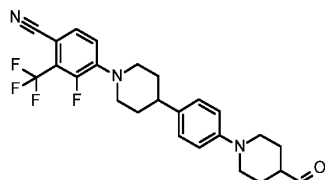
Intermediate 6c: 3-Fluoro-4-(4-(4-(4-(hydroxymethyl)piperidin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



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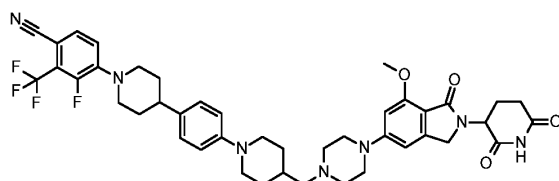
- CuI (44.6 mg, 0.23 mmol) was added to a mixture of 4-(4-(4-bromophenyl)piperidin-1-yl)-3-fluoro-2-(trifluoro-methyl)benzonitrile (500 mg, 1.17 mmol), piperidin-4-ylmethanol (202 mg, 1.76 mmol), 2-((2,6-dimethyl-phenyl)amino)-2-oxoacetic acid (45.2 mg, 0.23 mmol) and K_3PO_4 (497 mg, 2.34 mmol) in DMSO (5 mL) under N_2 . The mixture was stirred at 110°C for 18h. The mixture was then cooled to RT and poured into water (50 mL) then extracted with EtOAc (3×50 mL). The combined organic solutions were washed with $NaHCO_3$ (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated. Purification by FSC (gradient: 0-100% EtOAc in heptane) gave the title compound (0.10 g, 19%) as a white solid; ^1H NMR: ($CDCl_3$) 1.28 (1H, d), 1.41 (2H, qd), 1.53 (1H, s), 1.57-1.71 (1H, m), 1.82-1.91 (3H, m), 1.91-1.99 (2H, m), 2.53-2.79 (3H, m), 2.98 (2H, td), 3.55 (2H, d), 3.63-3.81 (4H, m), 6.88-6.95 (2H, m), 7.05-7.16 (3H, m), 7.48 (1H, d); m/z : ES^+ $[M+H]^+ = 462.2$.

Intermediate 6d: 3-Fluoro-4-(4-(4-(4-formylpiperidin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



- Dess Martin periodinane (101 mg, 0.24 mmol) was added to 3-fluoro-4-(4-(4-(4-(hydroxymethyl)piperidin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (100 mg, 0.22 mmol) in DCM (3 mL) at 0°C. The resulting mixture was stirred at RT for 1h. The mixture was then diluted with DCM (15 mL) and poured into a mixture of sat. $NaHCO_3$ (25 mL) and sodium thiosulfate solution (25 mL). The resulting suspension was stirred vigorously for 10 mins and the layers separated. The organic layer was dried (Na_2SO_4) and concentrated to give the title compound as a yellow dry film, which was used in the next step without further purification (assumed 100% yield); m/z : ES^+ $[M+H]^+ = 460.3$.

Example 6: 4-(4-{4-[4-{4-[2-(2,6-Dioxopiperidin-3-yl)-7-methoxy-1-oxo-2,3-dihydro-1H-isoindol-5-yl]-piperazin-1-yl}methyl]piperidin-1-yl}phenyl}piperidin-1-yl)-2-(trifluoromethyl)benzonitrile

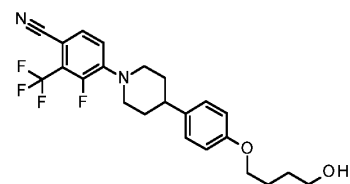


- 3-Fluoro-4-(4-(4-(4-formylpiperidin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (0.100 g, 0.22 mmol), 3-[7-methoxy-1-oxo-5-(piperazin-1-yl)-1,3-dihydro-2H-isoindol-2-yl]piperidine-2,6-dione hydrochloride salt (0.086 g, 0.22 mmol) and NaOAc (0.054 g, 0.65 mmol) were dissolved in DCM (3 mL) at RT and stirred for 10 mins. $NaBH(OAc)_3$ (0.092 g, 0.44 mmol) was added and the mixture stirred for 1h. The mixture was diluted with DCM (20 mL), washed (sat. $NaHCO_3$ (20 mL), water (20 mL) then sat. brine (20 mL)), dried (Na_2SO_4) and concentrated. Purification by preparative HPLC (Column A, Eluent A) gave the title

compound as a formate salt (42 mg, 24%) as a white solid; ^1H NMR: 1.23 (2H, q), 1.62-1.78 (3H, m), 1.82-1.84 (4H, m), 1.89-1.97 (1H, m), 2.23 (2H, d), 2.26-2.38 (2H, m), 2.52-2.54 (4H, m), 2.56-2.67 (3H, m), 2.83-2.96 (1H, m), 3.04 (2H, t), 3.31 (4H, s), 3.68 (4H, dd), 3.84 (3H, s), 4.12 (1H, d), 4.24 (1H, d), 4.96 (1H, dd), 6.49 (1H, s), 6.61 (1H, s), 6.88 (2H, d), 7.11 (2H, d), 7.46 (1H, t), 7.80 (1H, d), 10.88 (1H, s); m/z : ES^+

5 $[\text{M}+\text{H}]^+ = 802.7$.

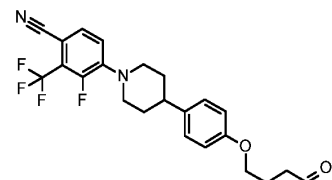
Intermediate 7a: 3-Fluoro-4-(4-(4-(4-hydroxybutoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)-benzonitrile



4-(4-(4-Bromophenyl)piperidin-1-yl)-3-fluoro-2-(trifluoromethyl)benzonitrile (0.500 g, 1.17 mmol), Cs_2CO_3 (1.335 g, 4.10 mmol) and butane-1,4-diol (0.501 mL, 5.85 mmol) were dissolved in toluene (15 mL) and degassed with N_2 . Rockphos Pd G3 (0.049 g, 0.06 mmol) was added and the mixture was heated at 90°C for

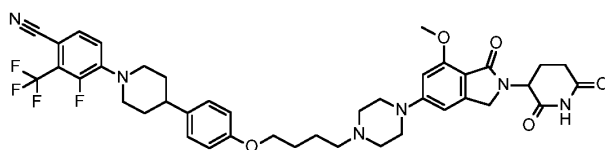
15 18h. The mixture was then diluted with EtOAc (100 mL), washed with water (100 mL) then sat. brine (100 mL), dried (Na_2SO_4) and concentrated. Purification by FSC (gradient: 0-50% EtOAc in heptane) gave the title compound (0.363 g, 71%) as a pale yellow solid; ^1H NMR: (CDCl_3) 1.52 (1H, s), 1.69-1.8 (2H, m), 1.82-1.99 (6H, m), 2.67 (1H, tt), 2.98 (2H, td), 3.73-3.74 (4H, m), 4.00 (2H, t), 6.82-6.92 (2H, m), 7.06-7.18 (3H, m), 7.44-7.53 (1H, m); m/z : ES^+ $[\text{M}+\text{H}]^+ = 437.1$.

Intermediate 7b: 3-Fluoro-4-(4-(4-(4-oxobutoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile

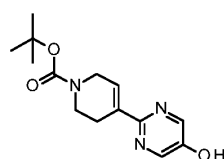


3-Oxo-115-benzo[d][1,2]iodaoxole-1,1,1(3*H*)-triyl triacetate (192 mg, 0.45 mmol) was added to 3-fluoro-4-(4-(4-(4-hydroxybutoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (180 mg, 0.41 mmol) in DCM (2 mL) at 0°C and warmed to RT for 1h. The mixture was then diluted with DCM (15 mL) and poured into mixture of sat. NaHCO_3 (25 mL) and sodium thiosulfate solution (25 mL). The resulting suspension was stirred vigorously for 10 mins then the phases were separated. The organic solution was dried (Na_2SO_4) and concentrated to give the title compound (0.120 g, 67%) as a yellow film, which was used in the next step without further purification; m/z : ES^+ $[\text{M}+\text{H}]^+ = 435.1$.

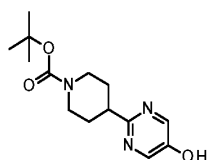
Example 7: 4-{4-[4-(4-[2-(2,6-Dioxopiperidin-3-yl)-7-methoxy-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]-

piperazin-1-yl}butoxy)phenyl]piperidin-1-yl]-3-fluoro-2-(trifluoromethyl)benzonitrile

- 3-Fluoro-4-(4-(4-(4-oxobutoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (0.120 g, 0.28 mmol), 3-[7-methoxy-1-oxo-5-(piperazin-1-yl)-1,3-dihydro-2H-isindol-2-yl]piperidine-2,6-dione hydrochloride salt (0.109 g, 0.28 mmol) and NaOAc (0.068 g, 0.83 mmol) were dissolved in DCM (3 mL) at RT and stirred for 10 mins. NaBH(OAc)₃ (0.117 g, 0.55 mmol) was then added and the mixture stirred for 1h. The mixture was then diluted with DCM (20 mL) and washed (sat. NaHCO₃ (20 mL), water (20 mL) then sat. brine (20 mL)), dried (Na₂SO₄) and concentrated. Purification by preparative HPLC (Column A, Eluent A) gave the title compound (0.084 g, 39%) as a white solid; ¹H NMR: 1.61 (2H, p), 1.75-1.76 (4H, m), 1.86 (2H, d), 1.89-1.98 (1H, m), 2.28 (1H, dd), 2.39 (2H, t), 2.52-2.53 (4H, m), 2.54-2.62 (1H, m), 2.67-2.78 (1H, m), 2.89 (1H, ddd), 2.99-3.08 (2H, m), 3.27-3.32 (4H, m), 3.72 (2H, d), 3.84 (3H, s), 3.98 (2H, t), 4.05-4.18 (1H, m), 4.24 (1H, d), 4.96 (1H, dd), 6.48 (1H, d), 6.60 (1H, s), 6.8-6.92 (2H, m), 7.18 (2H, d), 7.46 (1H, t), 7.80 (1H, d), 10.88 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 777.3.

Intermediate 8a: *tert*-Butyl 4-(5-hydroxypyrimidin-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate

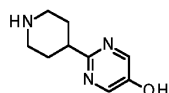
- Na₂CO₃ (1.211 g, 11.43 mmol) was added to a solution of 2-bromopyrimidin-5-ol (1.00 g, 5.71 mmol) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (2.65 g, 8.57 mmol) in toluene (8.0 mL), EtOH (2.0 mL) and water (4.0 mL). The mixture was degassed with N₂ for 15 mins. Pd(dppf)₂Cl₂-DCM complex (0.467 g, 0.571 mmol) was then added and the resulting mixture was heated to 100°C for 3h, then cooled to RT. The mixture was then diluted with water (150 mL) and extracted with EtOAc (2 × 200 mL). The combined organic solutions were washed with brine (80 mL), dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-40% EtOAc in heptane) gave the title compound (1.10 g, 65%) as a pale brown sticky liquid; ¹H NMR: 1.43 (9H, s), 2.56 (2H, d), 3.51 (2H, t), 4.04 (2H, s), 6.91 (1H, s), 8.34 (2H, s), 10.42 (1H, br s); *m/z*: ES⁺ [M-56]⁺ = 222.2.

Intermediate 8b: *tert*-Butyl 4-(5-hydroxypyrimidin-2-yl)piperidine-1-carboxylate

tert-Butyl 4-(5-hydroxypyrimidin-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.10 g, 3.97 mmol) was

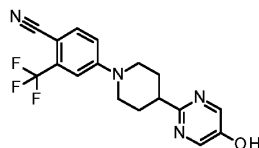
- dissolved in EtOH (30 mL) and the solution bubbled with N₂ for a period of 15 mins. Pd-on-C (0.55 g, 0.517 mmol) (10% w/w) was added under N₂ and the mixture was then stirred under an atmosphere of H₂ at RT for 5h. The mixture was then filtered through celite and the filter cake washed with MeOH (250 mL). The filtrate was concentrated to give the title compound (1.05 g, 70%) as a pale brown sticky liquid which was used in the next step without further purification; ¹H NMR: 1.41 (9H, s), 1.48-1.65 (2H, m), 1.86 (2H, d), 2.76-2.95 (3H, m), 3.99 (2H, d), 8.23 (2H, s); *m/z*: ES- [M-H]⁻ = 278.3.

Intermediate 8c: 2-(Piperidin-4-yl)pyrimidin-5-ol



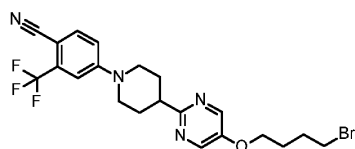
- 10 4N HCl in 1,4-dioxane (5 mL, 20.00 mmol) was added to a solution of *tert*-butyl 4-(5-hydroxypyrimidin-2-yl)-piperidine-1-carboxylate (500 mg, 1.79 mmol) in DCM (10 mL) at 0°C. The mixture was stirred at 0°C to RT for 2h and then concentrated. The resulting solid was triturated with hexanes (10 mL) gave the title compound as a hydrochloride salt (460 mg, 99%) as an off-white solid; ¹H NMR: 1.90-2.00 (2H, m), 2.03-2.15 (2H, m), 2.95-3.11 (3H, m), 3.29 (2H, d), 8.36 (2H, s), 8.89 (1H, br s), 9.14 (1H, br s), 10.60 (1H, br s); *m/z*: ES⁺ [M+H]⁺ = 180.2.

Intermediate 8d: 4-(4-(5-Hydroxypyrimidin-2-yl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



- 20 DIPEA (0.831 mL, 4.76 mmol) was added to a solution of 4-fluoro-2-(trifluoromethyl)benzonitrile (300 mg, 1.586 mmol) and 2-(piperidin-4-yl)pyrimidin-5-ol hydrochloride salt (513 mg, 2.380 mmol) in DMSO (5 mL) at RT under air. The mixture was heated at 50°C for 6h, then cooled to RT, diluted with water (100 mL) and extracted with EtOAc (2 × 150 mL). The combined organic solutions were washed with cold water (2 × 80 mL), dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-6% MeOH in DCM) gave the title compound (380 mg, 64%) as a pale yellow sticky liquid; ¹H NMR: (CDCl₃) 1.92-2.05 (2H, m), 2.14 (2H, d), 3.11-3.21 (3H, m), 4.03 (2H, d), 7.00 (1H, dd), 7.17 (1H, d), 7.62 (1H, d), 8.37 (2H, s); *m/z*: ES⁺ [M+H]⁺ = 349.2.

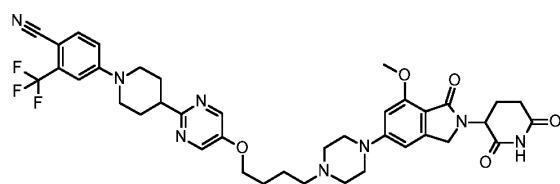
Intermediate 8e: 4-[4-[5-(4-Bromobutoxy)pyrimidin-2-yl]-1-piperidyl]-2-(trifluoromethyl)benzonitrile



- 30 Cs₂CO₃ (711 mg, 2.182 mmol) and 1,4-dibromobutane (0.391 mL, 3.27 mmol) were added to a solution of 4-

- (4-(5-hydroxypyrimidin-2-yl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (380 mg, 1.091 mmol) in DMF (5 mL) at RT. The mixture was stirred at RT for 2h, then diluted with water (50 mL) and extracted with EtOAc (2 × 100 mL). The combined organic solutions were washed with brine (50 mL), dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-40% EtOAc in heptane) gave the title compound (390 mg, 71%) as an off-white solid; ¹H NMR: (CDCl₃) 1.96-2.21 (8H, m), 3.12-3.22 (3H, m), 3.51 (2H, t), 4.02 (2H, d), 4.11 (2H, t), 7.01 (1H, dd), 7.17 (1H, d), 7.62 (1H, d), 8.39 (2H, s); *m/z*: ES⁺ [M+H]⁺ = 483.1.

Example 8: 4-[4-[5-[4-[4-[2-(2,6-Dioxo-3-piperidyl)-7-methoxy-1-oxo-isoindolin-5-yl]piperazin-1-yl]-butoxy]pyrimidin-2-yl]-1-piperidyl]-2-(trifluoromethyl)benzonitrile

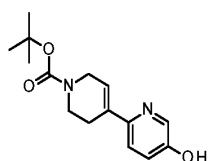


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- A mixture of DIPEA (0.216 mL, 1.241 mmol), 3-[7-methoxy-1-oxo-5-(piperazin-1-yl)-1,3-dihydro-2H-isoindol-2-yl]piperidine-2,6-dione hydrochloride salt (137 mg, 0.348 mmol), 4-(4-(5-(4-bromobutoxy)pyrimidin-2-yl)-piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (120 mg, 0.248 mmol) and KI (124 mg, 0.745 mmol) were stirred in DMSO (4 mL) at RT under N₂. The mixture was then heated to 80°C for 16h, cooled to RT and diluted with DCM (30 mL). The phases were separated and the organic solution was washed (5% AcOH in water (20 mL), water (20 mL), sat. NaHCO₃ (20 mL) then sat. brine (20 mL)), dried (Na₂SO₄) and concentrated. The crude material was purified by preparative HPLC (Column B, Eluent C). Fractions containing the desired compound were combined, concentrated cold to a minimum amount of solvent and basified with sat. NaHCO₃ solution. The phases were separated and the aqueous phase was extracted with DCM (4 × 30 mL). The combined organic solutions were washed with water (20 mL), dried over a phase separator and lyophilized to give the title compound (55 mg, 29%) as an off white solid; ¹H NMR: 1.57-1.67 (2H, m), 1.69-1.83 (4H, m), 1.92-2.04 (3H, m), 2.34-2.42 (3H, m), 2.59 (1H, d), 2.85-2.97 (1H, m), 3.06-3.20 (3H, m), 3.26 (4H, s), 4.08-4.25 (5H, m), 4.30-4.38 (1H, m), 5.05 (1H, dd), 7.07 (2H, s), 7.27 (1H, dd), 7.32 (1H, s), 7.52 (1H, d), 7.82 (1H, d), 8.49 (2H, s), 10.95 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 761.2.

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Intermediate 9a: *tert*-Butyl 5-hydroxy-3',6'-dihydro-[2,4'-bipyridine]-1'(2'*H*)-carboxylate

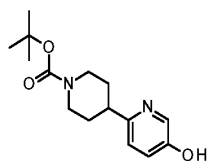


- Na₂CO₃ (1.218 g, 11.49 mmol) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-pyridine-1(2H)-carboxylate (2.67 g, 8.62 mmol) were added to a solution of 6-bromopyridin-3-ol (1.0 g, 5.75 mmol) in EtOH (4.0 mL), toluene (8.0 mL) and water (2.0 mL) at RT. The mixture was degassed with N₂ for 15 min, then Pd(dppf)Cl₂·DCM (0.079 g, 0.575 mmol) was then added and the mixture was heated to 100°C for 3h. The mixture was then cooled to RT, diluted with water (120 mL) and the phases separated. The

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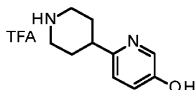
- aqueous phase was extracted with EtOAc (2×150 mL) and the combined organic solutions were washed with brine (100 mL), dried (Na_2SO_4) and concentrated. Purification by FSC (gradient: 0-35% EtOAc in heptane) gave the title compound (1.52 g, 95%) as a pale yellow sticky liquid; ^1H NMR: (CDCl_3) 1.51 (9H, s), 2.61 (2H, d), 3.64 (2H, t), 4.11 (2H, d), 6.40 (1H, s), 7.18 (1H, dd), 7.30 (1H, d), 8.21 (1H, d); m/z : $\text{ES}^+ [\text{M}+\text{H}]^+ = 277.2$.

Intermediate 9b: *tert*-Butyl 4-(5-hydroxypyridin-2-yl)piperidine-1-carboxylate



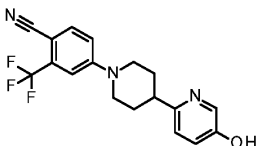
- 10 10% Pd-on-C (125 mg, 1.175 mmol) was added to a solution of *tert*-butyl 5-hydroxy-3',6'-dihydro-[2,4'-bipyridine]-1'-(2*H*)-carboxylate (500 mg, 1.809 mmol) in MeOH (10 mL) under N_2 . The resulting suspension was purged with H_2 and stirred at RT for 2h under an atmosphere of H_2 . The mixture was then filtered through celite and washed through with MeOH (150 mL). Concentration of the filtrate gave the title compound (410 mg, 81%) as an off-white solid; ^1H NMR: 1.41 (9H, s), 1.46-1.59 (2H, m), 1.76 (2H, d), 2.67-2.83 (3H, m), 4.03 (2H, d), 7.08 (2H, d), 8.05 (1H, s), 9.63 (1H, br s); m/z : $\text{ES}^+ [\text{M}+\text{H}]^+ = 279.4$.

Intermediate 9c: 6-(piperidin-4-yl)pyridine-3-ol. TFA salt



- 20 TFA (0.886 mL, 11.50 mmol) was added to a solution of *tert*-butyl 4-(5-hydroxypyridin-2-yl)piperidine-1-carboxylate (400 mg, 1.437 mmol) in DCM (8.0 mL) at 0°C . The mixture was then warmed to RT over 2h and then concentrated. Trituration with MTBE (50 mL) gave the title compound as a trifluoroacetate salt (430 mg, 99%) as an off white solid; ^1H NMR: 1.77-1.91 (2H, m), 1.94-2.03 (2H, m), 2.91-3.08 (3H, m), 3.37 (2H, d), 7.19-7.34 (2H, m), 8.13 (1H, d), 8.40 (1H, br s), 8.69 (1H, br s), 10.26 (1H, br s); m/z : $\text{ES}^+ [\text{M}+\text{H}]^+ = 179.1$.

Intermediate 9d: 4-(4-(5-Hydroxypyridin-2-yl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile

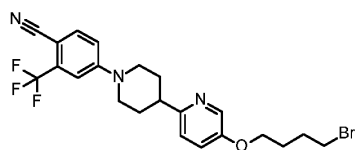


- 25 DIPEA (0.831 mL, 4.76 mmol) and 6-(piperidin-4-yl)pyridine-3-ol (424 mg, 2.380 mmol) were added to a stirred solution of 4-fluoro-2-(trifluoromethyl)benzonitrile (300 mg, 1.586 mmol) in DMSO (5.0 mL) at RT. The mixture was then heated to 50°C for 5h, then cooled to RT and diluted with water (80 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2×120 mL). The combined organic

solutions were dried (Na_2SO_4) and concentrated. Trituration with hexanes (100 mL) gave the title compound (530 mg, 96%) as an off-white solid; ^1H NMR: 1.69 (2H, qd), 1.88 (2H, d), 2.86-2.99 (1H, m), 3.09 (2H, t), 4.16 (2H, d), 7.08-7.12 (2H, m), 7.27 (1H, dd), 7.32 (1H, s), 7.81 (1H, d), 8.04 (1H, d), 9.66 (1H, s); m/z : ES^+ $[\text{M}+\text{H}]^+ = 348.1$.

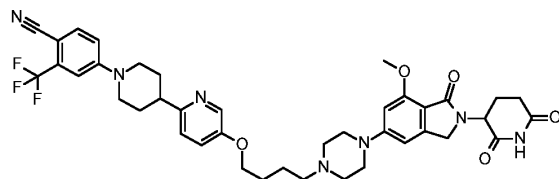
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Intermediate 9c: 4-(4-(5-(4-Bromobutoxy)pyridin-2-yl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



- 10 K_2CO_3 (80 mg, 0.576 mmol) and 1,4-dibromobutane (186 mg, 0.864 mmol) were added to a stirred solution of 4-(4-(5-hydroxypyridin-2-yl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (100 mg, 0.288 mmol) in acetone (3.0 mL) at RT. The mixture was then heated to 60°C for 4h, then cooled to RT and concentrated. The mixture was then partitioned between water (80 mL) and EtOAc (100 mL). The aqueous portion was extracted with EtOAc (2×100 mL) and the combined organic solutions were washed with sat. brine (50 mL), dried (Na_2SO_4)
- 15 and concentrated to give crude compound (170 mg). The same method was repeated with Cs_2CO_3 (188 mg, 0.576 mmol) instead of K_2CO_3 and the mixture was stirred at RT for 2h. After the same workup as previously described, the crude products from both reactions were combined. Purification by FSC (gradient: 0-20% EtOAc in heptane) gave the title compound (160 mg, 58%) as an off-white solid; ^1H NMR: (CDCl_3) 1.84-2.03 (4H, m), 2.05-2.14 (4H, m), 2.93-3.02 (1H, m), 3.13 (2H, td), 3.51 (2H, t), 4.02-4.10 (4H, m), 7.01 (1H, dd),
- 20 7.12 (1H, d), 7.17 (2H, dd), 7.63 (1H, d), 8.25 (1H, d); m/z : ES^+ $[\text{M}+\text{H}]^+ = 482.1$.

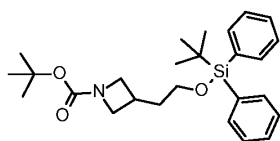
Example 9: 4-(4-(5-(4-(2-(2,6-Dioxopiperidin-3-yl)-7-methoxy-1-oxoisindolin-5-yl)piperazin-1-yl)butoxy)pyridin-2-yl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



- 25 DIPEA (0.221 mL, 1.266 mmol), 4-(4-(5-(4-bromobutoxy)pyridin-2-yl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (147 mg, 0.304 mmol) and KI (126 mg, 0.760 mmol) were added to a solution of 3-[7-methoxy-1-oxo-5-(piperazin-1-yl)-1,3-dihydro-2H-isoindol-2-yl]piperidine-2,6-dione hydrochloride salt (100 mg, 0.253 mmol) in DMSO (3.0 mL) RT under N_2 . The mixture was then heated to 80°C for 12h, then cooled to RT and diluted with DCM (20 mL). The solution was washed (5% AcOH in water (20 mL), water (20 mL), sat.
- 30 NaHCO_3 (20 mL) then sat. brine (20 mL)), dried (Na_2SO_4) and concentrated. The crude material was purified by preparative HPLC (Column C, Eluent C). Fractions containing the desired compound were combined, concentrated cold to a minimum amount of solvent and basified with sat. NaHCO_3 solution. The phases were

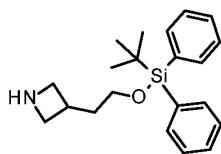
- separated and the aqueous portion was extracted with DCM (4 × 30 mL). The combined organic solutions were washed with water (20 mL), dried over a phase separator and lyophilized to give the title compound (28 mg, 14%) as an off white solid; ¹H NMR: 1.62-1.95 (10H, m), 2.34-2.40 (1H, m), 2.59 (2H, s), 2.75-3.03 (5H, m), 3.10 (4H, t), 3.84 (3H, s), 4.03-4.29 (7H, m), 4.97 (1H, dd), 6.52 (1H, s), 6.64 (1H, s), 7.21-7.38 (4H, m), 7.82 (1H, d), 8.21 (1H, s), 10.91 (1H, br s); *m/z*: ES⁺ [M+H]⁺ = 760.3.

Intermediate 10a: *tert*-Butyl 3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)azetidine-1-carboxylate



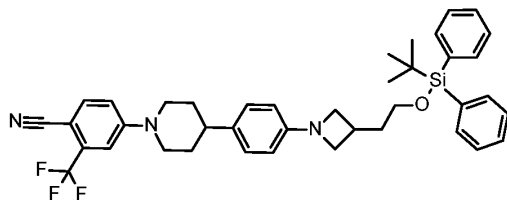
- Imidazole (0.474 g, 6.96 mmol) and *tert*-butylchlorodiphenylsilane (1.48 g, 5.37 mmol) were added to a solution of *tert*-butyl 3-(2-hydroxyethyl)azetidine-1-carboxylate (1.00 g, 4.97 mmol) in DCM (8 mL) at 0°C. The mixture was stirred at RT for 2h and then partitioned between water (2 mL) and DCM (10 mL). The organic phase was dried (Na₂SO₄) and concentrated to give the title compound (1.10 g, 90%) which was used in the next step without further purification; ¹H NMR: 0.99 (9H, s), 1.21 (9H, s), 1.74-1.86 (2H, m), 2.61-2.79 (1H, m), 3.42-3.54 (2H, m), 3.58-3.68 (2H, m), 3.81-3.94 (2H, m), 7.42-7.52 (6H, m), 7.58-7.65 (4H, m).

Intermediate 10b: 3-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)azetidine



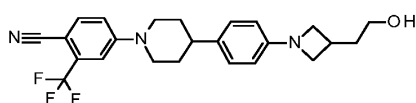
- TFA (1.92 mL, 25.0 mmol) was carefully added to a solution of *tert*-butyl 3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)azetidine-1-carboxylate (1.10 g, 2.502 mmol) in DCM (8 mL) at 0°C. The mixture was then stirred at 0°C for 2h then further diluted with DCM (5 mL) and washed with sat NaHCO₃ (20 mL). The organic solution was dried (Na₂SO₄) and concentrated to give the title compound (810 mg, 91%) as thick liquid that was used in the next step without further purification; *m/z*: ES⁺ [M+H]⁺ = 340.4.

- Intermediate 10c: 4-(4-(4-(3-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)azetidin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile**



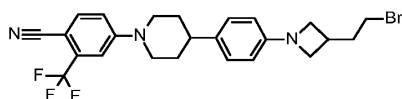
- 3-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)azetidine (809 mg, 2.382 mmol) and Cs₂CO₃ (1.04 g, 3.18 mmol) were added to a solution of 4-(4-(4-bromophenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (650 mg, 1.588 mmol) in 1,4-dioxane (12 mL). The mixture was purged with N₂ for 15 min at which point Pd₂dba₃ (145 mg, 0.159 mmol) and SPhos (85 mg, 0.318 mmol) were added. The mixture was then stirred at 120°C for 3h, cooled to RT and diluted with DCM (25 mL). The mixture was then filtered through celite. The filtrate was concentrated under reduced pressure and diluted with DCM (50 mL). The organic layer was separated, dried (Na₂SO₄) and concentrated to give the title compound (1.20 g, 43%) as a grey solid that was used in the next step without further purification; *m/z*: ES⁺ [M+H]⁺ = 668.2.

10 **Intermediate 10d: 4-(4-(4-(3-(2-Hydroxyethyl)azetidin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile**



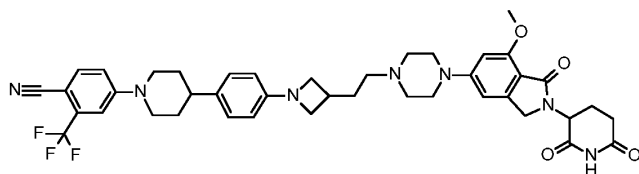
- Tetra *n*-butylammonium fluoride (1N solution in THF, 0.843 mL, 0.843 mmol) was added to a solution of 4-(4-(4-(3-(2-((*tert*-butyl-diphenylsilyl)oxy)ethyl)azetidin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (512 mg, 0.767 mmol) in THF (4 mL) at 0°C and the resulting mixture was stirred for 3h. The mixture was then concentrated and dissolved into DCM (25 mL). The resulting solution was washed with sat. NaHCO₃ solution (25 mL), dried (Na₂SO₄) and concentrated to give the title compound (360 mg, 67%) as a thick liquid; *m/z*: ES⁺ [M+H]⁺ = 430.2.

20 **Intermediate 10e: 4-(4-(4-(3-(2-Bromoethyl)azetidin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile**



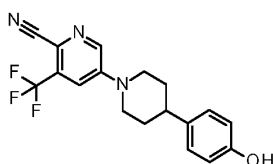
- PPh₃ (286 mg, 1.090 mmol) was added to a solution of 4-(4-(4-(3-(2-hydroxyethyl)azetidin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (360 mg, 0.838 mmol) in DCM (5 mL) and the mixture was stirred for 5 min at RT. CBr₄ (361 mg, 1.090 mmol) was then added and the mixture was stirred at RT for 2h. The solvent was reduced to half quantity (2 mL) after concentration then the product was triturated with pentane to give the title compound that was used in the next step without further purification; *m/z*: ES⁺ [M+H]⁺ = 492.0.

30 **Example 10: 4-(4-(4-(3-(2-(4-(2-(2,6-Dioxopiperidin-3-yl)-7-methoxy-1-oxoisindolin-5-yl)piperazin-1-yl)ethyl)azetidin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile**



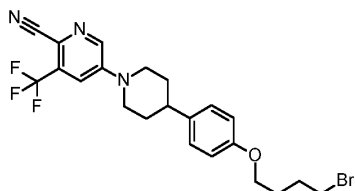
- A mixture of DIPEA (0.25 mL, 1.422 mmol), 4-(4-(3-(2-bromoethyl)azetidin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoro-methyl)benzonitrile (140 mg, 0.284 mmol), 3-[7-methoxy-1-oxo-5-(piperazin-1-yl)-1,3-dihydro-2H-isindol-2-yl]piperidine-2,6-dione hydrochloride salt (112 mg, 0.284 mmol) and KI (142 mg, 0.853 mmol) was stirred in DMSO (5 mL) at RT. The mixture was then heated to 80°C for 12h, then concentrated and slowly poured into ice-water. The resulting solids were collected by filtration, washed with water (10 mL) and dried under vacuum. Purification by preparative HPLC (Column B, Eluent C, Basic Work-Up A) gave the title compound (34 mg, 15%) as an off white solid; ¹H NMR: 1.50-1.66 (2H, m), 1.66-1.77 (1H, m), 1.77-1.87 (2H, m), 1.87-1.99 (1H, m), 2.09-2.18 (1H, m), 2.24-2.43 (4H, m), 2.54-2.61 (4H, m), 2.65-2.75 (2H, m), 2.79-2.93 (1H, m), 2.93-3.10 (4H, m), 3.17-3.26 (2H, m), 3.84 (3H, s), 4.04-4.30 (4H, m), 4.94 (1H, dd), 6.39-6.51 (3H, m), 6.57-6.68 (1H, m), 6.96-7.11 (2H, m), 7.23-7.37 (2H, m), 7.81 (1H, d), 11.0 (1H, br s); *m/z*: ES⁺ [M+H]⁺ = 770.2.

Intermediate 11a: 5-(4-(4-Hydroxyphenyl)piperidin-1-yl)-3-(trifluoromethyl)picolinonitrile



- K₂CO₃ (826 mg, 5.98 mmol) was added to a solution of 5-bromo-3-(trifluoromethyl)picolinonitrile (500 mg, 1.992 mmol), 4-(piperidin-4-yl)phenol hydrobromide (771 mg, 2.99 mmol) and *N,N*-dimethylethane-1,2-diamine (35.1 mg, 0.398 mmol) in 1,4-dioxane (8 mL). The mixture was degassed with N₂ for 15 mins and then CuI (37.9 mg, 0.199 mmol) was added. The mixture was heated to 120°C for 16h, then cooled to RT, diluted with water (100 mL) and extracted with EtOAc (2 × 150 mL). The combined organic solutions were washed with brine (80 mL), dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-30% EtOAc in heptane) gave the title compound (310 mg, 43%) as a pale yellow solid; ¹H NMR: 1.56-1.69 (2H, m), 1.84 (2H, d), 2.66-2.79 (1H, m), 3.06-3.15 (2H, m), 4.29 (2H, d), 6.69 (2H, d), 7.05 (2H, d), 7.63 (1H, d), 8.65 (1H, d), 9.18 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 348.0.

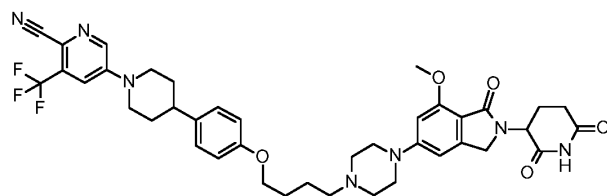
Intermediate 11b: 5-(4-(4-(4-Bromobutoxy)phenyl)piperidin-1-yl)-3-(trifluoromethyl)picolinonitrile



- K₂CO₃ (119 mg, 0.864 mmol) was added to a solution of 5-(4-(4-hydroxyphenyl)piperidin-1-yl)-3-(trifluoromethyl)picolinonitrile (150 mg, 0.432 mmol) and 1,4-dibromobutane (140 mg, 0.648 mmol) in DMF (3.0 mL) at RT. The mixture was heated to 70°C for 6h, then cooled to RT, diluted with water (50 mL) and extracted with EtOAc (2 × 80 mL). The combined organic solutions were washed with sat. brine (30 mL), dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-30% EtOAc in heptane) gave the title compound (145 mg, 65%) as an off-white semi-solid; ¹H NMR: 1.23-1.32 (4H, m), 1.60-1.73 (2H, m), 1.91-2.04 (2H, m), 2.75-2.90 (1H, m), 3.11 (2H, t), 3.54-3.67 (2H, m), 3.97 (2H, t), 4.30 (2H, d), 6.86 (2H, d), 7.17 (2H, d), 7.64 (1H, d), 8.66 (1H, d); *m/z*: ES⁺ [M+H]⁺ = 482.1.

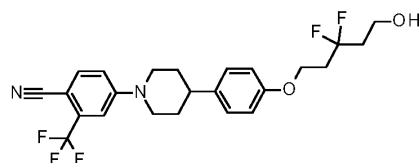
10

Example 11: 5-(4-(4-(4-(2-(2,6-Dioxopiperidin-3-yl)-7-methoxy-1-oxoisindolin-5-yl)piperazin-1-yl)butoxy)phenyl)piperidin-1-yl)-3-(trifluoromethyl)picolinonitrile



- DIPEA (0.332 mL, 1.899 mmol) was added to a solution of 3-[7-methoxy-1-oxo-5-(piperazin-1-yl)-1,3-dihydro-2H-isindol-2-yl]piperidine-2,6-dione hydrochloride salt (150 mg, 0.380 mmol), 5-(4-(4-bromobutoxy)-phenyl)piperidin-1-yl)-3-(trifluoromethyl)picolinonitrile (220 mg, 0.456 mmol) and KI (189 mg, 1.140 mmol) in DMSO (4 mL) at RT under N₂. The mixture was stirred at 80°C for 16h, then cooled to RT and diluted with DCM (20 mL). This solution was washed (5% AcOH in water (20 mL), water (20 mL), sat. NaHCO₃ (20 mL) then sat. brine (20 mL)), dried (Na₂SO₄) and concentrated. Purification by preparative HPLC (Column B, Eluent C, Basic Work-Up A) and trituration with pentane (10 mL) gave the title compound (52 mg, 18 %) as an off white solid; ¹H NMR: 1.58-1.78 (6H, m), 1.81-2.01 (3H, m), 2.27-2.38 (3H, m), 2.60-2.78 (2H, m), 2.80-2.98 (2H, m), 3.11 (3H, t), 3.83 (3H, s), 3.97 (2H, s), 4.06-4.34 (4H, m), 4.97 (1H, d), 6.48 (1H, s), 6.61 (1H, s), 6.86 (2H, d), 7.17 (2H, d), 7.65 (1H, s), 8.65 (1H, s), 10.91 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 760.4.

Intermediate 12a: 4-(4-(4-((3,3-Difluoro-5-hydroxypentyl)oxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile

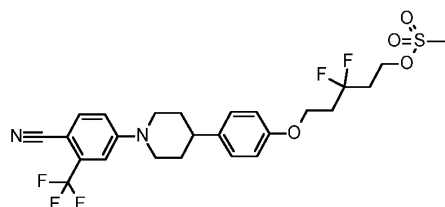


- RockPhos Pd G3 (0.290 g, 0.34 mmol) was added to 4-(4-(4-bromophenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (1.39 g, 3.40 mmol), 3,3-difluoropentane-1,5-diol (1.19 g, 8.49 mmol) and Cs₂CO₃ (239

- mg, 0.73 mmol) in 1,4-dioxane (50 mL) at RT. The resulting mixture was then stirred at 100°C for 1h. The mixture was then cooled to RT and concentrated. The resulting residue was dissolved into EtOAc (50 mL) and brine (50 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic solutions were dried (MgSO₄) and concentrated. Purification by FSC (gradient: 0-50% EtOAc in heptane) gave the title compound (0.60 g, 38%) as a yellow gum; ¹H NMR: (CDCl₃) 1.62 (1H, t), 1.7-1.89 (2H, m), 1.94-2.04 (2H, m), 2.25 (2H, tt), 2.43 (2H, tt), 2.66-2.82 (1H, m), 2.96-3.16 (2H, m), 3.91 (2H, q), 4.02 (2H, d), 4.17 (2H, t), 6.76-6.92 (2H, m), 6.99 (1H, dd), 7.09-7.21 (3H, m), 7.61 (1H, d).

10

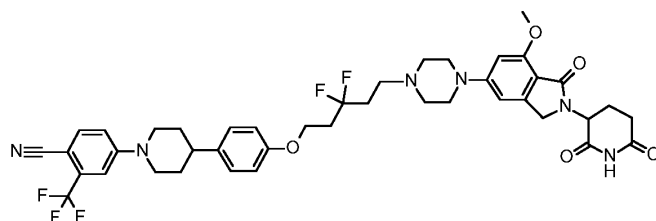
Intermediate 12b: 5-(4-(1-(4-Cyano-3-(trifluoromethyl)phenyl)piperidin-4-yl)phenoxy)-3,3-difluoropentyl methanesulfonate



- 15 Methanesulfonic anhydride (167 mg, 0.96 mmol) was added in one portion to 4-(4-(3,3-difluoro-5-hydroxy-pentyl)oxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (180 mg, 0.38 mmol) and NEt₃ (160 μL, 1.15 mmol) in DCM (2 mL) at RT and the mixture was stirred for 18h. The mixture was then diluted with DCM (25 mL) and washed sequentially with sat NH₄Cl (10 mL), sat NaHCO₃ (10 mL), water (20 mL) and sat. brine (10 mL). The solution was then dried with a phase separating cartridge, filtered and concentrated to give the title compound which was used in the next step without further purification; *m/z*: ES⁺ [M+H]⁺ 547.2.

20

Example 12: 4-(4-(4-((5-(4-(2-(2,6-Dioxopiperidin-3-yl)-7-methoxy-1-oxoisindolin-5-yl)piperazin-1-yl)-3,3-difluoropentyl)oxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



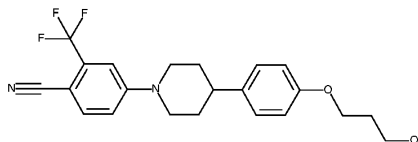
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KI (200 mg, 1.21 mmol), 5-(4-(1-(4-cyano-3-(trifluoromethyl)phenyl)piperidin-4-yl)phenoxy)-3,3-difluoropentyl methanesulfonate (220 mg, 0.40 mmol), 3-[7-methoxy-1-oxo-5-(piperazin-1-yl)-1,3-dihydro-2H-isindol-2-yl]piperidine-2,6-dione hydrochloride salt (166 mg, 0.42 mmol) and DIPEA (0.247 mL, 1.41 mmol) were dissolved in MeCN (3 mL) and stirred at 80°C for 18h. The mixture was then cooled to RT,

- concentrated. The resulting residue was dissolved with DCM (20 mL), washed with water (20 mL), separated through a phase separator and concentrated. Purification by preparative HPLC (Column A, Eluent A, Basic Work-Up A) gave the title compound (10.2 mg, 3%) as a yellow dry film; ¹H NMR: (CDCl₃) 1.75 (2H, qd), 1.97 (2H, d), 2.13-2.34 (4H, m), 2.34-2.48 (2H, m), 2.64-2.93 (9H, m), 3.06 (2H, td), 3.29-3.39 (4H, m), 3.94 (3H, s), 4.02 (2H, d), 4.13-4.26 (3H, m), 4.36 (1H, d), 5.13 (1H, dd), 6.36 (1H, d), 6.46 (1H, s), 6.79-6.9 (2H, m), 6.99 (1H, dd), 7.09-7.19 (3H, m), 7.61 (1H, d), 7.89 (1H, s); *m/z*: ES⁺ [M-H]⁺ 807.5.

10

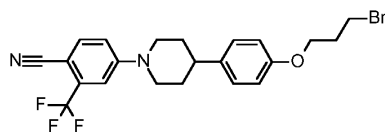
Intermediate 13a: 4-(4-(4-(3-Hydroxypropoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



- Prepared from 4-(4-(4-bromophenyl)piperidin-1-yl)-2-(trifluoro-methyl)benzonitrile according to the procedure described in Example 12 but using propane-1,3-diol.

15

Intermediate 13b: 4-(4-(4-(3-Bromopropoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile

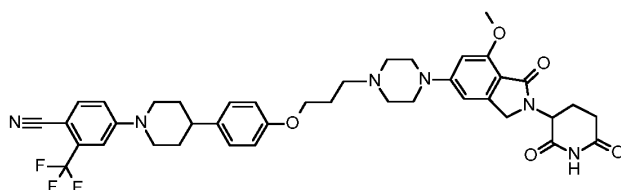


- A solution of PPh₃ (419 mg, 1.60 mmol) in THF (10 mL) was added dropwise to a stirred mixture of 4-(4-(4-(3-hydroxypropoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (323 mg, 0.80 mmol) and CBr₄ (530 mg, 1.60 mmol) in THF (10 mL) at 0°C. The resulting mixture was stirred at RT for 1h, then filtered and washed with EtOAc (20 mL). The combined filtrate was concentrated. Purification by FSC (gradient: 0-50% EtOAc in heptane) gave the title compound (346 mg, 93%) as a pale yellow solid; ¹H NMR: (CDCl₃) 1.76 (2H, qd), 1.98 (2H, dd), 2.31 (2H, p), 2.74 (1H, tt), 3.06 (2H, td), 3.60 (2H, t), 4.02 (2H, dd), 4.09 (2H, t), 6.83-6.91 (2H, m), 6.99 (1H, dd), 7.09-7.19 (3H, m), 7.58-7.64 (1H, m).

20

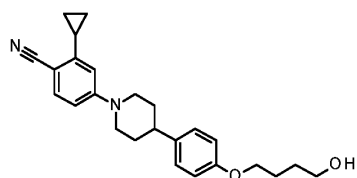
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Example 13: 4-(4-(4-(3-(4-(2-(2,6-Dioxopiperidin-3-yl)-7-methoxy-1-oxoisindolin-5-yl)piperazin-1-yl)propoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



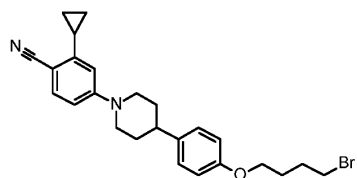
- A mixture of 3-[7-methoxy-1-oxo-5-(piperazin-1-yl)-1,3-dihydro-2H-isoindol-2-yl]piperidine-2,6-dione hydrochloride salt (100 mg, 0.253 mmol), DIPEA (164 mg, 1.266 mmol), 4-(4-(4-(3-bromopropoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (142 mg, 0.304 mmol) and KI (126 mg, 0.760 mmol) was stirred in DMSO (4 mL) at RT under N₂. The mixture was then heated at 80°C for 12h, then cooled to RT and diluted DCM (20 mL). The solution was washed (5% AcOH in water (20 mL), water (20 mL), sat. NaHCO₃ (20 mL) then sat. brine (20 mL)), dried (Na₂SO₄) and concentrated. Purification by preparative HPLC (Column B, Eluent C, Basic Work-Up A) with lyophilizing and washing with hexanes gave the title compound (26 mg, 13%) as brown solid; ¹H NMR: 1.55-1.72 (2H, m), 1.80-1.97 (5H, m), 2.22-2.31 (1H, m), 2.58 (2H, br s), 2.75-2.82 (1H, m), 2.85-2.96 (1H, m), 3.05 (2H, br t), 3.44-3.59 (4H, m), 3.83 (3H, s), 4.00 (2H, br t), 4.07-4.29 (5H, m), 4.96 (1H, br dd), 6.49 (1H, s), 6.61 (1H, s), 6.87 (2H, br d), 7.16 (2H, br d), 7.27 (1H, br d), 7.33 (1H, br s), 7.81 (1H, br d), 10.90 (1H, br s); *m/z*: ES⁺ [M+H]⁺ 745.4.

Intermediate 14a: 2-Cyclopropyl-4-(4-(4-(4-hydroxybutoxy)phenyl)piperidin-1-yl)benzonitrile



- RockPhos Pd G3 (88 mg, 0.10 mmol) was added to a mixture of butane-1,4-diol (142 mg, 1.57 mmol), Cs₂CO₃ (1.03 g, 3.15 mmol) and 4-(4-(4-bromophenyl)piperidin-1-yl)-2-cyclopropylbenzonitrile (400 mg, 1.05 mmol) in 1,4-dioxane (5 mL) at RT under N₂. The resulting mixture was stirred at 100°C for 16h and then concentrated. Purification by FSC (gradient: 0-50% EtOAc in petroleum ether) gave the title compound (0.10 g, 25%) as a white solid; ¹H NMR: (300 MHz) 0.77-0.88 (2H, m), 0.93-1.08 (2H, m), 1.43-1.91 (8H, m), 1.98-2.13 (1H, m), 2.60-2.74 (1H, m), 2.79-2.93 (2H, m), 3.36-3.48 (2H, m), 3.86-3.96 (2H, m), 3.99 (1H, s), 4.03 (1H, s), 4.36-4.46 (1H, m), 6.44 (1H, d), 6.77-6.88 (3H, m), 7.07-7.17 (2H, m), 7.45 (1H, d); *m/z* ES⁺ [M+H]⁺ = 391.3.

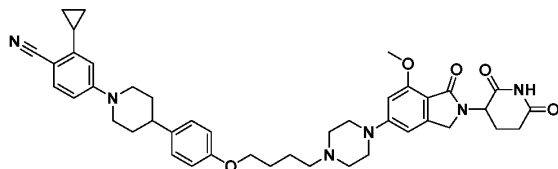
Intermediate 14b 4-(4-(4-(4-Bromobutoxy)phenyl)piperidin-1-yl)-2-cyclopropylbenzonitrile



- CBr₄ (153 mg, 0.46 mmol) was added to a mixture of PPh₃ (121 mg, 0.46 mmol) and 2-cyclopropyl-4-(4-(4-(4-hydroxybutoxy)phenyl)piperidin-1-yl)benzonitrile (90 mg, 0.23 mmol) in DCM (1 mL) at RT and the mixture was stirred for 2h then concentrated. Purification by FSC (gradient: 0-23% EtOAc in petroleum ether) gave the title compound (81 mg, 78%) as a white solid; ¹H NMR: 0.79-0.90 (2H, m), 1.00-1.10 (2H, m), 1.60 (2H, m), 1.78-1.86 (4H, m), 1.91-2.03 (2H, m), 2.08 (1H, m), 2.65-2.75 (1H, m), 2.85-2.95 (2H, m), 3.61 (2H, t), 3.94-4.07 (4H, m), 6.47 (1H, d), 6.83-6.89 (3H, m), 7.12-7.19 (2H, m), 7.48 (1H, d); *m/z* ES⁺ [M+H]⁺ =

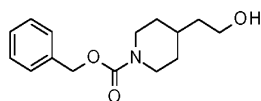
453.2.

Example 14: 2-Cyclopropyl-4-(4-(4-(4-(2-(2,6-dioxopiperidin-3-yl)-7-methoxy-1-oxoisindolin-5-yl)piperazin-1-yl)butoxy)phenyl)piperidin-1-yl)benzonitrile



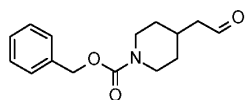
DIPEA (57.8 μ L, 0.33 mmol) was added to a mixture of KI (4 mg, 0.02 mmol), 4-(4-(4-(4-bromobutoxy)-phenyl)piperidin-1-yl)-2-cyclopropylbenzonitrile (50 mg, 0.11 mmol) and 3-[7-methoxy-1-oxo-5-(piperazin-1-yl)-1,3-dihydro-2H-isindol-2-yl]piperidine-2,6-dione hydrochloride salt (43.5 mg, 0.12 mmol) in MeCN (2 mL) at RT. The resulting mixture was stirred at 80°C for 16h and then concentrated. Purification by preparative TLC (DCM/MeOH = 20/1) gave the title compound (13 mg, 16%) as a white solid; ¹H NMR: 0.78-0.89 (3H, m), 0.97-1.08 (2H, m), 1.15 (1H, s), 1.24 (4H, s), 1.35 (1H, s), 1.45-1.67 (4H, m), 1.69-1.84 (4H, m), 1.91 (1H, d), 2.03-2.14 (2H, m), 2.14-2.21 (1H, m), 2.22-2.34 (2H, m), 2.37 (2H, s), 2.82-2.96 (3H, m), 3.83 (3H, s), 3.94-4.05 (4H, m), 4.10 (1H, d), 4.23 (1H, d), 4.91-5.01 (1H, m), 6.43-6.50 (2H, m), 6.60 (1H, s), 6.81-6.89 (3H, m), 7.11-7.18 (2H, m), 7.47 (1H, d), 10.89 (1H, s); *m/z* ES⁺ [M+H]⁺ = 731.3.

Intermediate 15a: Benzyl 4-(2-hydroxyethyl)piperidine-1-carboxylate



To a solution of 2-(piperidin-4-yl)ethan-1-ol (5.00 g, 38.7 mmol) in DCM (100 mL) was added Na₂CO₃ (18.46 g, 174.1 mmol) in water (100 mL) at 0°C, and then benzyl carbonochloridate (6.08 mL, 42.6 mmol) was added dropwise. The mixture was stirred for 6h at RT, then diluted with water (100 mL) and extracted with DCM (2 $\times$ 100 mL). The combined organic solutions were washed with sat. brine (100 mL), dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-70% EtOAc in heptane) gave the title compound (8.34 g, 82%) as a pale yellow oil; ¹H NMR: (CDCl₃) 1.15 (2H, qd), 1.43 (1H, t), 1.52 (2H, q), 1.62 (1H, dddd), 1.69 (2H, t), 2.78 (2H, t), 3.69 (2H, q), 4.14 (2H, dd), 5.12 (2H, s), 7.28-7.45 (5H, m); *m/z*: ES⁺ [M+H]⁺ 264.3.

Intermediate 15b: Benzyl 4-(2-oxoethyl)piperidine-1-carboxylate

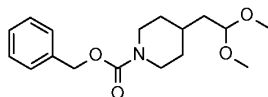


To a solution of benzyl 4-(2-hydroxyethyl)piperidine-1-carboxylate (8.34 g, 31.7 mmol) in DCM (150 mL) at 0°C was added Dess-Martin periodinane (14.78 g, 34.84 mmol). The reaction was stirred at RT for 3h, then quenched by the addition of sat. NaHCO₃ solution (50 mL) and filtered to remove solid residue. The solid residue was washed with DCM (50 mL). The phases were separated and the organic solution was washed with

sat. brine (20 mL $\times$ 2), dried (Na_2SO_4) and concentrated. Purification by FSC (gradient: 0-50% EtOAc in heptane) gave the title compound (5.20 g, 63%) as a colourless oil; ^1H NMR: (CDCl_3) 1.20 (2H, q), 1.71 (2H, d), 2.07 (1H, tq), 2.38 (2H, dd), 2.82 (2H, t), 4.16 (2H, s), 5.12 (2H, s), 7.31-7.43 (5H, m), 9.77 (1H, t); m/z : $\text{ES}^+ [\text{M}+\text{H}]^+$ 262.2.

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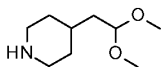
Intermediate 15c: Benzyl 4-(2,2-dimethoxyethyl)piperidine-1-carboxylate



To a solution of benzyl 4-(2-oxoethyl)piperidine-1-carboxylate (5.20 g, 19.9 mmol) in MeOH (60 mL) was added trimethoxymethane (10.9 mL, 99.5 mmol) and 4-methylbenzenesulfonic acid (0.17 g, 0.99 mmol) at 15°C. The mixture was stirred at this temperature for 1h. The reaction was then quenched by addition of water (50 mL) and diluted with DCM (100 mL). The phases were separated and the organic solution was washed with sat. brine (3×20 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give the title compound (5.90 g, 96%) as a colourless oil; ^1H NMR: (CDCl_3) 1.04-1.25 (2H, m), 1.5-1.57 (2H, m), 1.57-1.63 (1H, m), 1.68 (2H, t), 2.78 (2H, t), 3.31 (6H, s), 4.15 (2H, d), 4.46 (1H, t), 5.12 (2H, s), 7.27-7.37 (5H, m).

15

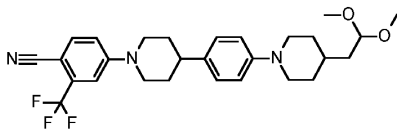
Intermediate 15d: 4-(2,2-Dimethoxyethyl)piperidine



10% $\text{Ph}(\text{OH})_2$ on carbon (0.54 g, 0.38 mmol) was added to benzyl 4-(2,2-dimethoxyethyl)piperidine-1-carboxylate (5.90 g, 19.2 mmol) in MeOH (60 mL) at RT under N_2 in a steel pressure reactor. The resulting suspension was purged with N_2 and then H_2 and then stirred at RT at a pressure of 4 atmospheres for 3 days. The mixture was then filtered through celite and washed through with MeOH (250 mL). The filtrate was concentrated to give the title compound (3.14 g, 94%) as a colourless oil; ^1H NMR: (CDCl_3) 1.15-1.28 (2H, m), 1.53-1.56 (2H, m), 1.72 (2H, d), 2.63 (2H, td), 3.04-3.14 (2H, m), 3.31 (8H, s), 4.47 (1H, t).

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Intermediate 15e: 4-(4-(4-(4-(2,2-Dimethoxyethyl)piperidin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile

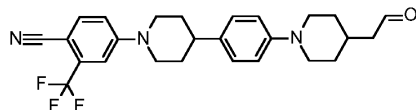


30 RuPhos Pd G3 (0.205 g, 0.24 mmol) was added to a mixture of 4-(4-(4-bromophenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (1.00 g, 2.44 mmol), 4-(2,2-dimethoxyethyl)piperidine (0.64 g, 3.67 mmol), Cs_2CO_3 (2.388 g, 7.33 mmol) and RuPhos (0.114 g, 0.24 mmol) in 1,4-dioxane (20 mL) at RT under N_2 . The resulting solution was stirred at 100°C for 10h and then concentrated. Purification by flash C18-flash

chromatography (gradient: 0-100% MeCN in water) gave the title compound (1.20 g, 98%) as a yellow solid; ¹H NMR: 1.21-1.31 (2H, m), 1.39-1.51 (3H, m), 1.52-1.67 (2H, m), 1.70-1.77 (2H, m), 1.79-1.87 (2H, m), 2.51-2.61 (2H, m), 2.71 (1H, t), 2.98-3.08 (2H, m), 3.22 (6H, s), 3.58 (2H, d), 4.16 (2H, d), 4.43-4.50 (1H, m), 6.84 (2H, d), 7.07 (2H, d), 7.26 (1H, d), 7.32 (1H, s), 7.80 (1H, d); *m/z* ES⁺ [M+H]⁺ = 502.2.

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Intermediate 15f: 4-(4-(4-(4-(2-Oxoethyl)piperidin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)-benzonitrile

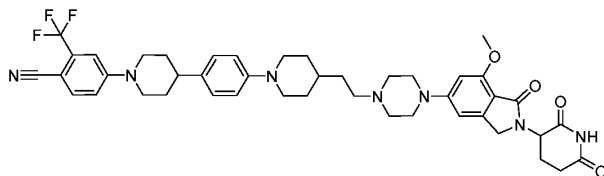


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A solution of 4-(4-(4-(4-(2,2-dimethoxyethyl)piperidin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)-benzonitrile (200 mg, 0.40 mmol) in formic acid (2 mL) was stirred at RT for 5h. The mixture was then concentrated to give the title compound (0.17 g, 94%) which was used in the next step without further purification; ¹H NMR: 1.23-1.33 (2H, m), 1.54-1.67 (2H, m), 1.67-1.76 (2H, m), 1.79-1.87 (2H, m), 1.95 (1H, s), 2.36-2.43 (2H, m), 2.57-2.69 (2H, m), 2.69-2.76 (1H, m), 3.03 (2H, t), 3.58 (2H, d), 4.16 (2H, d), 6.85 (2H, d), 7.07 (2H, d), 7.22-7.29 (1H, m), 7.31 (1H, s), 7.80 (1H, d), 9.70 (1H, d); *m/z* ES⁺ [M+H]⁺ = 456.1.

15

Example 15: 4-(4-(4-(4-(2-(4-(2-(2,6-Dioxopiperidin-3-yl)-7-methoxy-1-oxoisindolin-5-yl)piperazin-1-yl)ethyl)piperidin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



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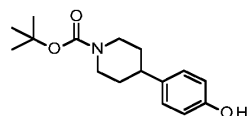
tert-Butyl 4-(2-(2,6-dioxopiperidin-3-yl)-7-methoxy-1-oxoisindolin-5-yl)piperazine-1-carboxylate (50 mg, 0.11 mmol) was added to a solution of 4-(4-(4-(4-(2-oxoethyl)piperidin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (50 mg, 0.11 mmol) in formic acid (2 mL) at RT. The resulting solution was stirred at 40°C for 1h, then cooled to RT and concentrated. The resulting residue was dissolved in DCM (2 mL) and then NaBH(OAc)₃ (47 mg, 0.22 mmol) was added. This mixture was stirred at RT for 1h. The mixture was then diluted with DCM, washed (AcOH (5%, aq), water (20 mL) then sat. brine (20 mL)), dried

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(Na₂SO₄) and concentrated. Purification by preparative SFC (Column: Torus 2-PIC; Mobile Phase A: CO₂, Mobile Phase B: MeOH (0.5% 2M NH₃-MeOH); Flow rate: 50 mL/min; isocratic gradient: 30% B) gave the title compound (6.1 mg, 7%) as a pale yellow solid; ¹H NMR: (300 MHz) 1.15- 1.30 (2H, m), 1.30-1.50 (3H, m), 1.52-1.70 (2H, m), 1.71-1.97 (5H, m), 2.29-2.43 (3H, m), 2.60 (3H, d), 2.75-3.10 (4H, m), 3.10-3.50 (8H, m), 3.61 (2H, d), 3.84 (3H, s), 4.04-4.29 (4H, m), 4.97 (1H, dd), 6.49 (1H, s), 6.61 (1H, s), 6.86 (2H, d), 7.08 (2H, d), 7.19-7.39 (2H, m), 7.82 (1H, d), 10.91 (1H, s); *m/z* ES⁺ [M+H]⁺ = 798.4.

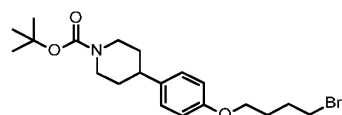
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Intermediate 16a: *tert*-Butyl 4-(4-(4-(4-(2-(2,6-Dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazin-1-yl)butoxy)phenyl)piperidine-1-carboxylate



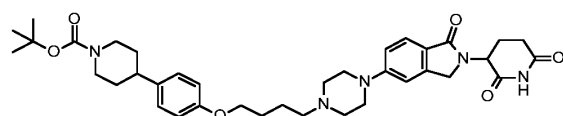
4-(Piperidin-4-yl)phenol hydrobromide salt (5.14 g, 19.91 mmol) and di-*tert*-butyl dicarbonate (4.56 g, 20.91 mmol) was slurried in DCM (60 mL) at RT. NEt₃ (5.53 mL, 39.82 mmol) was then added in one portion and the mixture was stirred for 45 mins. The mixture was then diluted with DCM (200 mL), washed with water (3 × 100 mL), dried over a phase separator and concentrated to give the title compound (5.70 g, 100%) as a white solid; ¹H NMR: 1.34-1.46 (11H, m), 1.70 (2H, d), 2.54-2.6 (1H, m), 2.77 (2H, br s), 4.05 (2H, d), 6.59-6.73 (2H, m), 6.94-7.06 (2H, m), 9.12 (1H, s). *m/z*: ES- [M-H]⁻ = 276.3.

Intermediate 16b: *tert*-Butyl 4-(4-(4-(4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazin-1-yl)butoxy)phenyl)piperidine-1-carboxylate



tert-Butyl 4-(4-hydroxyphenyl)piperidine-1-carboxylate (2.20 g, 7.93 mmol), K₂CO₃ (1.32 g, 9.52 mmol) and 1,4-dibromobutane (2.37 mL, 19.83 mmol) were dissolved in anhydrous MeCN (80 mL) under N₂. The mixture was stirred at 80°C for 3h then cooled to RT. The mixture was then filtered and washed through with DCM (200 mL). The filtrate was then concentrated. Purification by FSC (gradient: 0-30% EtOAc in heptane) gave the title compound (1.08 g, 33%) as a white oil which solidified on standing; ¹H NMR: (CDCl₃) 1.48 (9H, s), 1.51-1.69 (2H, m), 1.75-1.86 (2H, m), 1.89-1.98 (2H, m), 2-2.13 (2H, m), 2.58 (1H, tt), 2.78 (2H, t), 3.48 (2H, t), 3.97 (2H, t), 4.16-4.32 (2H, m), 6.75-6.89 (2H, m), 7.10 (2H, dt). (1H, m); *m/z*: ES⁺ [M-*t*Bu]⁺ 356.0.

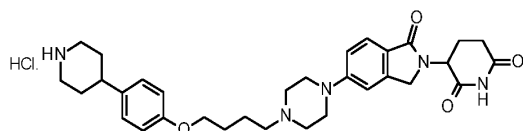
Intermediate 16c: *tert*-Butyl 4-(4-(4-(4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazin-1-yl)butoxy)phenyl)piperidine-1-carboxylate



DIPEA (2.3 mL, 13.10 mmol) was added to 3-[1-oxo-5-(piperazin-1-yl)-1,3-dihydro-2*H*-isindol-2-yl]-piperidine-2,6-dione hydrochloride salt (1.05 g, 2.88 mmol) in DMSO (20 mL) at RT. The mixture was sonicated until a hazy solution was obtained and was then stirred at RT for 0.5h. KI (1.30 g, 7.86 mmol) then a solution of *tert*-butyl 4-(4-(4-bromobutoxy)phenyl)piperidine-1-carboxylate (1.08 g, 2.62 mmol) in DMSO (7 mL) were then added and the mixture was stirred at 70°C for 18h. After cooling the mixture was diluted with EtOAc (200 mL), washed with water (3 × 100 mL) then brine (2 × 100 mL), dried (MgSO₄) and concentrated. Purification by FSC (gradient: 0-10% MeOH in DCM) gave the title compound (1.08 g, 63%) as a pale yellow gum; ¹H NMR: 1.48 (9H, s), 1.53-1.89 (9H, m), 2.14-2.25 (1H, m), 2.32 (1H, qd), 2.41-2.52 (2H, m), 2.53-2.65 (5H, m), 2.71-2.95 (4H, m), 3.26-3.39 (3H, m), 3.98 (2H, t), 4.15-4.31 (3H, m), 4.41 (1H, d), 5.18 (1H,

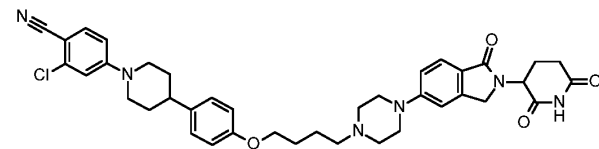
dd), 6.79-6.89 (3H, m), 6.99 (1H, dd), 7.08-7.16 (2H, m), 7.73 (1H, d), 8.01-8.25 (1H, m); m/z : ES^+ $[M+H]^+$ 660.3.

5 Intermediate 16d: 3-(1-Oxo-5-(4-(4-(4-(piperidin-4-yl)phenoxy)butyl)piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione



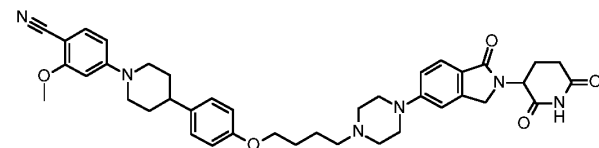
4M HCl in dioxane (2 mL, 8.00 mmol) was added in one portion to *tert*-butyl 4-(4-(4-(4-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazin-1-yl)butoxy)phenyl)piperidine-1-carboxylate (1.07 g, 1.62 mmol) in DCM (5 mL) at RT under air and the mixture was stirred for 2h. The mixture was then concentrated, slurried in Et₂O (30 mL) and filtered to give the title compound as a hydrochloride salt as a beige solid that was used in the next step without further purification; m/z : ES^+ $[M+H]^+$ 560.3.

10 Example 16: 2-Chloro-4-{4-[4-(4-[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl)butoxy]phenyl]piperidin-1-yl}benzonitrile



A mixture of 3-(1-oxo-5-(4-(4-(4-(piperidin-4-yl)phenoxy)butyl)piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride salt (100 mg, 0.17 mmol), 2-chloro-4-fluorobenzonitrile (27.4 mg, 0.18 mmol) and K₂CO₃ (58.0 mg, 0.42 mmol) was suspended in DMSO (1 mL) and stirred at 90°C for 1.5h. Purification by preparative HPLC (Column A, Eluent A) gave the title compound (65 mg, 56%) as a white solid; ¹H NMR: 1.55-1.65 (4H, m), 1.68-1.77 (2H, m), 1.81 (2H, d), 1.89-2.02 (1H, m), 2.34-2.43 (3H, m), 2.52-2.64 (1H, m), 2.7-2.94 (2H, m), 2.99 (2H, t), 3.21-3.4 (8H, m), 3.97 (2H, t), 4.09 (2H, d), 4.21 (1H, d), 4.33 (1H, d), 5.04 (1H, dd), 6.85 (2H, d), 7.00 (1H, dd), 7.05 (2H, d), 7.11-7.18 (3H, m), 7.51 (1H, d), 7.62 (1H, d), 10.91 (1H, s); m/z : ES^+ $[M+H]^+$ 695.5.

25 Example 17: 4-{4-[4-(4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl)butoxy]phenyl]piperidin-1-yl}-2-methoxybenzonitrile

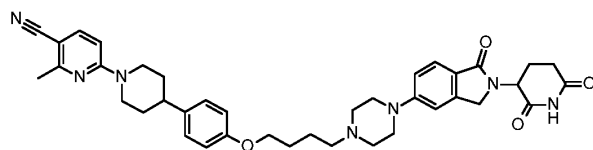


A mixture of 3-(1-oxo-5-(4-(4-(4-(piperidin-4-yl)phenoxy)butyl)piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride salt (100 mg, 0.17 mmol), 4-fluoro-2-methoxybenzonitrile (26.6 mg, 0.18 mmol) and K₂CO₃ (58.0 mg, 0.42 mmol) was suspended in DMSO (1 mL) and stirred at 90°C for 2.5h. After cooling to

30

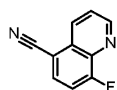
- RT, purification by preparative HPLC (Column A, Eluent A) gave the title compound (40 mg, 35%) as a white solid; ^1H NMR: 1.54-1.68 (4H, m), 1.74 (2H, q), 1.83 (2H, d), 1.92-2.02 (1H, m), 2.29-2.44 (4H, m), 2.56-2.8 (3H, m), 2.82-3.02 (3H, m), 3.11-3.49 (6H, m), 3.88 (3H, s), 3.98 (2H, t), 4.08 (2H, d), 4.21 (1H, d), 4.33 (1H, d), 5.05 (1H, dd), 6.53-6.67 (2H, m), 6.87 (2H, d), 7.06 (2H, d), 7.16 (2H, d), 7.41 (1H, d), 7.52 (1H, d), 10.92 (1H, s); m/z : ES^+ $[\text{M}+\text{H}]^+$ 691.5.

Example 18: 6-{4-[4-(4-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl}butoxy)phenyl]piperidin-1-yl}-2-methylpyridine-3-carbonitrile



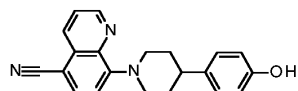
- 10 A mixture of 3-(1-oxo-5-(4-(4-(4-(piperidin-4-yl)phenoxy)butyl)piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride salt (68 mg, 0.11 mmol), 6-fluoro-2-methylnicotinonitrile (16.3 mg, 0.12 mmol) and K_2CO_3 (39.4 mg, 0.29 mmol) was suspended in DMSO (1.5 mL) and then stirred at 120°C for 1h in a microwave. Purification by preparative HPLC (Column A, Eluent A) gave the title compound (0.018 g, 23%) as a beige solid; ^1H NMR: (CDCl_3) 1.62-1.77 (4H, m), 1.79-1.88 (2H, m), 1.93 (2H, d), 2.20 (1H, ddq), 2.32 (1H, qd), 2.42-2.51 (2H, m), 2.56 (3H, s), 2.59-2.64 (4H, m), 2.71-2.9 (3H, m), 2.91-3.02 (2H, m), 3.24-3.41 (4H, m), 3.98 (2H, t), 4.25 (1H, d), 4.41 (1H, d), 4.60 (2H, d), 5.19 (1H, dd), 6.47 (1H, d), 6.81-6.9 (3H, m), 6.99 (1H, dd), 7.07-7.16 (2H, m), 7.54 (1H, d), 7.73 (1H, d), 7.91 (1H, s); m/z : ES^+ $[\text{M}+\text{H}]^+$ = 676.6.

Intermediate 19a: 8-Fluoroquinoline-5-carbonitrile



- 20 KOAc (0.104 g, 1.062 mmol) and potassium hexacyanoferrate(II) trihydrate (1.869 g, 4.42 mmol) were added to 5-bromo-8-fluoroquinoline (2.00 g, 8.85 mmol) in 1,4-dioxane (30 mL) and water (30 mL). The mixture was degassed under N_2 for 5 min at RT followed by the addition of XPhos (0.422 g, 0.885 mmol) and Xphos Pd G3 (0.374 g, 0.442 mmol). The mixture was then stirred at 100°C for 3h and then cooled to RT. The mixture was extracted with EtOAc (2×100 mL). The combined organic solutions were washed with sat. brine (100 mL), dried (Na_2SO_4) and concentrated. Purification by FSC (gradient: 0-30% EtOAc in hexanes) gave the title compound (0.4 g, 26%) as off white solid; ^1H NMR: 7.82 (1H, dd), 7.91 (1H, dd), 8.35 (1H, dd), 8.56 (1H, dt), 9.15 (1H, dd); m/z : ES^+ $[\text{M}+\text{H}]^+$ = 173.0.

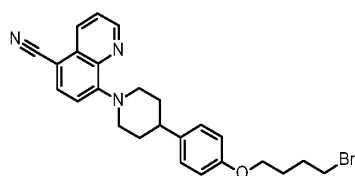
- 30 **Intermediate 19b: 8-(4-(4-Hydroxyphenyl)piperidin-1-yl)quinoline-5-carbonitrile**



4-(Piperidin-4-yl)phenol hydrobromide (0.900 g, 3.49 mmol) and DIPEA (1.217 mL, 6.97 mmol) were added

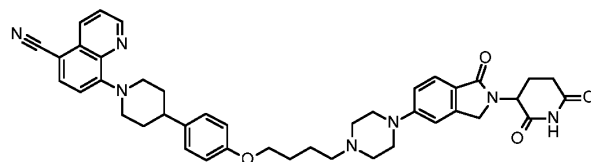
- to 8-fluoroquinoline-5-carbonitrile (0.400 g, 2.323 mmol) in DMSO (10 mL) at RT. The mixture was stirred at 50°C for 6h, then cooled to RT and concentrated. The mixture was slowly poured into ice-water. A solid was collected by filtration, washed with water (20 mL) and dried under vacuum to give the title compound (0.700 g, 89%) as yellow solid; ¹H NMR: 1.81-1.98 (4H, m), 2.63-2.79 (1H, m), 2.95-3.16 (2H, m), 4.37 (2H, d), 6.63-6.78 (2H, m), 7.11 (2H, d), 7.21 (1H, d), 7.74 (1H, dd), 8.04 (1H, d), 8.40 (1H, dd), 8.97 (1H, dd), 9.14 (1H, s); *m/z*: ES- [M-H]⁻ = 328.0.

Intermediate 19c: 8-(4-(4-(4-Bromobutoxy)phenyl)piperidin-1-yl)quinoline-5-carbonitrile

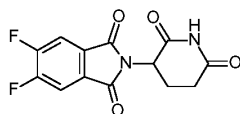


- 10 1,4-Dibromobutane (0.262 g, 1.214 mmol) and K₂CO₃ (0.252 g, 1.821 mmol) were added to 8-(4-(4-hydroxyphenyl)piperidin-1-yl)quinoline-5-carbonitrile (0.200 g, 0.607 mmol) in MeCN (5 mL) at RT. The mixture was then stirred at 60°C for 6h. Water (40 mL) was then added and the mixture was extracted with EtOAc (2 × 70 mL). The combined organic solutions were washed with sat. brine (50 mL), dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-30% EtOAc in hexanes) gave the title compound (0.200 g, 68%) as yellow solid; ¹H NMR: 1.76-2.02 (8H, m), 2.70-2.82 (1H, m), 3.00-3.12 (2H, m), 3.62 (2H, t), 3.99 (2H, t), 4.37 (2H, d), 6.89 (2H, d), 7.23 (3H, dd), 7.74 (1H, dd), 8.05 (1H, d), 8.40 (1H, dd), 8.98 (1H, dd).

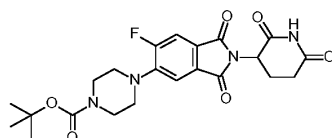
Example 19: 8-{4-[4-(4-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazin-1-yl]butoxy}phenyl]piperidin-1-yl}quinoline-5-carbonitrile



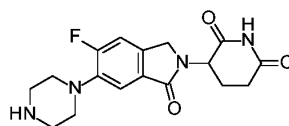
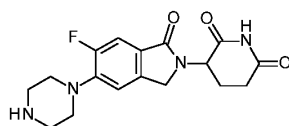
- 20 KI (0.205 g, 1.233 mmol) and DIPEA (0.359 mL, 2.056 mmol) were added to a mixture of 3-[1-oxo-5-(piperazin-1-yl)-1,3-dihydro-2*H*-isoindol-2-yl]piperidine-2,6-dione hydrochloride salt (0.150 g, 0.411 mmol) and 8-(4-(4-(4-bromobutoxy)phenyl)piperidin-1-yl)quinoline-5-carbonitrile (0.115 g, 0.247 mmol) in DMSO (5 mL) at RT. The mixture was then stirred at 80°C for 16h, then cooled to RT and concentrated. The residue
- 25 was slowly poured into ice-water. Solids were collected by filtration, washed with water (10 mL) and dried under vacuum. Preparative HPLC (Column C, Eluent C, Basic Work-Up A) gave the title compound (0.090 g, 30%) as off white solid; ¹H NMR: 1.57-1.67 (2H, m), 1.70-1.80 (2H, m), 1.84-2.00 (5H, m), 2.27-2.43 (3H, m), 2.51-2.64 (5H, m), 2.69-2.82 (1H, m), 2.84-2.97 (1H, m), 3.00-3.11 (2H, m), 3.24-3.31 (4H, m), 3.99 (2H, t), 4.17-4.25 (1H, m), 4.27-4.42 (3H, m), 5.05 (1H, dd), 6.89 (2H, d), 7.01-7.10 (2H, m), 7.22 (3H, dd), 7.52 (1H, d), 7.71-7.77 (1H, m), 8.05 (1H, d), 8.40 (1H, dd), 8.97 (1H, dd), 10.94 (1H, s); *m/z*: ES⁺ [M+H]⁺ =
- 30 712.4.

Intermediate 20a: 2-(2,6-Dioxopiperidin-3-yl)-5,6-difluoroisoindoline-1,3-dione

Potassium acetate (5.04 g, 51.37 mmol) was added in one portion to 3-aminopiperidine-2,6-dione hydrochloride salt (3 g, 18.23 mmol) and 4,5-difluorophthalic acid (3.35 g, 16.57 mmol) in AcOH (30 mL) at RT. The resulting solution was stirred at 90°C for 18h. The mixture was then cooled to RT and a solid formed. Water (30 mL) was added. The solid was collected by filtration, washed with water (2 × 5 mL) and dried at 45°C under vacuum overnight to give the title compound (3.43 g, 70%) as a dark grey/purple solid; ¹H NMR: 2.01-2.12 (1H, m), 2.53-2.7 (2H, m), 2.83-2.95 (1H, m), 5.17 (1H, dd), 8.15 (2H, t), 11.13 (1H, s); *m/z*: ES- [M-H]⁻ 293.

Intermediate 20b: *tert*-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1,3-dioxoisindolin-5-yl)piperazine-1-carboxylate

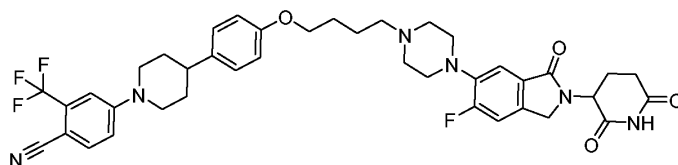
DMSO (0.5 mL) and then DIPEA (118 μL, 0.68 mmol) were added to a mixture of 2-(2,6-dioxopiperidin-3-yl)-5,6-difluoroisoindoline-1,3-dione (100 mg, 0.34 mmol) and *tert*-butyl piperazine-1-carboxylate (69.6 mg, 0.37 mmol). This mixture was then heated at 100°C for 2h. Sat. NH₄Cl solution (0.5mL) and water (1.5 mL) were then added. A brown precipitate was collected by filtration, washed with water and dried in a vacuum oven to give the title compounds (86 mg, 55%) as dark brown/black solid; ¹H NMR: 1.44 (9H, s), 2.04 (1H, dq), 2.55-2.62 (1H, m), 2.89 (1H, ddd), 3.09 (1H, d), 3.16-3.26 (4H, m), 3.45-3.55 (4H, m), 5.11 (1H, dd), 7.49 (1H, d), 7.75 (1H, d), 11.09 (1H, s); *m/z*: ES- [M-H]⁻ 459.

Intermediates 20c and 20d: 3-(5-Fluoro-1-oxo-6-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione and 3-(6-Fluoro-1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione

Zinc powder (72.4 mg, 1.11 mmol) was added in one portion to *tert*-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1,3-dioxoisindolin-5-yl)piperazine-1-carboxylate (170 mg, 0.37 mmol) in AcOH (3.4 mL) at RT. The resulting suspension was stirred at 60°C for 48h. Further Zn powder (72.4 mg, 1.11 mmol) was added and the mixture was stirred at 60°C for 24h. The mixture was then diluted with MeOH (25 mL), filtered and the filtrate was concentrated. The resulting gum was dissolved in TFA (5 mL) at RT and triethylsilane (587 μL, 3.68 mmol) was added in one portion. The resulting orange solution was stirred at RT for 1h. The mixture was then concentrated. Trituration with Et₂O and collection of a solid by filtration gave the title compounds (in the

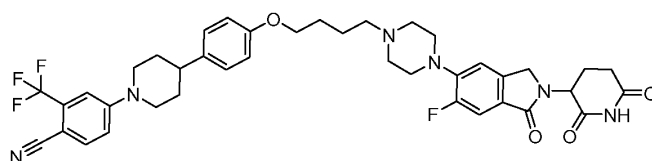
form of trifluoroacetate salts) as a mixture of isomers (170 mg, 57%) as beige solids that were used in the next step without further purification; m/z : ES^+ $[M+H]^+ = 347$.

5 **Example 20: 4-{4-[4-(4-{4-[2-(2,6-Dioxopiperidin-3-yl)-6-fluoro-3-oxo-2,3-dihydro-1H-isoindol-5-yl]-piperazin-1-yl}butoxy)phenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile**



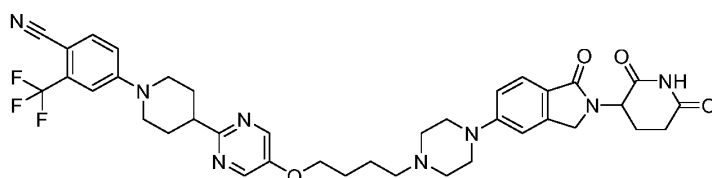
Intermediate 2d was reacted with Intermediates 20c and 20d using the general synthetic method illustrated by Example 1 to give the title compound after purification by HPLC (Column A, Eluent A). ^1H NMR: (500 MHz, $CDCl_3$) 1.85 (2H, q), 1.88-1.94 (1H, m), 1.94-2.01 (3H, m), 2.22 (1H, dtd), 2.35 (1H, qd), 2.77 (OH, s), 2.82-2.88 (1H, m), 2.88-2.98 (3H, m), 3.06 (2H, td), 3.13 (4H, s), 3.32-3.44 (4H, m), 3.98 (2H, t), 4.02 (2H, dq), 4.22-4.47 (2H, m), 5.18 (1H, dd), 6.81-6.88 (2H, m), 6.96-7.03 (2H, m), 7.1-7.15 (2H, m), 7.16 (1H, d), 7.52 (1H, d), 7.62 (1H, dd), 8-8.04 (1H, m), 8.21 (2H, s); m/z ES^+ $[M+H]^+ = 747.4$.

15 **Example 21: 4-{4-[4-(4-{4-[2-(2,6-Dioxopiperidin-3-yl)-6-fluoro-1-oxo-2,3-dihydro-1H-isoindol-5-yl]-piperazin-1-yl}butoxy)phenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile**



Intermediate 2d was reacted with Intermediate 20c and 20d using the general synthetic method illustrated by Example 2 to give the title compound after purification by HPLC (Column A, Eluent A); ^1H NMR: (500 MHz, $CDCl_3$) 0.87-0.94 (1H, m), 1.76 (2H, qd), 1.8-1.94 (1H, m), 1.94-2.01 (2H, m), 2.22 (1H, dtd), 2.34 (1H, qd), 2.74 (1H, tt), 2.84-2.89 (2H, m), 2.93 (1H, ddd), 3.01-3.1 (5H, m), 3.32 (3H, q), 3.48-3.55 (1H, m), 3.98 (2H, t), 4.02 (2H, dt), 4.28 (1H, d), 4.42 (1H, d), 5.19 (1H, dd), 6.65 (OH, s), 6.82-6.88 (2H, m), 6.99 (1H, dd), 7.09-7.18 (4H, m), 7.48 (1H, d), 7.55 (OH, dd), 7.61 (1H, d), 7.98 (1H, s), 8.16 (2H, s); m/z ES^+ $[M+H]^+ = 747.4$.

25 **Example 22: 4-{4-[5-(4-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl}butoxy)pyrimidin-2-yl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile**

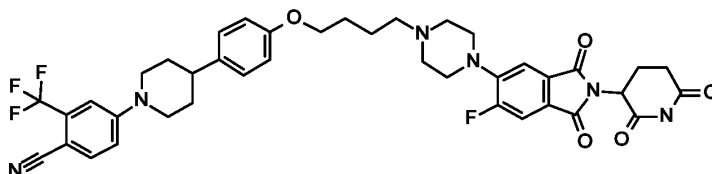


Intermediate 8e was reacted with Intermediate 2c using the general synthetic method illustrated by Example 8 to give the title compound after purification by HPLC (Column: Zorbax Eclipse Plus C18 50 × 2.1mm, 1.8

μm, Eluent C, Basic Work-Up A); ¹H NMR: 1.52-1.68 (2H, m), 1.66-1.84 (4H, m), 1.9-2.08 (3H, m), 2.26-2.49 (6H, m), 2.59 (2H, d), 2.8-2.98 (1H, m), 3.05-3.2 (3H, m), 3.23-3.3 (4H, m), 4.05-4.26 (5H, m), 4.33 (1H, d), 5.05 (1H, dd), 6.99-7.12 (2H, m), 7.27 (1H, d), 7.32 (1H, s), 7.52 (1H, d), 7.82 (1H, d), 8.49 (2H, s), 10.95 (1H, s); *m/z* ES⁺ [M+H]⁺ = 731.2.

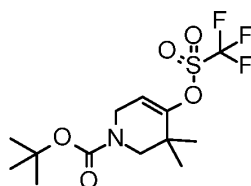
5

Example 23: 4-{4-[4-(4-{4-[2-(2,6-Dioxopiperidin-3-yl)-6-fluoro-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl]-piperazin-1-yl}butoxy)phenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile



Intermediate 1h was reacted with Intermediate 20b using the general synthetic method illustrated by Example 1 to give the title compound after purification by HPLC (Column A, Eluent A, Basic Work-Up A); ¹H NMR: (CDCl₃) 1.65-1.87 (6H, m), 1.92-2 (2H, m), 2.07-2.2 (1H, m), 2.41-2.53 (2H, m), 2.56-2.67 (4H, m), 2.67-2.96 (4H, m), 3.06 (2H, td), 3.22-3.35 (4H, m), 3.92-4.1 (4H, m), 4.93 (1H, dd), 6.78-6.92 (2H, m), 6.99 (1H, dd), 7.07-7.21 (3H, m), 7.37 (1H, d), 7.47 (1H, d), 7.61 (1H, d), 7.97 (1H, s); *m/z* ES⁺ [M+H]⁺ = 761.5.

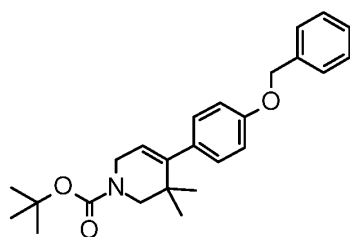
Intermediate 24a: *tert*-Butyl 3,3-dimethyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2*H*)-carboxylate



Lithium bis(trimethylsilyl)amide (60.7 mL, 60.71 mmol) was added slowly to *tert*-butyl 3,3-dimethyl-4-oxopiperidine-1-carboxylate (9.2 g, 40.47 mmol) in THF (80 mL) at -78°C over 20 min under N₂. The resulting mixture was stirred at -78°C for 0.5h. *N*-(5-Chloropyridin-2-yl)-1,1,1-trifluoro-*N*-((trifluoromethyl)sulfonyl)methanesulfonamide (23.84 g, 60.71 mmol) was then added and the resulting mixture was stirred at RT for 16h. The reaction was then quenched with sat. NH₄Cl solution. The mixture was diluted with EtOAc, washed with water then sat. brine, dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-5% EtOAc in petroleum ether) gave the title compound (11.00 g, 76 %) as a yellow liquid; ¹H NMR (300 MHz)

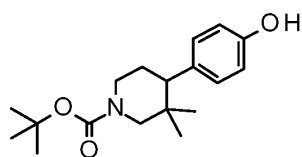
5.82 (s, 1H), 4.01 (d, 2H), 3.35 (s, 2H), 1.40 (s, 9H), 1.05 (s, 6H).

Intermediate 24b: *tert*-Butyl 4-(4-(benzyloxy)phenyl)-3,3-dimethyl-3,6-dihydropyridine-1(2*H*)-carboxylate



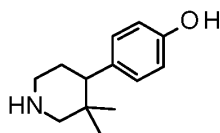
- 5 Pd(dppf)₂Cl₂-DCM (0.818 g, 1.00 mmol) was added to *tert*-butyl 3,3-dimethyl-4-(((trifluoromethyl)sulfonyl)-oxy)-3,6-dihydropyridine-1(2*H*)-carboxylate (3.600 g, 10.02 mmol), 2-(4-(benzyloxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.66 g, 15.03 mmol) and K₂CO₃ (4.15 g, 30.05 mmol) in 1,4-dioxane (40 mL) and water (10 mL) at RT under N₂. The resulting mixture was stirred at 100°C for 3h. The mixture was then diluted with EtOAc, washed with water then sat. brine, dried (Na₂SO₄) and concentrated. Purification by C18-
flash chromatography (gradient: 5- 90% MeCN in water (0.1% NH₄HCO₃)) gave the title compound (1.980 g, 50%) as a pale yellow solid; ¹H NMR: 7.47-7.43 (m, 2H), 7.42-7.37 (m, 2H), 7.36-7.30 (m, 1H), 7.12-7.05 (m, 2H), 6.99-6.93 (m, 2H), 5.40 (s, 1H), 5.08 (s, 2H), 3.94 (d, 2H), 3.26 (s, 2H), 1.43 (s, 9H), 0.97 (s, 6H); *m/z* ES⁺ [M-*t*Bu+MeCN]⁺ = 379.
- 10

Intermediate 24c: *tert*-butyl 4-(4-hydroxyphenyl)-3,3-dimethyl-piperidine-1-carboxylate



- 15 A mixture of *tert*-butyl 4-(4-(benzyloxy)phenyl)-3,3-dimethyl-3,6-dihydropyridine-1(2*H*)-carboxylate (1.00 g, 2.54 mmol) and Pd-on-C (0.27 g, 0.25 mmol) in MeOH (10 mL) was stirred under an atmosphere of H₂ at 20 atm and 80°C for 1h. Concentration of the mixture then gave the title compound (0.844 g, 109 %) which was used in the next step without further purification; ¹H NMR (300 MHz) 0.68 (s, 6H), 1.41 (s, 9H), 1.80-2.10 (m, 1H), 2.33-2.43 (m, 1H), 2.73 – 2.75 (m, 1H), 3.32 (s, 2H), 3.66-3.69 (m, 1H), 4.10-4.12 (m, 1H), 6.67 (d, 2H), 6.93 (d, 2H), 9.21 (s, 1H); *m/z* ES⁺ [M-*t*Bu]⁺ = 250.
- 20

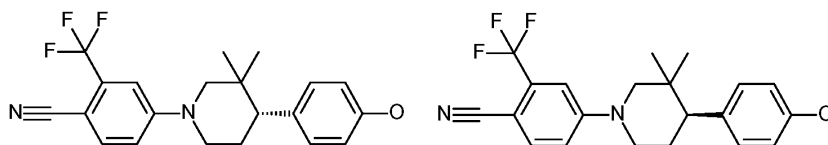
Intermediates 24d: 4-(3,3-Dimethylpiperidin-4-yl)phenol



- 4M HCl in dioxane (7.00 mL, 28.00 mmol) was added to *tert*-butyl 4-(4-hydroxyphenyl)-3,3-dimethyl-piperidine-1-carboxylate (820 mg, 2.68 mmol) in DCM (7 mL) at RT and the mixture was stirred for 16h.
Concentration of the mixture then gave the title compound as a hydrochloride salt (0.750 g, 116 %) which was used in the next step without further purification; ¹H NMR (300 MHz) 6.93 (d, 2H), 6.71 (d, 2H), 3.29 (d, 1H), 3.04 (d, 1H), 2.92 (d, 1H), 2.78 (d, 1H), 2.60 (m, 1H), 2.25-2.06 (m, 1H), 1.61 (d, 1H), 0.87 (s, 3H), 0.76 (s,
- 25

3H); m/z ES⁺ [M+H]⁺ = 206.

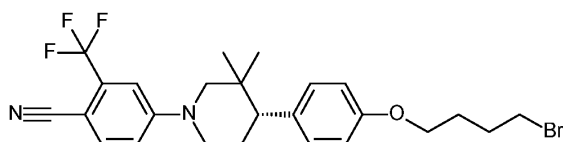
Intermediates 24e and 24f: *rel*-(*S*)-4-(4-(4-Hydroxyphenyl)-3,3-dimethylpiperidin-1-yl)-2-(trifluoromethyl)benzonitrile (isomer 1) and *rel*-(*R*)-4-(4-(4-Hydroxyphenyl)-3,3-dimethylpiperidin-1-yl)-2-(trifluoromethyl)benzonitrile (isomer 2)



4-Fluoro-2-(trifluoromethyl)benzonitrile (2017 mg, 10.67 mmol) was added to 4-(3,3-dimethylpiperidin-4-yl)phenol (730 mg, 3.56 mmol) and DIPEA (1863 μ L, 10.67 mmol) in DMSO (10 mL) at RT. The resulting mixture was stirred at 60°C for 16h. The mixture was then diluted with EtOAc, washed with water then sat.

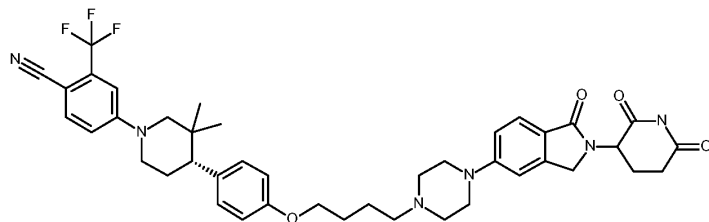
- 10 brine, dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-30% EtOAc in petroleum ether) gave material that was further purified by preparative chiral-HPLC (Column: CHIRALPAK AD-3, 3.0mm*100mm, 3 μ m; Mobile Phase A, Mobile Phase B:MeOH(0.1% diethylamine); Flow rate:2 mL/min; Gradient:10% B; 220 nm) to give the title compounds as pale yellow solids: Intermediate 24e (0.320 g, 24 %); Intermediate 24f (0.289 g, 22%). **Intermediate 24e (eluting first):** ¹H NMR: 0.69 (3H, s), 0.78 (3H, s), 1.53 (1H, d), 2.12 (1H, qd), 2.55 (1H, d), 2.82 (1H, d), 2.91-3.03 (1H, m), 3.90 (1H, dd), 4.19 (1H, d), 6.65-6.70 (2H, m), 6.92-6.98 (2H, m), 7.24-7.31 (2H, m), 7.77 (1H, d), 9.21 (1H, s); m/z ES⁺ [M+H]⁺ = 375. **Intermediate 24f:** ¹H NMR: 0.69 (3H, s), 0.78 (3H, s), 1.53 (1H, d), 2.12 (1H, m), 2.55 (1H, d), 2.82 (1H, d), 2.91-3.03 (1H, m), 3.85-3.93 (1H, m), 4.14-4.25 (1H, m), 6.56-6.78 (2H, m), 6.81-7.06 (2H, m), 7.16-7.35 (2H, m), 7.77 (1H, d), 9.21 (1H, s); m/z ES⁺ [M+H]⁺ = 375.

Intermediate 24g: *rel*-(*S*)-4-(4-(4-(4-bromobutoxy)phenyl)-3,3-dimethylpiperidin-1-yl)-2-(trifluoromethyl)benzonitrile



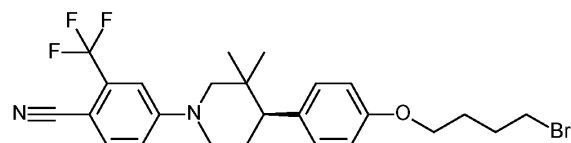
rel-(*S*)-4-(4-(4-Hydroxyphenyl)-3,3-dimethylpiperidin-1-yl)-2-(trifluoromethyl)benzonitrile (Intermediate 24e, Isomer 1, 100 mg, 0.27 mmol), K₂CO₃ (44.3 mg, 0.32 mmol) and 1,4-dibromobutane (80 μ L, 0.67 mmol) were dissolved in anhydrous MeCN (2.59 mL) under N₂. The mixture was stirred at 60°C for 5h then at 40°C for 2 days. The mixture was then cooled to RT, filtered and washed through with DCM (20 mL). The filtrate was then concentrated to give the title compound as a colourless oil which was used in the next step without further purification.

Example 24: *rel*-(*S*)-4-[4-[4-(4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazin-1-yl]butoxy)phenyl]-3,3-dimethylpiperidin-1-yl]-2-(trifluoromethyl)benzonitrile (absolute stereochemistry not yet confirmed)



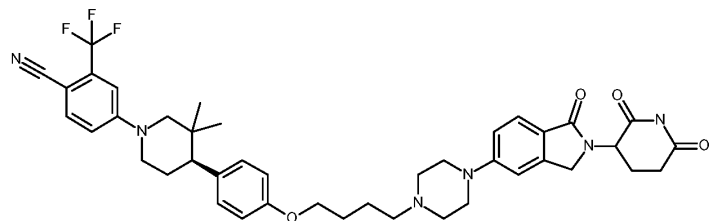
- Intermediate 2c was reacted with Intermediate 24g using the general synthetic method illustrated by Example 5 to give the title compound (as a formate salt) after purification by HPLC (Column A, Eluent A). ¹H NMR: (CDCl₃) 0.84 (3H, s), 0.86 (3H, s), 1.65-1.79 (1H, m), 1.77-1.95 (4H, m), 2.14-2.42 (3H, m), 2.54 (1H, dd), 2.7-3.05 (10H, m), 3.46 (4H, q), 3.63 (1H, dd), 3.93-4.14 (3H, m), 4.26 (1H, d), 4.42 (1H, d), 5.19 (1H, dd), 6.8-6.86 (2H, m), 6.89 (1H, d), 6.98 (2H, ddd), 7.02-7.08 (2H, m), 7.12 (1H, d), 7.58 (1H, d), 7.75 (1H, d), 8.07 (1H, s), 8.23 (1H, s); *m/z* ES⁺ [M+H]⁺ = 757.4.

Intermediate 25a: *rel*-(*R*)-4-(4-(4-(4-Bromobutoxy)phenyl)-3,3-dimethylpiperidin-1-yl)-2-(trifluoromethyl)benzonitrile



- rel*-(*R*)-4-(4-(4-Hydroxyphenyl)-3,3-dimethylpiperidin-1-yl)-2-(trifluoromethyl)benzonitrile (intermediate 24f, isomer 2, 250 mg, 0.67 mmol), K₂CO₃ (346 mg, 0.80 mmol) and 1,4-dibromobutane (0.199 mL, 1.67 mmol) were dissolved in anhydrous MeCN (4 mL) under N₂. The mixture was stirred at 70°C for 2h then cooled to RT. The mixture was filtered and washed through with DCM (20 mL). The filtrate was concentrated to give the title compound as a colourless oil that was use in the next step without further purification.

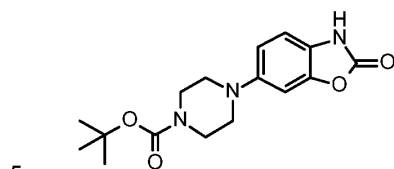
Example 25: *rel*-(*R*)-4-{4-[4-(4-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazin-1-yl}butoxy)phenyl]-3,3-dimethylpiperidin-1-yl}-2-(trifluoromethyl)benzonitrile (absolute stereochemistry not yet confirmed)



- Intermediate 2c was reacted with Intermediate 25a using the general synthetic method illustrated by Example 5 to give the title compound (as a formate salt) after purification by HPLC (Column A, Eluent A); ¹H NMR: (CDCl₃) 0.84 (3H, s), 0.86 (3H, s), 1.66-1.78 (1H, m), 1.81-2 (4H, m), 2.13-2.26 (2H, m), 2.33 (1H, qd), 2.54 (1H, dd), 2.76-2.91 (5H, m), 2.92-3.05 (5H, m), 3.49-3.59 (4H, m), 3.63 (1H, dd), 3.95-4.1 (3H, m), 4.27 (1H,

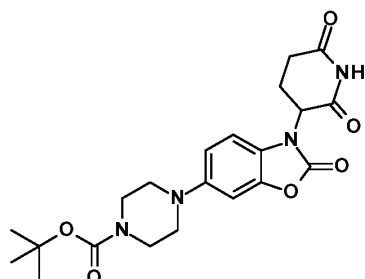
d), 4.42 (1H, d), 5.19 (1H, dd), 6.8-6.86 (2H, m), 6.90 (1H, d), 6.98 (2H, td), 7.02-7.09 (2H, m), 7.12 (1H, d), 7.59 (1H, d), 7.75 (1H, d), 7.97 (1H, s); m/z ES⁺ [M+H]⁺ = 757.4.

Intermediate 26a: *tert*-Butyl 4-(2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)piperazine-1-carboxylate



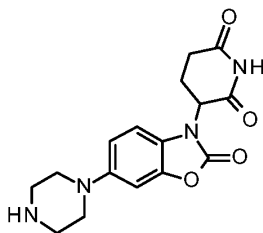
6-Bromobenzo[d]oxazol-2(3H)-one (0.321 g, 1.5 mmol) and Dave-phos-Pd G3 (0.114 g, 0.15 mmol) were added to an oven-dried microwave vial with stir bar. The vial was sealed by a rubber septum and then degassed by N₂. THF (3 mL), lithium bis(trimethylsilyl)amide (3.30 mL, 3.30 mmol) and *tert*-butyl piperazine-1-carboxylate (0.335 g, 1.80 mmol) were then added. The reaction was degassed by N₂ again. The resulting solution was stirred at 70°C for 16h. AcOH was then added and the mixture was concentrated. Purification by FSC (gradient: 0-80% EtOAc in hexanes) gave the title compound (0.250 g, 52 %) as a grey solid; ¹H NMR (500 MHz) 1.41 (11H, s), 2.35 (1H, br s), 2.51-2.53 (1H, m), 2.94-3.04 (5H, m), 3.26-3.32 (3H, m), 3.44 (5H, br s), 6.73 (1H, dd), 6.93 (1H, d), 6.98 (1H, d), 11.30 (1H, br s); m/z (ES⁻) [M-H]⁻ = 318.2.

15 **Intermediate 26b: *tert*-Butyl 4-(3-(2,6-dioxopiperidin-3-yl)-2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)piperazine-1-carboxylate**



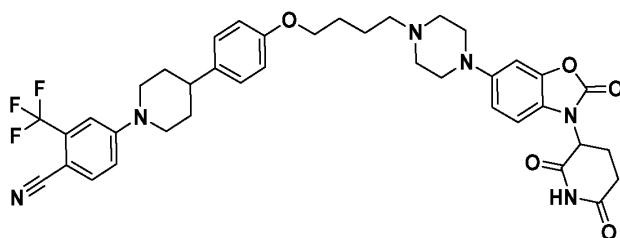
tert-Butyl 4-(2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)piperazine-1-carboxylate (0.048 g, 0.15 mmol), 3-bromopiperidine-2,6-dione (1.1 eq) and Cs₂CO₃ (0.147 g, 0.45 mmol) were added to an oven-dried microwave vial with stir bar. The vial was then purged with N₂. DMF (1 mL) was then added. The resulting slurry was stirred at 90°C for 16h and then concentrated. Purification by FSC (gradient: 0-100% EtOAc in hexanes) gave the title compound (0.027 g, 41.8 %) as a white solid; ¹H NMR (500 MHz, CDCl₃) 1.49-1.54 (9H, m), 2.28-2.41 (1H, m), 2.64-2.78 (1H, m), 2.79-2.90 (1H, m), 2.95-3.02 (1H, m), 3.05-3.23 (4H, m), 3.55-3.81 (4H, m), 4.95-5.15 (1H, m), 6.66-6.78 (1H, m), 6.79-6.92 (1H, m), 6.94-7.07 (1H, m), 7.95-8.13 (1H, m); m/z ES⁺ [M+H]⁺ = 431.

Intermediate 26c: 3-(2-Oxo-6-(piperazin-1-yl)benzo[d]oxazol-3(2H)-yl)piperidine-2,6-dione



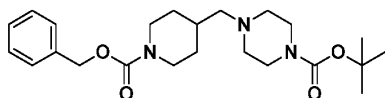
- 4M HCl in dioxane (2.3 mL, 9.3 mmol) was added to a solution of *tert*-butyl 4-(3-(2,6-dioxopiperidin-3-yl)-2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)piperazine-1-carboxylate (0.20 g, 0.46 mmol) in 1,4-dioxane (2.3 mL) at RT and the mixture was stirred at 40°C for 3h. Concentration of this mixture then gave the title compound as a hydrochloride salt (0.170 g, 100 %) as an off-white solid which was used without further purification; ¹H NMR (500MHz) 2.09-2.20 (1H, m), 2.60-2.74 (2H, m), 2.84-2.97 (1H, m), 3.22 (4H, br s), 3.33 (4H, br d), 5.33 (1H, br dd), 6.85 (1H, br d), 7.10-7.28 (2H, m), 9.13 (2H, br s), 11.18 (1H, s); *m/z* ES⁺ [M+H]⁺ = 331.

Example 26: 4-{4-[4-(4-{3-(2,6-Dioxopiperidin-3-yl)-2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl}piperazin-1-yl)butoxy]phenyl}piperidin-1-yl}-2-(trifluoromethyl)benzonitrile



- Intermediate 2d was reacted with Intermediate 26c using the general synthetic method illustrated by Example 2 to give the title compound (as a formate salt) after purification by HPLC (Column A, Eluent A). ¹H NMR: 1.56-1.69 (4H, m), 1.74 (2H, p), 1.85 (2H, d), 2.13 (1H, dt), 2.38 (2H, t), 2.53 (4H, d), 2.59-2.71 (2H, m), 2.71-2.83 (1H, m), 2.83-2.94 (1H, m), 2.99-3.06 (2H, m), 3.09 (4H, d), 3.31 (1H, s), 3.97 (2H, t), 4.17 (2H, d), 5.29 (1H, dd), 6.77 (1H, dd), 6.82-6.89 (2H, m), 7.03-7.12 (2H, m), 7.16 (2H, d), 7.27 (1H, dd), 7.32 (1H, d), 7.81 (1H, d), 8.18 (1H, s), 11.15 (1H, s); *m/z* ES⁺ [M+H]⁺ = 731.6.

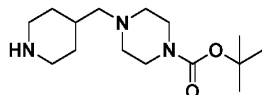
Intermediate 27a: *tert*-butyl 4-((1-((benzyloxy)carbonyl)piperidin-4-yl)methyl)piperazine-1-carboxylate



- NaBH(OAc)₃ (6.80 g, 32.08 mmol) was added in one portion to 1-Boc-piperazine (4.00 g, 21.48 mmol), 4-formyl-N-Cbz-piperidine (6.40 g, 25.88 mmol) and AcOH (1.50 mL, 26.23 mmol) in DCM (50 mL) at RT under air and the mixture was stirred at RT for 2h. The mixture was then diluted with sat. NaHCO₃ solution (60 mL) and the phases were separated. The aqueous layer was extracted with DCM (3 × 40 mL). The combined organic solutions were dried (MgSO₄) and concentrated. Purification by FSC (gradient: 50-70% EtOAc in heptane) gave the title compound (8.83 g, 98 %) as a colourless oil; ¹H NMR: 0.91-1.05 (2H, m), 1.40 (9H, s), 1.6-1.77 (3H, m), 2.12 (2H, d), 2.22-2.32 (4H, m), 2.79 (2H, s), 3.26-3.33 (4H, m), 3.99 (2H, d),

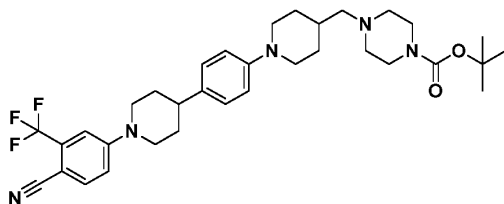
5.07 (2H, s), 7.28-7.44 (5H, m); m/z : ES^+ $[M+H]^+$ 418.3.

Intermediate 27b: *tert*-Butyl 4-(piperidin-4-ylmethyl)piperazine-1-carboxylate



- 5 A mixture of *tert*-butyl 4-((1-((benzyloxy)carbonyl)piperidin-4-yl)methyl)piperazine-1-carboxylate (9.50 g, 22.75 mmol) and 10% Pd(OH)₂ on activated charcoal (3.20 g, 2.28 mmol) in EtOH (40 mL) was stirred under an atmosphere of H₂ at 1 atm and RT for 18h. The mixture was then filtered through celite washing through with EtOH. The filtrate was concentrated. The residue was dissolved in EtOH (40 mL) and 10% Pd(OH)₂ on activated charcoal (3.20 g, 2.28 mmol) was added. The suspension was stirred under H₂ at 1 atm and RT for 3
- 10 days. The mixture was then filtered through celite and washed through with EtOH (100 mL). The filtrate was concentrated to dryness to give crude product (5.61 g, 87 %) as a grey solid. A portion of the crude product (2.32 g) was purified by ion exchange chromatography (SCX column, eluting with 1M NH₃/MeOH) to give the title compound (1.84 g, 79 %) as a grey oil; ¹H NMR: 0.83-0.99 (2H, m), 1.37 (9H, s), 1.45-1.54 (1H, m), 1.58 (2H, d), 2.07 (2H, d), 2.14-2.28 (4H, m), 2.40 (2H, td), 2.87 (2H, d), 3.2-3.35 (4H, m); m/z : ES^+ $[M+H]^+$
- 15 284.2.

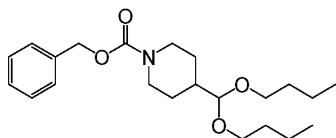
Intermediate 27c: *tert*-Butyl 4-((1-(4-(1-(4-cyano-3-(trifluoromethyl)phenyl)piperidin-4-yl)phenyl)piperidin-4-yl)methyl)piperazine-1-carboxylate



- 20 A mixture of 4-(4-(4-bromophenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (350 mg, 0.86 mmol), *tert*-butyl 4-(piperidin-4-ylmethyl)piperazine-1-carboxylate (242 mg, 0.86 mmol), RuPhos G3 (53.6 mg, 0.06 mmol), RuPhos (29.9 mg, 0.06 mmol) sodium *tert*-butoxide (247 mg, 2.57 mmol) and anhydrous 1,4-dioxane (50 mL) was degassed, the flask filled with N₂, and the mixture stirred at 100°C for 1h. The mixture was then cooled and concentrated to dryness. Water (10 mL) was added and the resulting mixture was extracted with
- 25 EtOAc (3 × 20 mL). The combined organic solutions were dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-100% EtOAc in heptane) gave the title compound (0.360 g, 69 %) as a pale yellow solid; ¹H NMR: 1.20 (2H, tt), 1.40 (9H, s), 1.53-1.67 (3H, m), 1.77 (2H, d), 1.84 (2H, d), 2.16 (2H, d), 2.26-2.31 (4H, m), 2.54-2.64 (2H, m), 2.68-2.77 (1H, m), 2.94-3.11 (2H, m), 3.31 (4H, d), 3.60 (2H, d), 4.17 (2H, d), 6.85 (2H, d), 7.07 (2H, d), 7.27 (1H, dd), 7.32 (1H, d), 7.81 (1H, d); m/z ES^+ $[M+H]^+$ = 611.9.

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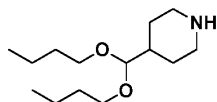
Intermediate 27d: Benzyl 4-(dibutoxymethyl)piperidine-1-carboxylate



4-Methylbenzenesulfonic acid hydrate (0.100 g, 0.53 mmol) was added to 4-formyl-*N*-Cbz-piperidine (20.0 g, 80.88 mmol) in *n*-butanol (40 mL) at RT under air. The resulting solution was stirred at 50°C for 1h. (Reaction incomplete). MgSO₄ (10.6 g, 88.07 mmol) was added and the suspension was stirred at 50°C for a further 1h.

- 5 The reaction was incomplete so the temperature was increased to 70°C and the mixture was stirred for a further 1 day. The mixture was then filtered, washing through with EtOAc (200 mL), where the filtrate was collected in a vessel containing 2M aq. K₂CO₃ (40 mL). The phases were separated. The organic solution was washed (2M aq. K₂CO₃ (2 × 40 mL) then sat. brine (2 × 20 mL)), dried (MgSO₄) and concentrated. Purification by FSC (gradient: 0-30% EtOAc in heptane) gave the title compound (20.5 g, 67 %) as a
- 10 colourless liquid; ¹H NMR: 0.88 (6H, t), 1.11 (2H, qd), 1.27-1.4 (4H, m), 1.47 (4H, dq), 1.65 (2H, d), 1.73 (1H, dt), 2.75 (2H, s), 3.37 (2H, dt), 3.54 (2H, dt), 3.95-4.06 (2H, m), 4.16 (1H, d), 5.07 (2H, s), 7.25-7.44 (5H, m).

Intermediate 27e: 4-(Dibutoxymethyl)piperidine

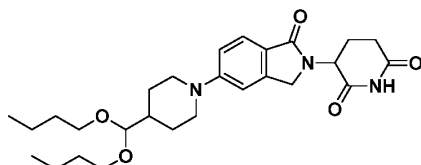


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A mixture of benzyl 4-(dibutoxymethyl)piperidine-1-carboxylate (20.5 g, 54.30 mmol) and 10% Pd(OH)₂ on activated charcoal (3.8 g, 2.71 mmol) in EtOH (120 mL) was stirred under H₂ (1 atm) at RT for 3 days. The mixture was then filtered through celite and washed though with EtOH (200 mL). The filtrate was concentrated to dryness to give the title compound (13.10 g, 99 %) as a colourless oil; ¹H NMR: 0.88 (6H, t),

20 1.07 (2H, qd), 1.26-1.4 (4H, m), 1.41-1.51 (4H, m), 1.51-1.65 (3H, m), 2.05 (1H, s), 2.31-2.46 (2H, m), 2.90 (2H, d), 3.36 (2H, dt), 3.52 (2H, dt), 4.10 (1H, d).

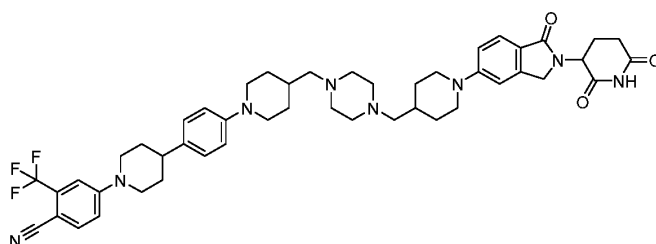
Intermediate 27f: 3-(5-(4-(Dibutoxymethyl)piperidin-1-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione



- 25 Pd-PEPPSI-IHepCl (0.23 g, 0.24 mmol) was added to a degassed mixture of 3-(5-bromo-1-oxoisindolin-2-yl)piperidine-2,6-dione (1.5 g, 4.64 mmol), 4-(dibutoxymethyl)piperidine (1.5 g, 6.16 mmol) and Cs₂CO₃ (4.54 g, 13.93 mmol) in 1,4-dioxane (45 mL) at RT under N₂. The resulting mixture was vacuum degassed, backfilling with N₂ and then stirred at 100°C for 3h. After cooling, the mixture was diluted with DCM (75 mL) and 10% aq. AcOH (50 mL) and the phases were separated. The aqueous portion was extracted with DCM (75
- 30 mL). The combined organic layers were washed with sat. NaHCO₃ (50 mL), dried (MgSO₄) and concentrated. The residue was partitioned between DCM (50 mL) and water (20 mL) and the aqueous portion was extracted

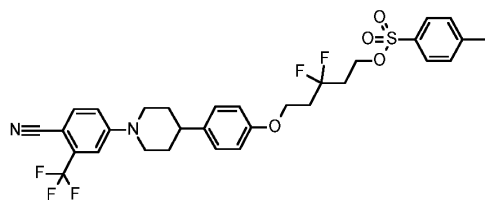
with DCM (50 mL). The combined organic solutions were then dried (MgSO₄) and concentrated. Trituration with EtOAc (15 mL) gave a solid which was collected by filtration, washed sequentially with EtOAc (2 × 5 mL), EtOAc:Et₂O (1:1; 5 mL), and Et₂O (5 mL) then dried under vacuum to give the title compound (1.659 g, 74 %) as a white solid; ¹H NMR: 0.89 (6H, t), 1.23-1.42 (6H, m), 1.43-1.56 (4H, m), 1.67-1.85 (3H, m), 1.96 (1H, ddd), 2.28-2.44 (1H, m), 2.55-2.64 (1H, m), 2.72-2.84 (2H, m), 2.90 (1H, ddd), 3.40 (2H, dt), 3.56 (2H, dt), 3.89 (2H, d), 4.09-4.25 (2H, m), 4.32 (1H, d), 5.04 (1H, dd), 7.04 (2H, d), 7.50 (1H, d), 10.91 (1H, s); *m/z* ES⁺ [M+H]⁺ = 486.0.

Example 27: 4-{4-[4-(4-{4-({1-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperidin-4-yl}methyl)piperazin-1-yl)methyl}piperidin-1-yl)phenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile



Intermediate 27c was reacted with Intermediate 27f using the general synthetic method illustrated by Example 1 to give the title compound (as a formate salt) after purification by HPLC (Column A, Eluent A). ¹H NMR: 1.09-1.27 (4H, m), 1.53-1.69 (3H, m), 1.77 (5H, d), 1.84 (2H, d), 1.92-2.01 (1H, m), 2.15 (4H, d), 2.28-2.42 (9H, m), 2.56-2.64 (3H, m), 2.74 (1H, d), 2.82 (2H, t), 2.86-2.95 (1H, m), 3.04 (2H, t), 3.60 (2H, d), 3.86 (2H, d), 4.11-4.26 (3H, m), 4.32 (1H, d), 5.04 (1H, dd), 6.85 (2H, d), 7.05 (4H, q), 7.27 (1H, dd), 7.32 (1H, d), 7.50 (1H, d), 7.81 (1H, d), 8.17 (1H, s), 10.91 (1H, s); *m/z* ES⁺ [M+H]⁺ = 851.6.

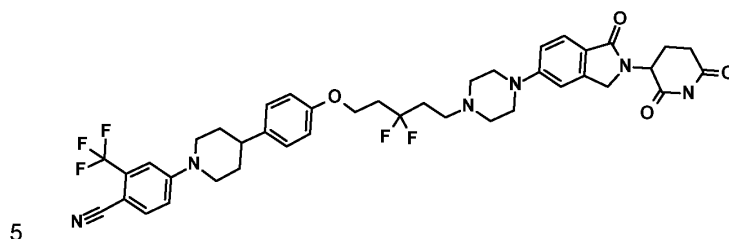
Intermediate 28a: 5-(4-(1-(4-Cyano-3-(trifluoromethyl)phenyl)piperidin-4-yl)phenoxy)-3,3-difluoropentyl 4-methylbenzenesulfonate



4-Methylbenzenesulfonyl chloride (131 mg, 0.69 mmol) was added in one portion to 4-(4-(4-(3,3-difluoro-5-hydroxypentyl)oxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (190 mg, 0.41 mmol) and Et₃N (113 μL, 0.81 mmol) in DCM (2 mL) at RT and the solution was stirred for 2h. The reaction was incomplete and further 4-methylbenzenesulfonyl chloride (131 mg, 0.69 mmol) and Et₃N (113 μL, 0.81 mmol) were added in one portion and the solution was stirred at RT for a further 18h. The reaction was incomplete and further 4-methylbenzenesulfonyl chloride (131 mg, 0.69 mmol) and Et₃N (113 μL, 0.81 mmol) were added in one portion and the solution was stirred at RT for a further 3h. The mixture was then diluted with DCM (25 mL), washed (sat. NH₄Cl (10 mL), sat. NaHCO₃ (10 mL), water (20 mL) then sat. brine (10 mL)), dried with a phase separating cartridge and concentrated. Purification by FSC (gradient: 0-60% EtOAc in heptane) gave the

title compound (0.147 g, 58%) as a yellow gum; m/z : ES^+ $[M+H]^+$ 623.3

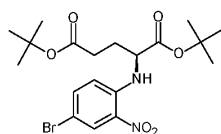
Example 28: 4-(4-{4-[(5-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl}-3,3-difluoropentyl)oxy]phenyl}piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



Intermediate 2c was reacted with Intermediate 28a using the general synthetic method illustrated by Example 12 to give the title compound after purification by HPLC (Column A, Eluent A). ^1H NMR: ($CDCl_3$) 1.69-1.83 (2H, m), 1.97 (2H, d), 2.15-2.52 (6H, m), 2.65-2.96 (9H, m), 3.05 (2H, td), 3.32-3.46 (4H, m), 4.02 (2H, d), 4.16 (2H, t), 4.26 (1H, d), 4.42 (1H, d), 5.19 (1H, dd), 6.83-6.91 (3H, m), 6.99 (2H, dd), 7.09-7.18 (3H, m), 7.61 (1H, d), 7.74 (1H, d), 7.90 (1H, s); m/z ES^+ $[M+H]^+$ = 779.4.

10

Intermediate 29a: di-*tert*-Butyl (4-bromo-2-nitrophenyl)-L-glutamate

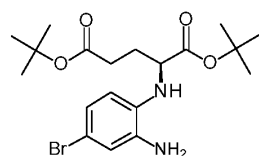


4-Bromo-1-fluoro-2-nitrobenzene (11.69 mL, 93.91 mmol) was added to a stirred milky suspension of di-*tert*-butyl *L*-glutamate hydrochloride salt (50.00 g, 169.03 mmol) and Et_3N (52.4 mL, 375.62 mmol) in THF (500 mL) at RT. The mixture was then stirred at 70°C for 72h. Water (500 mL) was then added and this mixture was extracted with EtOAc (2 × 500 mL). The combined organic solutions were then washed with brine (500 mL), passed through phase separating cartridge and concentrated. Purification by FSC (gradient: 0-20% EtOAc in heptane) gave the title compound (49.50 g, 115 %) as a yellow gum; ^1H NMR ($CDCl_3$) 1.44 (9H, s), 1.48 (9H, s), 2.16 (2H, q), 2.38 (2H, t), 4.22 (1H, q), 6.77 (1H, d), 7.50 (1H, dd), 8.34 (2H, d).

15

20

Intermediate 29b: di-*tert*-Butyl (2-amino-4-bromophenyl)-L-glutamate

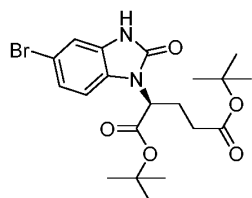


Iron powder (26.20 g, 469.15 mmol) was added in one portion to di-*tert*-butyl (4-bromo-2-nitrophenyl)-*L*-glutamate (43.10 g, 93.83 mmol) and NH_4Cl (25.09 g, 469.15 mmol) in IPA (400 mL) and water (80 mL) at RT. The resulting mixture was stirred at 80°C for 16h. After cooling the mixture was filtered through celite and washed through with EtOAc (500 mL). The dark red filtrate was washed with water (250 mL), sat. brine (250 mL), dried ($MgSO_4$) and concentrated. Purification by FSC (gradient 0-30% EtOAc in heptane) gave the title

25

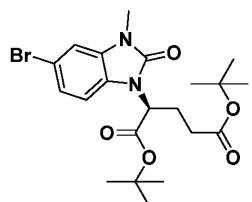
compound (36.1 g, 90 %) as an orange gum; ^1H NMR (CDCl_3) 1.44 (9H, s), 1.44 (9H, s), 1.89-2.17 (2H, m), 2.27-2.53 (2H, m), 3.53 (2H, s), 3.68-3.97 (2H, m), 6.48 (1H, d), 6.71-6.95 (2H, m); m/z : ES^+ $[\text{M}+\text{H}]^+$ 429.

Intermediate 29c: di-*tert*-Butyl (*S*)-2-(5-bromo-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)pentanedioate



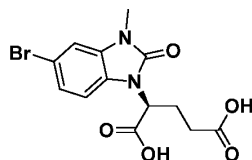
CDI (14.30 g, 88.19 mmol) was added in one portion to di-*tert*-butyl (2-amino-4-bromophenyl)-*L*-glutamate (36.1 g, 83.99 mmol) in THF (500 mL) at RT. The resulting dark red solution was stirred at 60°C for 2h. The mixture was cooled to RT and concentrated. The residue was dissolved in EtOAc (500 mL). This solution was washed with water (500 mL) and brine (200 mL), dried (MgSO_4) and concentrated to give the title compound (41.0 g, 107 %) as a beige solid; ^1H NMR (CDCl_3) 1.40 (18H, d), 2.13-2.43 (3H, m), 2.46-2.64 (1H, m), 5.07 (1H, dd), 6.86 (1H, d), 7.17 (1H, dd), 7.23 (1H, d), 9.98 (1H, s)

Intermediate 29d: Di-*tert*-butyl (*S*)-2-(5-bromo-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)pentanedioate



di-*tert*-Butyl (*S*)-2-(5-bromo-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)pentanedioate (38.0 g, 83.45 mmol) was dissolved in DMF.DMA (333 mL) and the solution was stirred at 100°C for 16h then concentrated. Purification by FSC (gradient: 0-25% EtOAc in heptane) gave the title compound (35.0 g, 89 %) as a pale yellow gum that solidified on standing; ^1H NMR (CDCl_3) 1.39 (9H, s), 1.40 (9H, s), 2.09-2.41 (3H, m), 2.43-2.63 (1H, m), 3.39 (3H, s), 5.06 (1H, dd), 6.85 (1H, d), 7.11 (1H, d), 7.17 (1H, dd).

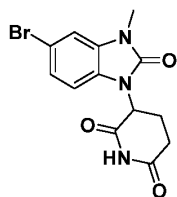
Intermediate 29e: (*S*)-2-(5-Bromo-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)pentanedioic acid



TFA (200 mL) was added to a stirred solution of di-*tert*-butyl (*S*)-2-(5-bromo-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)pentanedioate (35.0 g, 74.57 mmol) in DCM (200 mL) at 0°C. This mixture was stirred

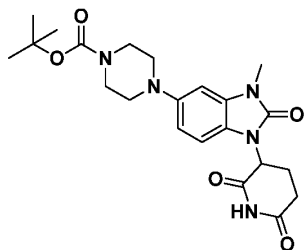
- for 15 mins then warmed to RT and stirred for a further 3h. The mixture was then concentrated and the residue was azeotroped twice with toluene to give a yellow solid. This was then triturated in 3:1 heptane:MTBE overnight. A solid was collected by filtration and dried to give the title compound (25.2 g, 95 %) as a pale yellow solid; ^1H NMR: 2-2.44 (4H, m), 3.33 (3H, s), 5.04 (1H, dd), 7.05 (1H, d), 7.21 (1H, dd), 7.44 (1H, d), 12.16 (1H, s), 13.07 (1H, s);

Intermediate 29f: 3-(5-Bromo-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione



- 10 (S)-2-(5-Bromo-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)pentanedioic acid (1.0 g, 2.48 mmol) was dissolved in DCM (30 mL). DIPEA (2.163 mL, 12.42 mmol) and 1-(bis(dimethylamino)methylene)-1H-[1,2,3]triazolo[4,5-b]pyridine-1-ium 3-oxide hexafluorophosphate(V) (1.889 g, 4.97 mmol) was then added and the mixture was stirred for 10 mins at RT. 2,2,2-Trifluoroacetamide (0.281 g, 2.48 mmol) was then added and the mixture stirred for 1h. The mixture was then poured into 5% AcOH in water (200 mL). This mixture
- 15 was extracted with DCM (2 × 150 mL) and the combined organic solutions were washed with sat. NaHCO_3 solution (200 mL) then passed through a phase separating cartridge and concentrated *in vacuo* to almost dryness (~75 mL). Purification by FSC (gradient: 0-80% EtOAc in heptane) gave crude product. The crude solid (0.8 g) was suspended in 1:1 MTBE:heptane (10 mL) and triturated overnight. The resulting solid was collected by filtration and dried to give the title compound (0.70 g, 83 %) as a white solid; ^1H NMR (CDCl_3)
- 20 2.11-2.33 (1H, m), 2.6-3.03 (3H, m), 3.42 (3H, s), 5.18 (1H, dd), 6.68 (1H, d), 7.1-7.24 (2H, m), 8.05 (1H, s); m/z: ES^+ $[\text{M}+\text{H}]^+$ 338. Material has racemized in this step.

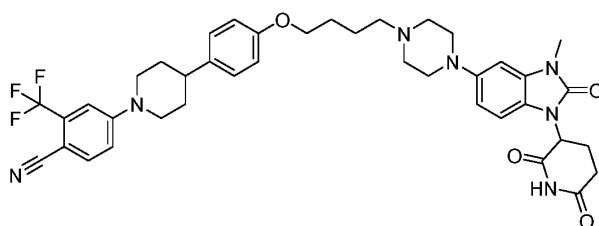
Intermediate 29g: tert-Butyl-4-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)piperazine-1-carboxylate



- 25 (DiMeIHept $^{\text{Cl}}$)Pd(cinnamyl)Cl (commercially available from Total Synthesis Ltd. Toronto, Canada, 0.031 g, 0.03 mmol) was added to 3-(5-bromo-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (0.100 g, 0.30 mmol), Cs_2CO_3 (0.289 g, 0.89 mmol) and *tert*-butyl piperazine-1-carboxylate (0.138 g, 0.74 mmol) in 1,4-dioxane (4.5 mL) at RT under N_2 . The resulting suspension was stirred at 100°C for 6h. The
- 30 mixture was then diluted with DCM (25 mL), washed (5% AcOH in water (20 mL), water (20 mL), sat.

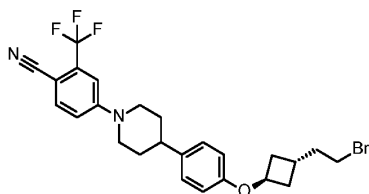
- NaHCO₃ solution (20 mL) then sat. brine (20 mL)), dried (MgSO₄) and concentrated. Trituration with EtOAc gave a solid which was collected by filtration, washed with Et₂O and dried under vacuum to give the title compound (0.107 g, 82 %) as a cream solid; ¹H NMR: 1.43 (9H, s), 1.91-1.99 (1H, m), 2.54-2.65 (2H, m), 2.74-2.88 (1H, m), 3-3.07 (4H, m), 3.31 (3H, s), 3.45-3.51 (4H, m), 5.11-5.26 (1H, m), 6.65 (1H, dd), 6.87 (1H, d), 6.92 (1H, d); *m/z*: ES⁺ [M+H]⁺ 444.2.

Example 29: 4-{4-[4-(4-{4-[1-(2,6-Dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl]piperazin-1-yl}butoxy)phenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile

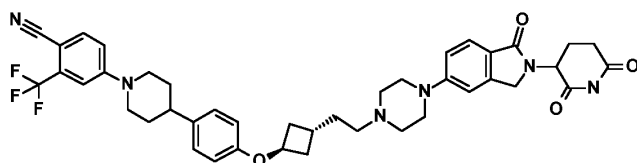


- 10 Intermediate 1h was reacted with Intermediate 29g using the general synthetic method illustrated by Example 1 to give the title compound (as a formate salt) after purification by HPLC (Column A, Eluent A); ¹H NMR: 1.56-1.68 (4H, m), 1.69-1.79 (2H, m), 1.85 (2H, d), 1.94-2.04 (1H, m), 2.39 (2H, t), 2.52-2.54 (4H, m), 2.58-2.65 (1H, m), 2.67-2.71 (1H, m), 2.72-2.82 (1H, m), 2.85-2.96 (1H, m), 3.00-3.12 (6H, m), 3.31 (5H, br), 3.97 (2H, t), 4.17 (2H, d), 5.29 (1H, dd), 6.62 (1H, dd), 6.81-6.91 (3H, m), 6.94 (1H, d), 7.16 (2H, d), 7.27 (1H, dd), 7.32 (1H, d), 7.81 (1H, d), 8.17 (1H, s), 11.04 (1H, s); *m/z* ES⁺ [M+H]⁺ = 743.9.

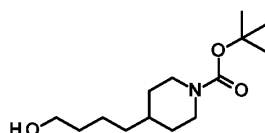
Intermediate 30a: *trans*-4-(4-(4-((1*r*,3*r*)-3-(2-Bromoethyl)cyclobutoxy)phenyl)piperidin-1-yl)-2-(trifluoro-methyl)benzonitrile



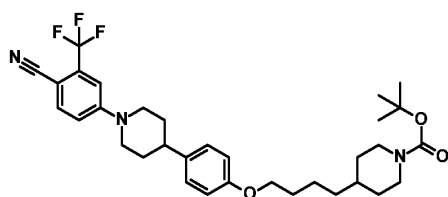
- 20 A solution of PPh₃ (63.7 mg, 0.24 mmol) in THF (1 mL) was added dropwise to a stirred mixture of *trans*-4-(4-(4-((1*s*,3*r*)-3-(2-hydroxyethyl)cyclobutoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (Intermediate 5c) (54.0 mg, 0.12 mmol) and CBr₄ (81.0 mg, 0.24 mmol) in THF (1.0 mL) at 0°C. The resulting mixture was stirred at RT for 1 week. The mixture was then filtered, washed through with EtOAc (20 mL) and the filtrate was concentrated. Purification by FSC (gradient: 0-30% EtOAc in heptane) gave the title compound (0.034 g, 55%) as a colourless oil; ¹H NMR (CDCl₃) 1.75 (2H, qd), 1.97 (2H, d), 2.07 (2H, q), 2.14-2.23 (2H, m), 2.36 (2H, dddd), 2.54 (1H, ddq), 2.72 (1H, tt), 3.05 (2H, td), 3.36 (2H, t), 4.02 (2H, d), 4.72 (1H, t), 6.62-6.8 (2H, m), 6.98 (1H, dd), 7.04-7.14 (2H, m), 7.15 (1H, d), 7.61 (1H, d); *m/z*: ES⁺ [M+H]⁺ = 507.2.
- 25
- 30 **Example 30: *trans*-4-[4-(4-{[(1*s*,3*r*)-3-(2-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isindol-**

5-yl]-piperazin-1-yl}ethyl)cyclobutyl]oxy}phenyl)piperidin-1-yl]-2-(trifluoromethyl)benzonitrile

- Intermediate 2c was reacted with Intermediate 30a using the general synthetic method illustrated by Example 5 to give the title compound (as a formate salt) after purification by HPLC (Column A, Eluent A). ¹H NMR: 1.56-1.69 (2H, m), 1.76 (2H, s), 1.85 (2H, d), 1.91-2.03 (1H, m), 2.16-2.20 (4H, m), 2.29 (1H, d), 2.36-2.44 (2H, m), 2.51-2.53 (4H, m), 2.60 (2H, d), 2.78 (1H, d), 2.86-2.96 (1H, m), 3.04 (2H, t), 4.20 (3H, dd), 4.34 (1H, d), 4.79 (1H, q), 5.05 (1H, dd), 6.75 (2H, d), 7.09 (2H, d), 7.15 (2H, d), 7.22-7.37 (2H, m), 7.54 (1H, d), 7.81 (1H, d), 10.92 (1H, s); 4H under solvent peak; *m/z* ES⁺ [M+H]⁺ = 755.4.

10 Intermediate 31a: *tert*-Butyl 4-(4-hydroxybutyl)piperidine-1-carboxylate

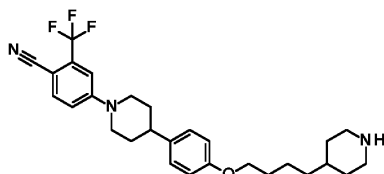
- Di-*tert*-butyl carbonate (8.86 mL, 38.15 mmol) was added to 4-(piperidin-4-yl)butan-1-ol (4.00 g, 25.44 mmol) in THF (50 mL) and sat. Na₂CO₃ solution (50 mL) at RT and the mixture was stirred for 16h. The mixture was then diluted with EtOAc (300 mL), washed with sat. brine (200 mL), dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-50% petroleum ether in EtOAc) gave the title compound (5.30 g, 81 %) as a white liquid; ¹H NMR: 0.86-1.00 (2H, m), 1.13-1.22 (2H, m), 1.25-1.33 (2H, m), 1.35-1.40 (12H, m), 1.57-1.65 (2H, m), 2.65 (2H, s), 3.34-3.42 (2H, m), 3.91 (2H, d), 4.31 (1H, t); *m/z*: ES⁺ [M-*t*Bu]⁺ = 202.

20 Intermediate 31b: *tert*-Butyl 4-(4-(4-(1-(4-cyano-3-(trifluoromethyl)phenyl)piperidin-4-yl)phenoxy)butyl)piperidine-1-carboxylate

- RockPhos Pd G3 (0.488 g, 0.58 mmol) was added to *tert*-butyl 4-(4-hydroxybutyl)piperidine-1-carboxylate (1.50 g, 5.83 mmol), 4-(4-(4-bromophenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (3.58 g, 8.74 mmol) and Cs₂CO₃ (5.70 g, 17.48 mmol) in 1,4-dioxane (30 mL) at RT over 10 mins under N₂. The resulting mixture was stirred at 100°C for 16h. The mixture was then diluted with EtOAc (200 mL), washed with sat. brine (100 mL), dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-15% EtOAc in petroleum ether) gave the title compound (1.50 g, 44 %) as a yellow liquid; ¹H NMR: 0.88-0.99 (2H, m), 1.22-1.28 (2H, m), 1.33-

1.45 (14H, m), 1.55-1.69 (6H, m), 1.79-1.88 (2H, m), 2.72-2.80 (1H, m), 2.98-3.08 (2H, m), 3.87-3.96 (4H, m), 4.16 (2H, d), 6.81-6.86 (2H, m), 7.11-7.17 (2H, m), 7.23-7.28 (1H, m), 7.32 (1H, d), 7.78-7.82 (1H, m); m/z : ES^+ $[M-tBu]^+ = 530$.

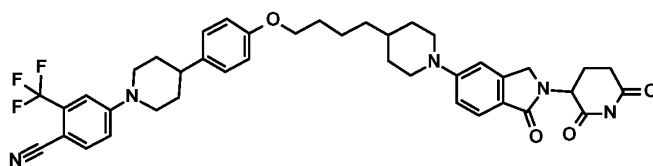
5 **Intermediate 31c: 4-(4-(4-(4-(Piperidin-4-yl)butoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile**



tert-Butyl 4-(4-(4-(1-(4-cyano-3-(trifluoromethyl)phenyl)piperidin-4-yl)phenoxy)butyl)piperidine-1-carboxylate (500 mg, 0.85 mmol) was added to DCM (2 mL) and HCl in dioxane (7 mL) at RT and the

- 10 mixture was stirred for 16h. Concentration under reduced pressure then gave the title compound which was used in the next step without further purification; ^1H NMR (300 MHz) 1.19-1.31 (4H, m), 1.32-1.54 (4H, m), 1.54-1.70 (3H, m), 1.73-1.84 (4H, m), 2.68-2.88 (3H, m), 3.02 (2H, t), 3.19 (2H, d), 3.90 (2H, t), 4.16 (2H, d), 6.82 (2H, d), 7.13 (2H, d), 7.21-7.29 (1H, m), 7.30 (1H, d), 7.79 (1H, d); m/z : ES^+ $[M+H]^+ = 486$.

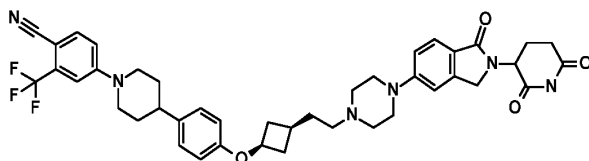
15 **Example 31: 4-(4-(4-(4-(1-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperidin-4-yl)butoxy)phenyl]piperidin-1-yl)-2-(trifluoromethyl)benzonitrile**



- Pd-PEPPSI-IPent (40.8 mg, 0.05 mmol) was added to 4-(4-(4-(4-(piperidin-4-yl)butoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (250 mg, 0.51 mmol), 3-(5-bromo-1-oxoisindolin-2-yl)piperidine-2,6-dione (166 mg, 0.51 mmol) and CS_2CO_3 (503 mg, 1.54 mmol) in 1,4-dioxane (5 mL) at RT under N_2 . The resulting mixture was stirred at 100°C for 16h. The mixture was then diluted with DCM, washed (5% AcOH (aq), water, then sat. brine), dried (Na_2SO_4) and concentrated. Purification by flash C18-flash chromatography (gradient: 5-85% MeCN in water (0.1% NH_4HCO_3)) gave material that was further purified by preparative SFC (Column: Viridis BEH 2-Ethylpyridine Prep OBD, 30*150mm, 5 μ m; Mobile Phase A: CO_2 , Mobile Phase B: MeOH (0.5% 2M NH_3 -MeOH)-HPLC; Flow rate:50 mL/min; Gradient:28% B; 254 nm; RT1:4.25; Injection Volumn:1 mL; Number Of Runs:5) to give the title compound (7 mg, 2 %) as a white solid; ^1H NMR: 1.13-1.33 (5H, m), 1.40-1.55 (3H, m), 1.55-1.77 (6H, m), 1.81-1.91 (2H, m), 1.92-2.04 (1H, m), 2.30-2.42 (1H, m), 2.55-2.64 (1H, m), 2.71-2.96 (4H, m), 2.99-3.10 (2H, m), 3.86 (2H, d), 3.93 (2H, t), 4.13-4.26 (3H, m), 4.31 (1H, d), 4.98-5.07 (1H, m), 6.82-6.88 (2H, m), 7.00-7.07 (2H, m), 7.13-7.18 (2H, m), 7.24-7.30 (1H, m), 7.32 (1H, d), 7.47-7.52 (1H, m), 7.81 (1H, d); m/z ES^+ $[M+H]^+ = 728.4$.

Example 32: 4-(4-(4-(4-(1-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]-

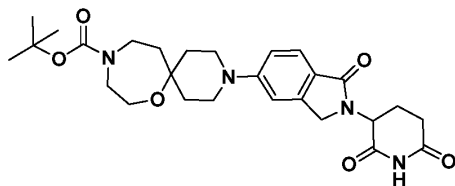
piperazin-1-yl}ethyl)cyclobutyl}oxyl}phenyl)piperidin-1-yl]-2-(trifluoromethyl)benzonitrile



Intermediate 2c was reacted with Intermediate 5d using the general synthetic method illustrated by Example 5 to give the title compound (as a formate salt) after purification by HPLC (Column A, Eluent A); ¹H NMR:

- 5 1.55-1.7 (6H, m), 1.85 (2H, d), 1.9-2.02 (2H, m), 2.25-2.31 (2H, m), 2.39 (2H, dd), 2.56-2.64 (3H, m), 2.75 (1H, d), 2.82-2.95 (1H, m), 3.04 (2H, t), 3.29 (8H, br), 4.11-4.27 (3H, m), 4.33 (1H, d), 4.51 (1H, p), 5.04 (1H, dd), 6.77 (2H, d), 7.06 (2H, d), 7.14 (2H, d), 7.27 (1H, dd), 7.32 (1H, d), 7.52 (1H, d), 7.81 (1H, d), 8.14 (1H, s), 10.92 (1H, s); *m/z* ES⁺ [M+H]⁺ = 755.7.

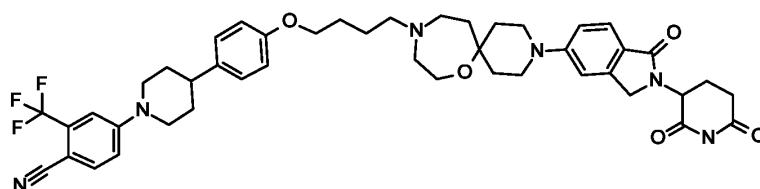
10 Intermediate 33a: *tert*-Butyl-3-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)-7-oxa-3,10-diazaspiro[5.6]dodecane-10-carboxylate



Pd-PEPPSI-IHept.Cl (0.083 g, 0.09 mmol) was added to *tert*-butyl 7-oxa-3,10-diazaspiro[5.6]dodecane-10-carboxylate (0.603 g, 2.23 mmol), Cs₂CO₃ (1.66 g, 5.11 mmol) and 3-(5-bromo-1-oxoisindolin-2-

- 15 yl)piperidine-2,6-dione (0.550 g, 1.70 mmol) in 1,4-dioxane (12 mL) at RT under N₂. The resulting suspension was stirred at 100°C for 20h. The mixture was then diluted with DCM (25 mL), washed (5% AcOH in water (10 mL), water (10 mL), and then sat. brine (10 mL)), dried (MgSO₄) and concentrated. Purification by FSC (gradient 0-5% MeOH in DCM) gave the title compound (0.490 g, 56 %) as a yellow solid. ¹H NMR: 1.41 (9H, s), 1.49-1.6 (2H, m), 1.7-1.85 (4H, m), 1.91-2.02 (1H, m), 2.33-2.44 (1H, m), 2.55-2.64 (1H, m), 2.84-2.96 (1H, m), 3.09-3.17 (2H, m), 3.38-3.47 (4H, m), 3.49-3.61 (2H, m), 3.62-3.69 (2H, m), 4.20 (1H, d), 4.32 (1H, d), 5.04 (1H, dd), 7-7.11 (2H, m), 7.50 (1H, d), 10.91 (1H, s); *m/z* ES⁺ [M+H]⁺ = 513.3.

Example 33: 4-{4-[4-(4-{3-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isindol-5-yl]-7-oxa-3,10-diazaspiro[5.6]dodecan-10-yl}butoxy)phenyl]piperidin-1-yl]-2-(trifluoromethyl)benzonitrile

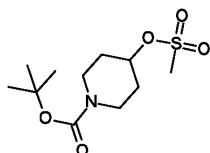


Intermediate 1h was reacted with Intermediate 33a using the general synthetic method illustrated by Example 1 to give the title compound (as a formate salt) after purification by HPLC (Column A, Eluent A). ¹H NMR:

1.43-1.53 (2H, m), 1.53-1.67 (4H, m), 1.67-1.81 (6H, m), 1.85 (2H, d), 1.91-2 (1H, m), 2.35-2.4 (1H, m), 2.41-2.47 (2H, m), 2.54-2.63 (4H, m), 2.77 (1H, t), 2.85-2.95 (1H, m), 3.05 (2H, t), 3.16 (2H, t), 3.30 (2H, s), 3.54 (2H, d), 3.62 (2H, d), 3.95 (2H, t), 4.18 (3H, dd), 4.32 (1H, d), 5.04 (1H, dd), 6.85 (2H, d), 7.04 (2H, d), 7.15 (2H, d), 7.27 (1H, dd), 7.33 (1H, d), 7.50 (1H, d), 7.81 (1H, d), 8.16 (1H, s), 10.91 (1H, s); m/z ES⁺

5 [M+H]⁺ = 813.4.

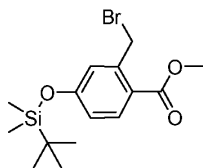
Intermediate 34a: *tert*-Butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate



10 Methanesulfonyl chloride (1.38 mL, 17.89 mmol) was added dropwise to a stirred solution of *tert*-butyl 4-hydroxypiperidine-1-carboxylate (3.00 g, 14.91 mmol) and DIPEA (3.89 mL, 22.36 mmol) in DCM (55 mL) at 0°C. The mixture was then stirred at RT for 2h before being diluted with DCM (125 mL). This solution was washed with water (75 mL), citric acid solution (50 mL), brine (50 mL), then dried (MgSO₄) and concentrated to give the title compound (4.69 g, 113 %) as a brown solid; ¹H NMR (CDCl₃) 1.46 (9H, s), 1.81 (2H, dtd), 1.96 (2H, dtd), 3.03 (3H, s), 3.30 (2H, ddd), 3.64-3.76 (2H, m), 4.88 (1H, tt).

15

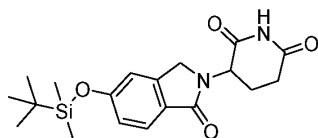
Intermediate 34b: Methyl 2-(bromomethyl)-4-((*tert*-butyldimethylsilyl)oxy)benzoate



20 AIBN (0.094 g, 0.57 mmol) was added to methyl 4-((*tert*-butyldimethylsilyl)oxy)-2-methylbenzoate (8 g, 28.53 mmol) and NBS (6.60 g, 37.08 mmol) in EtOAc (71 mL) at 80°C under N₂. The resulting mixture was stirred at 80°C for 3h. The mixture was then poured into water (100 mL). This mixture was then extracted with EtOAc (3 × 50 mL). The combined organic solutions were washed with brine (50 mL), dried (MgSO₄) and concentrated. Purification by FSC (gradient: 0-30% EtOAc in petroleum ether) gave the title compound (6.90 g, 67%) as a colourless liquid; ¹H NMR (CDCl₃) 0.22 (6H, s), 0.99 (9H, s), 2.15-2.24 (1H, m), 2.33 (1H, qd), 2.75-2.95 (2H, m), 4.22-4.46 (2H, m), 5.18 (1H, dd), 6.88 (1H, s), 6.89-6.96 (1H, m), 7.74 (1H, d), 8.02-8.19 (1H, m).

25

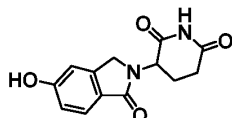
Intermediate 34c: 3-(5-((*tert*-Butyldimethylsilyl)oxy)-1-oxoisindolin-2-yl)piperidine-2,6-dione



30 DIPEA (9.89 mL, 56.77 mmol) was added to a stirred solution of methyl 2-(bromomethyl)-4-((*tert*-butyldimethylsilyl)oxy)benzoate (6.80 g, 18.92 mmol) and 3-aminopiperidine-2,6-dione hydrochloride salt (3.11 g,

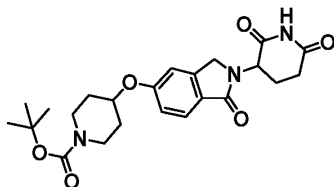
- 18.92 mmol) in MeCN (60 mL) at RT under N₂ and the mixture was stirred for 25h. The mixture was then diluted with water (50 mL). This mixture was then extracted with EtOAc (25 mL × 3) and the combined organic solutions were dried (MgSO₄) and concentrated to give the title compound (2.00 g, 28 %); ¹H NMR (CDCl₃) 0.22-0.25 (6H, m), 0.98-0.99 (9H, m), 3.87-3.92 (3H, m), 4.93 (2H, s), 6.76-6.82 (1H, m), 6.93 (1H, d), 7.91 (1H, d).

Intermediate 34d: 3-(5-Hydroxy-1-oxoisindolin-2-yl)piperidine-2,6-dione



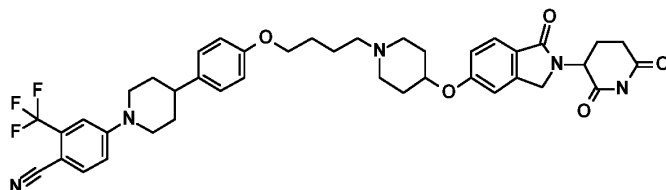
- A stirred solution of 3-((*tert*-butyldimethylsilyloxy)-1-oxoisindolin-2-yl)piperidine-2,6-dione (1.50 g, 4.01 mmol) in 1,4-dioxane (10 mL) was treated with 4M HCl (5.56 mL, 160.21 mmol) under N₂. The resulting slurry was stirred at RT for 18h. The mixture was then concentrated under reduced. The residue was then dissolved with hot MeCN before being allowed to cool to RT, then to 0°C. A solid was collected by filtration and washed with cold MeCN and dried in a vacuum desiccator for 18h to give the title compound (1.16 g, 111 %)

Intermediate 34e: *tert*-Butyl-4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)oxy)piperidine-1-carboxylate



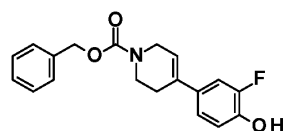
- K₂CO₃ (0.320 g, 2.31 mmol) was added in one portion to a stirred solution of *tert*-butyl 4-((methylsulfonyl)-oxy)piperidine-1-carboxylate (0.644 g, 2.31 mmol) and 3-(5-hydroxy-1-oxoisindolin-2-yl)piperidine-2,6-dione (0.500 g, 1.92 mmol) in DMF (10 mL) at RT under N₂. The resulting solution was stirred for 18h at 100°C. The mixture was then diluted with water (50 mL). This mixture was then extracted with EtOAc (3 × 30mL) and the combined organic solutions were washed with brine (75 mL), dried (MgSO₄) and concentrated. The residue (500mg) was dissolved into 4.5 mL 7:2 DMSO:MeOH (111 mg/mL), then purified by preparative HPLC (Column A, Eluent A) to give the title compound (0.461 g, 54%) as a white solid; ¹H NMR: 1.42 (9H, s), 1.56 (2H, d), 1.91-2.02 (3H, m), 2.40 (1H, td), 2.55-2.65 (1H, m), 2.8-2.98 (1H, m), 3.20 (2H, t), 3.68 (2H, dt), 4.27 (1H, d), 4.39 (1H, d), 4.70 (1H, dt), 5.07 (1H, dd), 7.09 (1H, dd), 7.22 (1H, d), 7.63 (1H, d), 10.94 (1H, s); *m/z* (ES-) [M-H]⁻ = 442.2.

- Example 34: 4-(4-{4-[4-{2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isindol-5-yl}oxy}piperidin-1-yl)butoxy}phenyl}piperidin-1-yl)-2-(trifluoromethyl)benzonitrile**



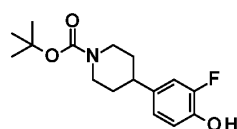
- Intermediate 1h was reacted with Intermediate 34e using the general synthetic method illustrated by Example 1 to give the title compound after purification by HPLC (Column A, Eluent A). ¹H NMR: 1.54-1.75 (8H, m), 1.85 (2H, d), 1.92-2.05 (3H, m), 2.21-2.32 (2H, m), 2.35-2.41 (3H, m), 2.56-2.65 (1H, m), 2.7-2.82 (3H, m), 2.84-2.95 (1H, m), 3.05 (3H, t), 3.96 (2H, t), 4.17 (2H, d), 4.26 (1H, d), 4.38 (1H, d), 4.51 (1H, dt), 5.07 (1H, dd), 6.81-6.91 (2H, m), 7.06 (1H, dd), 7.13-7.22 (3H, m), 7.27 (1H, dd), 7.32 (1H, d), 7.61 (1H, d), 7.81 (1H, d), 8.15 (1H, s), 10.94 (1H, s); *m/z* ES⁺ [M+H]⁺ = 744.4.

Intermediate 35a: Benzyl 4-(3-fluoro-4-hydroxyphenyl)-3,6-dihydropyridine-1(2H)-carboxylate



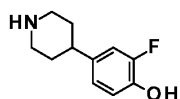
- 10 Pd(dppf)₂Cl₂-DCM (0.824 g, 1.01 mmol) was added to 2-fluoro-4-iodophenol (2.40 g, 10.08 mmol), benzyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (5.19 g, 15.13 mmol) and K₂CO₃ (4.18 g, 30.25 mmol) in 1,4-dioxane (1.6 mL) and water (0.4 mL) at RT under N₂. The resulting mixture was stirred at 80°C for 16h. The mixture was then diluted with EtOAc, washed with water then sat.
- 15 brine, dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-30% EtOAc in petroleum ether) gave the title compound (2.20 g, 67%) as a yellow solid; ¹H NMR (300 MHz) 2.45 (2H, s), 3.58 (2H, d), 4.05 (2H, d), 5.11 (2H, s), 6.06 (1H, s), 6.90 (1H, t), 7.07 (1H, dd), 7.21 (1H, dd), 7.29-7.42 (5H, m), 9.85 (1H, s); *m/z* ES⁺ [M+H]⁺ = 328.

20 **Intermediate 35b: *tert*-Butyl 4-(3-fluoro-4-hydroxyphenyl)piperidine-1-carboxylate**



- 10% Pd-on-C (1.365 g, 1.28 mmol) was added to di-*tert*-butyl carbonate (1.520 g, 7.06 mmol) and benzyl 4-(3-fluoro-4-hydroxyphenyl)-3,6-dihydropyridine-1(2H)-carboxylate (2.100 g, 6.42 mmol) in MeOH (10 mL) at RT under H₂. The resulting mixture was stirred at 80°C for 16h. The mixture was then filtered through celite and the filtrate was concentrated. Purification by FSC (gradient: 0-30% EtOAc in petroleum ether) gave the title compound (1.00 g, 53 %) as a white solid; ¹H NMR: 1.35-1.48 (11H, m), 1.70 (2H, d), 2.57 (1H, tt), 2.76 (2H, s), 3.99-4.10 (2H, m), 6.83-6.86 (2H, m), 6.97-7.02 (1H, m), 9.56 (1H, s); *m/z* ES⁺ [MH-tBu]⁺ = 240.1.

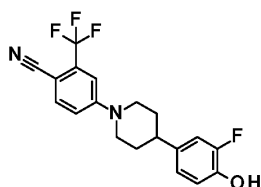
Intermediate 35c: 2-Fluoro-4-(piperidin-4-yl)phenol



- tert*-Butyl 4-(3-fluoro-4-hydroxyphenyl)piperidine-1-carboxylate (500 mg, 1.69 mmol) was added to 4M HCl in 1,4-dioxane (8 mL, 32.00 mmol) at RT and the mixture was stirred for 2h. Concentration under reduced pressure then gave the title compound as a hydrochloride salt (0.430 g, 130 %) as a white solid; ^1H NMR (300 MHz) 1.66-1.96 (4H, m), 2.72 (1H, tt), 2.91 (2H, q), 3.29 (2H, d), 6.82 (1H, dd), 6.89 (1H, d), 6.94 (1H, dd), 8.85 (OH, s), 9.72 (1H, s); m/z ES $^+$ [M+H] $^+$ = 196.0.

10

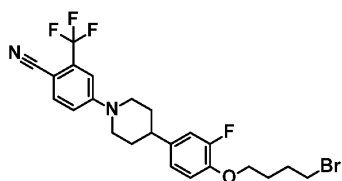
Intermediate 35d: 4-(4-(3-Fluoro-4-hydroxyphenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



- DIPEA (1.923 mL, 11.01 mmol) was added to 2-fluoro-4-(piperidin-4-yl)phenol (430 mg, 2.20 mmol) and 4-fluoro-2-(trifluoromethyl)benzonitrile (417 mg, 2.20 mmol) in DMSO (2 mL) at RT. The resulting solution was stirred at 60°C for 2h. The mixture was then poured into water (20 mL). This mixture was then extracted with EtOAc (3 × 250 mL) and the combined organic solutions were dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-30% EtOAc in petroleum ether) gave the title compound (0.507 g, 63%) as a white solid; ^1H NMR: 1.59 (2H, qd), 1.78-1.87 (2H, m), 2.73 (1H, tt), 3.02 (2H, td), 4.16 (2H, dt), 6.84-6.89 (2H, m), 7.02 (1H, dd), 7.26 (1H, dd), 7.31 (1H, d), 7.80 (1H, d), 9.58 (1H, s); m/z ES $^+$ [M+H] $^+$ = 365.

20

Intermediate 35e: 4-(4-(4-(4-Bromobutoxy)-3-fluorophenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



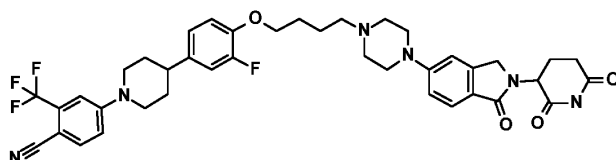
25

K₂CO₃ (228 mg, 1.65 mmol) was added to 4-(4-(3-fluoro-4-hydroxyphenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (200 mg, 0.55 mmol) and 1,4-dibromobutane (593 mg, 2.74 mmol) in DMF (2 mL) at RT under air and the mixture was stirred for 2h. The mixture was then poured into water (20 mL). This mixture was extracted with EtOAc (3 × 20 mL) and the combined organic solutions were dried (Na₂SO₄) and

concentrated. Purification by flash C18-flash chromatography (gradient: 0-100% MeCN in water) gave the title compound (0.210 g, 77 %) as a white solid; ¹H NMR (300 MHz) 1.62 (2H, qd), 1.78-1.92 (4H, m), 1.92-2.04 (2H, m), 2.79 (1H, t), 3.03 (2H, dd), 3.61 (2H, t), 4.05 (2H, t), 4.18 (2H, d), 7.01 (1H, dd), 7.07 (1H, d), 7.13 (1H, dd), 7.27 (1H, dd), 7.33 (1H, d), 7.82 (1H, d); *m/z* ES⁺ [M+H]⁺ = 499.

5

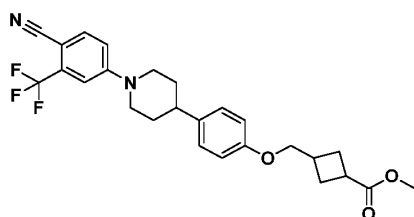
Example 35: 4-{4-[4-(4-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazin-1-yl]butoxy)-3-fluorophenyl]piperidin-1-yl]-2-(trifluoromethyl)benzonitrile



Intermediate 2c was reacted with Intermediate 35e using the general synthetic method illustrated by Example 5 to give the title compound after purification by preparative TLC (eluent: DCM:MeOH;10:1); ¹H NMR: (300 MHz) 1.23-1.28 (2H, m), 1.54-1.89 (8H, m), 1.89-2.02 (1H, m), 2.30-2.48 (4H, m), 2.53-2.65 (2H, m), 2.70-2.83 (1H, m), 2.81-2.97 (1H, m), 3.03 (2H, t), 3.10-3.29 (4H, m), 4.06 (2H, t), 4.13-4.27 (3H, m), 4.34 (1H, d), 5.06 (1H, dd), 6.97-7.18 (5H, m), 7.23-7.35 (2H, m), 7.54 (1H, d), 7.82 (1H, d), 10.95 (1H, s); *m/z* ES⁺ [M+H]⁺ = 747.4.

15

Intermediates 36a: Methyl 3-((4-(1-(4-cyano-3-(trifluoromethyl)phenyl)piperidin-4-yl)phenoxy)methyl)-cyclobutane-1-carboxylate

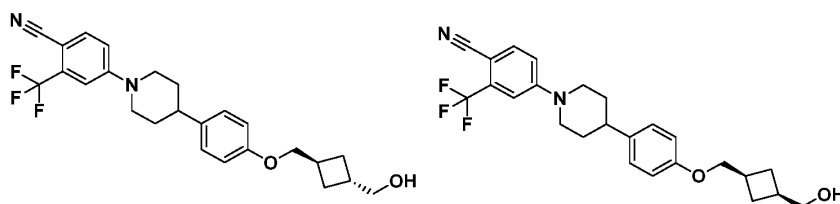


RockPhos Pd G3 (291 mg, 0.35 mmol) was added to methyl 3-(hydroxymethyl)cyclobutane-1-carboxylate (500 mg, 3.47 mmol), Cs₂CO₃ (3.39 g, 10.40 mmol) and 4-(4-(4-bromophenyl)piperidin-1-yl)-2-(trifluoromethyl)-benzonitrile (1.42 g, 3.47 mmol) in 1,4-dioxane (5 mL) at RT under N₂. The resulting mixture was stirred at 100°C for 16h then concentrated. Purification by FSC (gradient: 0-20% EtOAc in petroleum ether) gave the title compound (1.20 g, 73%) as a pale yellow solid; ¹H NMR (300 MHz) 1.51-1.68 (2H, m), 1.82 (2H, d), 1.95-2.10 (2H, m), 2.20-2.37 (2H, m), 2.56-2.82 (2H, m), 2.94-3.10 (2H, m), 3.37-3.52 (1H, m), 3.59 (3H, d), 3.85 (1H, d), 3.96 (1H, d), 4.15 (2H, d), 6.83 (2H, t), 7.13 (2H, dd), 7.25 (1H, dd), 7.30 (1H, d), 7.79 (1H, d); *m/z* ES⁺, [M+H]⁺ = 473.4.

25

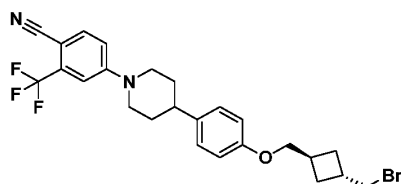
Intermediates 36b and 36c: 4-(4-(4-(((1*r*,3*r*)-3-(Hydroxymethyl)cyclobutyl)methoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile and 4-(4-(4-(((1*s*,3*s*)-3-(Hydroxymethyl)cyclobutyl)methoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile

30



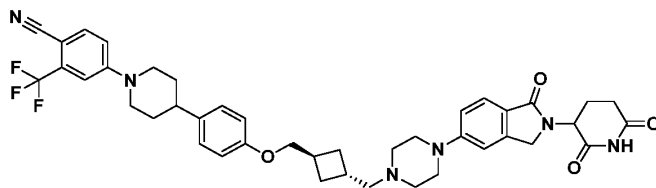
- Methyl 3-((4-(1-(4-cyano-3-(trifluoromethyl)phenyl)piperidin-4-yl)phenoxy)methyl)cyclobutane-1-carboxylate (1.10 g, 2.33 mmol) was added to NaBH₄ (0.264 g, 6.98 mmol) in MeOH (10 mL) at RT and the mixture was stirred for 16h. After concentration under reduced pressure the mixture was poured into water (100 mL). This mixture was extracted with EtOAc (250 mL × 3), dried (Na₂SO₄) and concentrated.
- Purification by FSC (gradient: 0-10% EtOAc in petroleum ether) gave the title compounds (700 mg) as a mixture of *cis/trans* isomers. Further purification by preparative Prep-SFC (Column: CHIRAL ART Amylose-SA S, 3*25cm, 5μm; Mobile Phase A:CO₂, Mobile Phase B:MeOH (0.5% 2M NH₃-MeOH)--HPLC; Flow rate:6.1 mL/min; Gradient:40% B; 220 nm; **36b** RT1:9.47; **36c** RT2:10.97; Injection Volumn:1.5 mL; Number Of Runs:33) gave **36b** (0.123 g, 12 %) and **36c** (0.154 g, 15 %) as pale yellow solids.
- Intermediate 36b:** ¹H NMR (CDCl₃, 300 MHz) 1.76 (2H, qd), 1.90-2.06 (6H, m), 2.54 (1H, dt), 2.67-2.81 (2H, m), 3.06 (2H, td), 3.69 (2H, d), 3.97 (2H, d), 4.03 (2H, d), 6.84-6.92 (2H, m), 6.99 (1H, dd), 7.08-7.20 (3H, m), 7.62 (1H, d); *m/z* ES⁺, [M+H]⁺ = 445.2.
- Intermediate 36c:** ¹H NMR (CDCl₃, 300 MHz) 1.59-1.86 (4H, m), 1.93-2.08 (2H, m), 2.14-2.29 (2H, m), 2.37-2.56 (1H, m), 2.60-2.80 (2H, m), 2.98-3.13 (2H, m), 3.60 (2H, d), 3.87 (2H, d), 4.02 (2H, d), 6.80-6.91 (2H, m), 6.94-7.04 (1H, m), 7.07-7.21 (3H, m), 7.61 (1H, d); *m/z* ES⁺, [M+H]⁺ = 445.2

Intermediate 36d: 4-(4-(4-(((1*r*,3*r*)-3-(Bromomethyl)cyclobutyl)methoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



- CBr₄ (74.6 mg, 0.22 mmol) was added to PPh₃ (59.0 mg, 0.22 mmol) and 4-(4-(4-(((1*r*,3*r*)-3-(hydroxymethyl)cyclobutyl)methoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (50 mg, 0.11 mmol) in DCM (1 mL) at RT and the mixture was stirred for 2h. After concentration under reduced pressure, purification by preparative TLC (eluent: petroleum ether: EtOAc = 5:1) gave the title compound (0.050 g, 88 %) as a colourless gum; ¹H NMR (300 MHz) 1.60 (2H, qd), 1.77-2.01 (6H, m), 2.56-2.80 (3H, m), 2.98-3.13 (2H, m), 3.63 (2H, d), 3.95 (2H, d), 4.16 (2H, d), 6.81-6.89 (2H, m), 7.09-7.18 (2H, m), 7.25 (1H, dd), 7.31 (1H, d), 7.80 (1H, d); *m/z* ES⁺, [M+H]⁺ = 507.

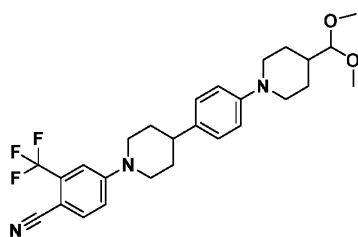
- Example 36: 4-[4-(4-(((1*r*,3*r*)-3-({4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]-piperazin-1-yl)methyl)cyclobutyl)methoxy}phenyl)piperidin-1-yl]-2-(trifluoromethyl)benzonitrile**



Intermediate 2c was reacted with Intermediate 36d using the general synthetic method illustrated by Example 5 to give the title compound after purification by preparative TLC (eluent: DCM:MeOH, 20:1); ¹H NMR: (300 MHz) 1.53-1.71 (2H, m), 1.79-2.09 (7H, m), 2.24-2.48 (5H, m), 2.53-2.98 (5H, m), 3.05 (2H, t), 3.29 (6H, d), 3.51 (1H, s), 3.99 (2H, d), 4.12-4.24 (2H, m), 4.27-4.38 (1H, m), 5.05 (1H, dd), 6.87 (2H, d), 7.05 (2H, d), 7.16 (2H, d), 7.27 (1H, dd), 7.33 (1H, d), 7.50 (1H, t), 7.82 (1H, d), 10.94 (1H, s); *m/z* ES⁺ [M+H]⁺ = 755.4.

10

Intermediate 37a: 4-(4-(4-(4-(Dimethoxymethyl)piperidin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile

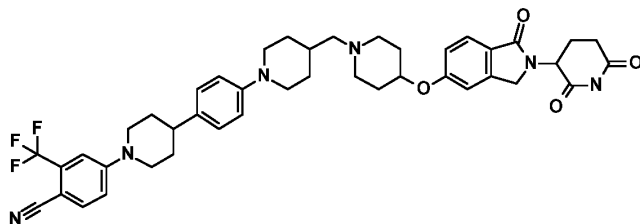


15

4-(4-(4-Bromophenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (1.00 g, 2.44 mmol), 4-(dimethoxymethyl)piperidine (0.467 g, 2.93 mmol), RuPhos G3 (0.153 g, 0.18 mmol), RuPhos (0.086 g, 0.18 mmol) sodium *tert*-butoxide (0.704 g, 7.33 mmol) and anhydrous 1,4-dioxane (24.4 mL) were added to a flask. The mixture was degassed, the flask filled with N₂. The mixture was then stirred at 100°C overnight, then concentrated after cooling to RT. Water (10 mL) was added and the resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic solutions were dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-100% EtOAc in heptane) gave the title compound (0.393 g, 33%) as a pale yellow solid; ¹H NMR (CDCl₃) 1.45 (2H, qd), 1.67-1.8 (3H, m), 1.8-1.89 (2H, m), 1.97 (2H, d), 2.55-2.77 (3H, m), 3.05 (2H, td), 3.37 (6H, s), 3.67 (2H, d), 4.01 (2H, d), 4.08 (1H, d), 6.88-6.92 (2H, m), 6.98 (1H, dd), 7.06-7.12 (2H, m), 7.15 (1H, d), 7.61 (1H, d); *m/z*: ES⁺ [M+H]⁺ 488.8.

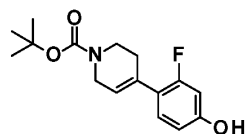
25

Example 37: 4-[4-(4-{4-[(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-indol-5-yl]oxy}-piperidin-1-yl)methyl]piperidin-1-yl]phenyl]piperidin-1-yl]-2-(trifluoromethyl)benzonitrile



- Intermediate 34e was reacted with Intermediate 37a using the general synthetic method illustrated by Example 1 to give the title compound after purification by HPLC (Column A, Eluent A); ^1H NMR: (CDCl_3) 1.42-1.59 (2H, m), 1.75 (2H, qd), 1.97 (5H, dd), 2.09-2.19 (2H, m), 2.22 (1H, ddq), 2.28-2.4 (1H, m), 2.4-2.5 (2H, m), 2.71 (3H, td), 2.77-2.86 (1H, m), 2.92 (3H, dd), 2.99-3.16 (4H, m), 3.41 (2H, d), 3.65 (2H, d), 4.01 (2H, d), 4.30 (1H, d), 4.45 (1H, d), 4.72 (1H, s), 5.20 (1H, dd), 6.89 (2H, dd), 6.96 (2H, dd), 6.98-7.04 (2H, m), 7.10 (2H, d), 7.15 (1H, d), 7.57-7.63 (1H, m), 7.82 (1H, d), 8.30 (2H, s); m/z ES^+ $[\text{M}+\text{H}]^+ = 769.0$.

Intermediate 38a: *tert*-Butyl 4-(2-fluoro-4-hydroxyphenyl)-3,6-dihydropyridine-1(2H)-carboxylate

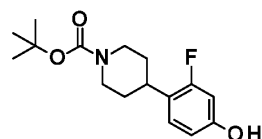


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$\text{PdCl}_2(\text{dppf})$ (118 mg, 0.16 mmol) was added to *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (500 mg, 1.62 mmol), 4-bromo-2-fluorophenol (340 mg, 1.78 mmol) and K_2CO_3 (670 mg, 4.85 mmol) in 1,4-dioxane (8 mL) and water (2 mL) at RT under N_2 . The resulting solution was stirred at 80°C for 4h. The mixture was then filtered through celite and the filtrate was concentrated.

- 15 Purification by FCC (gradient: 0-10% EtOAc in petroleum ether) gave the title compound (0.40 g, 84 %) as a colourless oil; ^1H NMR (300 MHz) 1.40 (9H, s), 2.35 (2H, s), 3.43-3.52 (2H, m), 3.93 (2H, d), 5.83 (1H, s), 6.46-6.61 (2H, m), 7.06-7.18 (1H, m), 9.86 (1H, s); m/z : ES^+ $[\text{M}-\text{tBu}]^+ 238$.

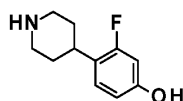
Intermediate 38b: *tert*-Butyl 4-(2-fluoro-4-hydroxyphenyl)piperidine-1-carboxylate



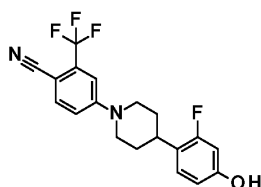
20

- 10% Pd-on-C (1.451 g, 1.36 mmol) was added to *tert*-butyl 4-(2-fluoro-4-hydroxyphenyl)-3,6-dihydropyridine-1(2H)-carboxylate (2.00 g, 6.82 mmol) in MeOH (10 mL) at RT under H_2 . The resulting mixture was stirred at 80°C for 16h. The mixture was then filtered through celite and the filtrate was concentrated. Purification by flash C18-flash chromatography (gradient: 0-70% MeCN in water(0.1% formic acid)) gave the title compound (1.20 g, 60 %) as a white solid; ^1H NMR: 1.42 (9H, s), 1.40-1.55 (2H, m), 1.63-1.72 (2H, m), 2.71-2.92 (3H, m), 3.99-4.13 (2H, m), 6.51 (1H, dd), 6.56 (1H, dd), 7.08 (1H, t), 9.65 (1H, s); m/z : ES^+ $[\text{M}-\text{tBu}]^+ 240$.

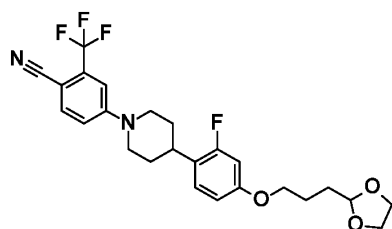
25

Intermediate 38c: 3-Fluoro-4-(piperidin-4-yl)phenol

- 5 A mixture of HCl in 1,4-dioxane (18.8 mL, 8.00 mmol) and *tert*-butyl 4-(2-fluoro-4-hydroxyphenyl)-piperidine-1-carboxylate (600 mg, 2.05 mmol) was stirred at RT for 2h. Concentration under reduced pressure then gave the title compound as a hydrochloride salt (0.580 g, 145 %) as a white solid; ¹H NMR (300 MHz) 1.72-1.97 (4H, m), 2.97 (3H, dq), 3.29 (2H, d), 6.49-6.62 (2H, m), 7.02 (1H, t), 8.92 (1H, br), 9.83 (1H, s); *m/z*: ES⁺ [M+H]⁺ 196.

Intermediate 38d: 4-[4-(2-fluoro-4-hydroxyphenyl)piperidin-1-yl]-2-(trifluoromethyl)benzonitrile

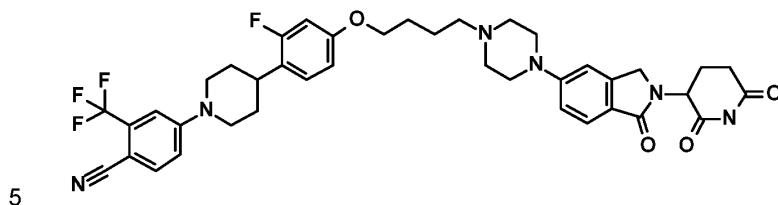
- 10 DIPEA (3.81 mL, 21.80 mmol) was added to 3-fluoro-4-(piperidin-4-yl)phenol hydrochloride salt (1.01 g, 4.36 mmol) and 4-fluoro-2-(trifluoromethyl)benzonitrile (0.989 g, 5.23 mmol) in DMSO (10 mL) at RT under air and the mixture was stirred for 18h then poured into water (20 mL). This mixture was stirred at RT for 0.5h and then filtered. The collected solid was washed with water (20 mL) and 5% AcOH/water (20 mL) and dried
- 15 under vacuum to give the title compound (1.51 g, 95 %) as a yellow solid; ¹H NMR: 1.67 (2H, qd), 1.80 (2H, d), 2.94-3.01 (1H, m), 3.03-3.18 (2H, m), 4.17 (2H, d), 6.45-6.63 (2H, m), 7.08 (1H, t), 7.19-7.38 (2H, m), 7.81 (1H, d), 9.65 (1H, s); *m/z*: ES⁺ [M+H]⁺ 365.2.

Intermediate 38e: 4-(4-(4-(3-(1,3-Dioxolan-2-yl)propoxy)-2-fluorophenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile

- 20 2-(3-Bromopropyl)-1,3-dioxolane (0.613 mL, 4.53 mmol) was added in one portion to 4-(4-(2-fluoro-4-hydroxyphenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (1.50 g, 4.12 mmol) and K₂CO₃ (1.707 g, 12.35 mmol) in MeCN (10 mL) at RT under N₂. The resulting suspension was stirred at 80°C for 5h. After cooling
- 25 the mixture was filtered and water (150 mL) was added to the filtrate. A white precipitate was then collected by filtration to give the title compound (1.85 g, 94 %) as a yellow solid; ¹H NMR: 1.62-1.84 (8H, m), 3.03-3.12 (3H, m), 3.75-3.8 (2H, m), 3.86-3.9 (2H, m), 3.98 (2H, t), 4.18 (2H, d), 4.85 (1H, t), 6.7-6.8 (2H, m), 7.20

(1H, t), 7.27 (1H, dd), 7.32 (1H, s), 7.81 (1H, d); m/z : ES^+ $[M+H]^+$ 479.4.

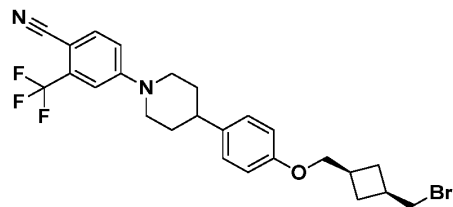
Example 38: 4-{4-[4-(4-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl}butoxy)-2-fluorophenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile



Intermediate 2b was reacted with Intermediate 38e using the general synthetic method illustrated by Example 1 to give the title compound after purification by HPLC (Column A, Eluent A, Basic Work-Up A); ^1H NMR: (300 MHz) 1.21-1.32 (1H, m), 1.56-1.86 (8H, m), 1.91-2.03 (1H, m), 2.26-2.49 (4H, m), 2.52-2.65 (3H, m), 2.84-2.98 (1H, m), 3.07 (3H, t), 3.20-3.33 (4H, m), 4.00 (2H, t), 4.12-4.28 (3H, m), 4.34 (1H, d), 5.05 (1H, dd), 6.70-6.84 (2H, m), 7.07 (2H, d), 7.20 (1H, t), 7.27 (1H, d), 7.33 (1H, d), 7.53 (1H, d), 7.82 (1H, d), 10.95 (1H, s); m/z ES^+ $[M+H]^+$ = 747.5.

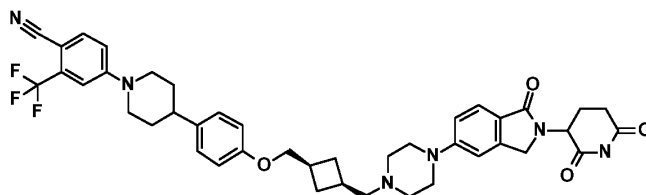
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Intermediate 39a: 4-(4-(4-(((1*r*,3*r*)-3-(Bromomethyl)cyclobutyl)methoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



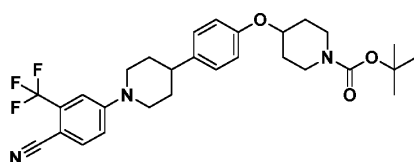
20 CBr₄ (74.6 mg, 0.22 mmol) was added to PPh₃ (59.0 mg, 0.22 mmol) and 4-(4-(4-(((1*s*,3*s*)-3-(hydroxymethyl)cyclobutyl)methoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (50 mg, 0.11 mmol) in DCM (1 mL) at RT and the mixture was stirred for 2h then concentrated. Purification by preparative TLC (eluent EtOAc: petroleum ether = 1:5) gave the title (0.050 g, 88 %) as a colourless gum; ^1H NMR: 1.51-1.70 (4H, m), 1.85 (2H, d), 2.13-2.24 (2H, m), 2.53-2.64 (2H, m), 2.71-2.83 (1H, m), 3.05 (2H, dd), 3.56 (2H, d), 3.88 (2H, d), 4.18 (2H, d), 6.85 (2H, d), 7.15 (2H, d), 7.27 (1H, dd), 7.33 (1H, d), 7.82 (1H, d); m/z ES^+ , [M+H]⁺ = 507.

Example 39: 4-[4-(4-{[(1*s*,3*s*)-3-({4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]-piperazin-1-yl}methyl)cyclobutyl]methoxy}phenyl)piperidin-1-yl]-2-(trifluoromethyl)benzonitrile



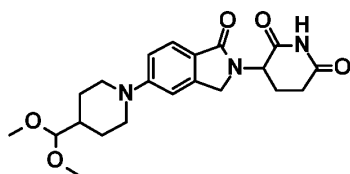
- Intermediate 2c was reacted with Intermediate 39a using the general synthetic method illustrated by Example 5 to give the title compound after purification by preparative TLC (eluent: DCM:MeOH, 20:1); ¹H NMR: (300 MHz) 1.43-1.75 (4H, m), 1.85 (2H, d), 1.91-2.10 (1H, m), 2.12-2.27 (2H, m), 2.31-2.44 (3H, m), 2.50 (4H, q), 2.52-2.67 (3H, m), 2.77-2.98 (2H, m), 2.99-3.11 (2H, m), 3.22-3.31 (4H, m), 3.86 (2H, d), 4.12-4.25 (3H, m), 4.33 (1H, d), 5.05 (1H, dd), 6.84 (2H, d), 7.05 (2H, d), 7.15 (2H, d), 7.27 (1H, dd), 7.33 (1H, d), 7.52 (1H, d), 7.82 (1H, d), 10.94 (1H, s); *m/z* ES⁺ [M+H]⁺ = 755.4.

10 Intermediate 40a: *tert*-Butyl 4-(4-(1-(4-cyano-3-(trifluoromethyl)phenyl)piperidin-4-yl)phenoxy)-piperidine-1-carboxylate



- DIAD (337 μ L, 1.73 mmol) was added to 4-(4-(4-hydroxyphenyl)piperidin-1-yl)-2-(trifluoromethyl)-benzonitrile (Example 1g) (300 mg, 0.87 mmol), *tert*-butyl 4-hydroxypiperidine-1-carboxylate (209 mg, 1.04 mmol) and PPh₃ (454 mg, 1.73 mmol) in DCM (1 mL) at 0°C. The resulting mixture was stirred at RT for 16h then concentrated. Purification by flash C18-flash chromatography (gradient: 0-100% MeCN in water (0.1% formic acid)) gave the title compound (0.100 g 22%) as a white solid; ¹H NMR: 1.40 (9H, s), 1.50 (2H, ddt), 1.62 (2H, qd), 1.78-1.93 (4H, m), 2.76 (1H, tt), 3.04 (2H, td), 3.13-3.21 (2H, m), 3.57-3.71 (2H, m), 4.17 (2H, d), 4.49 (1H, tt), 6.89 (2H, d), 7.15 (2H, d), 7.26 (1H, dd), 7.32 (1H, d), 7.81 (1H, d).

20 Intermediate 40b: 3-(5-(4-(Dimethoxymethyl)piperidin-1-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione

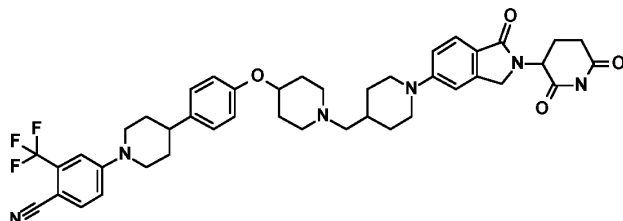


- Pd-PEPPSI-IPent (0.355 g, 0.45 mmol) was added to 3-(5-bromo-1-oxoisindolin-2-yl)piperidine-2,6-dione (1.45 g, 4.49 mmol), 4-(dimethoxymethyl)piperidine (1.00 g, 6.28 mmol) and Cs₂CO₃ (4.38 g, 13.46 mmol) in 1,4-dioxane (45 mL) at RT under N₂. The resulting suspension was vacuum degassed, backfilling with N₂ and stirred at 90°C for 4.5h. The mixture was then allowed to stand at RT for 16h. The mixture was then diluted with DCM (75 mL) and 10% aq. AcOH (150 mL) and the layers were separated. The aqueous layer was extracted with DCM (75 mL $\times$ 2). The combined organic solutions were washed with sat. brine (60 mL), dried

(MgSO₄) and concentrated. Purification by FSC (gradient: 0-8% EtOH in EtOAc) gave the title compound (0.800 g, 44 %) as an off-white solid; ¹H NMR: 1.24-1.39 (2H, m), 1.71 (2H, d), 1.76-1.9 (1H, m), 1.9-2.04 (1H, m), 2.26-2.43 (1H, m), 2.58 (1H, td), 2.73-3.02 (3H, m), 3.27 (1H, s), 3.28 (6H, s), 3.89 (2H, d), 4.20 (1H, d), 4.32 (1H, d), 5.04 (1H, dd), 7.04 (2H, d), 7.50 (1H, d), 10.92 (1H, s); *m/z* ES⁺, [M+H]⁺ = 402.

5

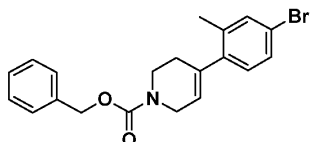
Example 40: 4-[4-(4-{[1-(1-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperidin-4-yl)methyl]piperidin-4-yl}oxy)phenyl]piperidin-1-yl]-2-(trifluoromethyl)benzonitrile



Intermediate 40a was reacted with Intermediate 40b using the general synthetic method illustrated by Example 1 to give the title compound after purification by preparative SFC (Column: DAICEL DCpak P4VP, 20mm*250mm, 5μm; Mobile Phase A:CO₂, Mobile Phase B:MeOH--HPLC; Flow rate:50 mL/min; Gradient:45% B; 254 nm; RT1:5.67; Injection Volume:1 mL; Number Of Runs:5); ¹H NMR: (300 MHz) 1.09-1.21 (2H, m), 1.52-1.68 (4H, m), 1.70-2.02 (8H, m), 2.10-2.44 (5H, m), 2.54-3.14 (9H, m), 3.87 (2H, d), 4.12-4.25 (3H, m), 4.26-4.39 (2H, m), 5.05 (1H, dd), 6.82-6.93 (2H, m), 7.04 (2H, d), 7.12-7.18 (2H, m), 7.25-7.35 (2H, m), 7.50 (1H, d), 7.82 (1H, d), 10.94 (1H, s); *m/z* ES⁺ [M+H]⁺ = 769.4.

15

Intermediate 41a: Benzyl 4-(4-bromo-2-methylphenyl)-3,6-dihydropyridine-1(2H)-carboxylate

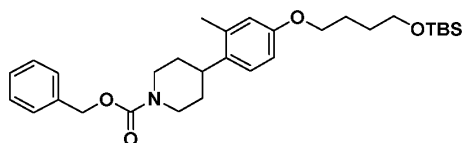


PdCl₂(dppf) (7.39 g, 10.10 mmol) was added to 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid benzyl ester (3.47 g, 10.10 mmol), 4-bromo-1-iodo-2-methylbenzene (3.00 g, 10.10 mmol) and K₂CO₃ (4.19 g, 30.31 mmol) in 1,4-dioxane (20 mL) and water (5 mL) at RT under N₂. The resulting solution was stirred at 80°C for 4h. The mixture was then diluted with EtOAc (50 mL). This solution was washed with water (20 mL × 3) then sat. brine (20 mL × 2), dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-30% EtOAc in petroleum ether) gave the title compound (2.00 g, 51%) as a pale yellow solid; ¹H NMR (300 MHz) 2.21 (3H, s), 2.21-2.33 (2H, m), 3.59 (2H, d), 4.01 (2H, d), 5.11 (2H, s), 5.58 (1H, s), 7.02 (1H, d), 7.25-7.36 (2H, m), 7.33-7.43 (5H, m); *m/z* ES⁺ [M+H]⁺ = 388.

25

Intermediate 41b: Benzyl 4-(4-(4-((tert-Butyldimethylsilyl)oxy)butoxy)-2-methylphenyl)-3,6-dihydropyridine-1(2H)-carboxylate

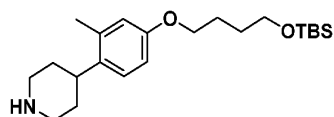
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Rockphos Pd G3 (0.217 g, 0.26 mmol) was added to benzyl 4-(4-bromo-2-methylphenyl)-3,6-dihydro-pyridine-1(2H)-carboxylate (1.00 g, 2.59 mmol), 4-((*tert*-butyldimethylsilyl)oxy)butan-1-ol (0.794 g, 3.88 mmol) and Cs₂CO₃ (2.53 g, 7.77 mmol) in 1,4-dioxane (1 mL) at RT under N₂. The resulting solution was stirred at 100°C for 12h and then concentrated. Purification by flash C18-flash chromatography (gradient: 0-100% MeCN in water) gave the title compound (0.700 g, 53 %) as a yellow solid; ¹H NMR (300 MHz) 0.02 (6H, s), 0.84 (9H, d), 1.49-1.64 (2H, m), 1.66-1.78 (2H, m), 2.17 (3H, s), 2.22-2.36 (2H, m), 3.31 (2H, s), 3.62 (2H, t), 3.92 (2H, t), 4.01 (2H, q), 5.11 (2H, s), 5.50 (1H, s), 6.67 (1H, dd), 6.72 (1H, d), 6.95 (1H, d), 7.35-7.39 (5H, m); *m/z* ES⁺ [M+H]⁺ = 510.

10

Intermediate 41c: 4-(4-(4-((*tert*-Butyldimethylsilyl)oxy)butoxy)-2-methylphenyl)piperidine

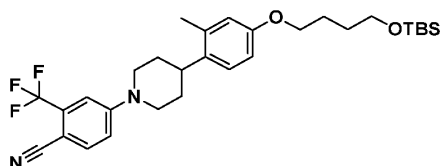


A mixture of benzyl 4-(4-(4-((*tert*-butyldimethylsilyl)oxy)butoxy)-2-methylphenyl)-3,6-dihydropyridine-1(2H)-carboxylate (600 mg, 1.18 mmol) and platinum (IV) oxide hydrate (60 mg, 0.24 mmol) in EtOAc (10 mL) was stirred under H₂ (20 atm) at 80°C for 10h. The mixture was then filtered through celite pad and the filtrate was concentrated to give the title compound (460 mg, 103%); *m/z* ES⁺ [M+H]⁺ = 378.

15

Intermediate 41d: 4-(4-(4-(4-((*tert*-butyldimethylsilyl)oxy)butoxy)-2-methylphenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile

20

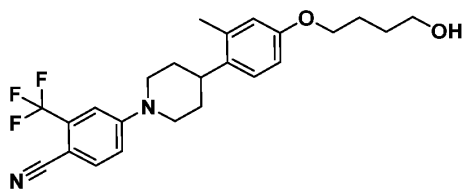


Cs₂CO₃ (518 mg, 1.59 mmol) was added to 4-(4-(4-((*tert*-butyldimethylsilyl)oxy)butoxy)-2-methylphenyl)-piperidine (200 mg, 0.53 mmol) and 4-fluoro-2-(trifluoromethyl)benzonitrile (150 mg, 0.79 mmol) in DMSO (5 mL) at RT under air. The resulting solution was stirred at 60°C for 2h and then concentrated. Purification by flash C18-flash chromatography (gradient: 10-100% MeCN in water) gave the title compound (0.125 g, 43%) as a white solid; ¹H NMR (CD₃OD, 300 MHz) 0.82 (6H, s), 1.65 (9H, s), 2.30-2.45 (4H, m), 2.44-2.60 (4H, m), 3.09 (3H, s), 3.74 (1H, t), 3.87 (2H, t), 4.42 (2H, t), 4.71 (2H, t), 4.98 (2H, d), 7.47 (1H, dd), 7.51 (1H, d), 7.84 (1H, d), 8.06 (1H, dd), 8.12 (1H, d), 8.61 (1H, d); *m/z* ES⁺ [M+H]⁺ = 547.

25

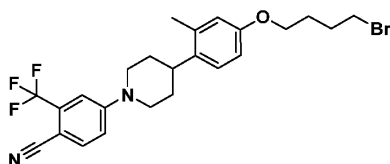
Intermediate 41e: 4-(4-(4-(4-Hydroxybutoxy)-2-methylphenyl)piperidin-1-yl)-2-(trifluoromethyl)-benzonitrile

30



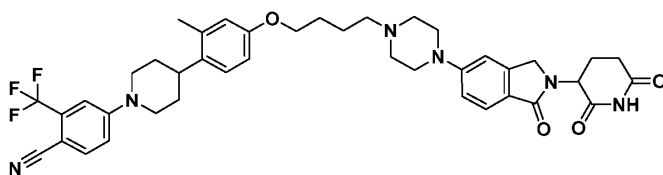
4-(4-(4-(4-((*tert*-Butyldimethylsilyl)oxy)butoxy)-2-methylphenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (90 mg, 0.16 mmol) was added to tetra-*n*-butylammonium fluoride (86 mg, 0.33 mmol) in THF (2 mL) at RT and the mixture was stirred for 16h, then concentrated. The residue was diluted with DCM (250 mL). This solution was washed with water (30 mL) then sat. brine (50 mL), dried (Na₂SO₄) and concentrated to give the title compound (0.085 g, 119 %); ¹H NMR: 1.51-1.58 (2H, m), 1.61 (2H, dd), 1.71 (2H, dd), 1.77 (2H, d), 2.31 (3H, s), 2.95 (1H, ddd), 3.08 (2H, t), 3.40-3.50 (2H, m), 3.91 (2H, t), 4.19 (2H, d), 4.43 (1H, t), 6.69 (1H, dd), 6.73 (1H, d), 7.05 (1H, d), 7.27 (1H, dd), 7.33 (1H, d), 7.82 (1H, d); *m/z* ES⁺ [M+H]⁺ = 433.2.

Intermediate 41f: 4-(4-(4-(4-Bromobutoxy)-2-methylphenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



4-(4-(4-(4-Hydroxybutoxy)-2-methylphenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (80.0 mg, 0.18 mmol) was added to PPh₃ (97.0 mg, 0.37 mmol) and CBr₄ (123 mg, 0.37 mmol) in DCM (2 mL) at RT and the mixture was stirred for 3h, then concentrated. Purification by FSC (gradient: 0-30% EtOAc in petroleum ether) gave the title compound (0.075 g, 82 %) as a colourless gum; ¹H NMR (300 MHz) 1.59 (2H, qd), 1.68-1.85 (4H, m), 1.93 (2H, dtd), 2.29 (3H, s), 2.88-2.99 (1H, m), 3.06 (2H, t), 3.58 (2H, t), 3.93 (2H, t), 4.17 (2H, d), 6.68 (1H, dd), 6.72 (1H, d), 7.04 (1H, d), 7.25 (1H, dd), 7.31 (1H, d), 7.80 (1H, d); *m/z* ES⁺ [M+H]⁺ = 495.2.

Example 41: 4-{4-[4-(4-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazin-1-yl}butoxy)-2-methylphenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile

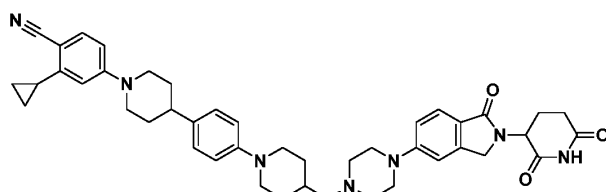


Intermediate 2c was reacted with Intermediate 41f using the general synthetic method illustrated by Example 5 to give the title compound after purification by preparative TLC (eluent: DCM:MeOH, 10:1); ¹H NMR: 1.54-1.67 (4H, m), 1.69-1.78 (4H, m), 1.92-2.01 (1H, m), 2.31 (3H, s), 2.31-2.44 (3H, m), 2.54-2.62 (1H, m), 2.84-2.98 (2H, m), 3.07 (2H, t), 3.23-3.31 (8H, m), 3.95 (2H, t), 4.14-4.25 (3H, m), 4.33 (1H, d), 5.04 (1H, dd),

6.70 (1H, dd), 6.74 (1H, d), 7.02-7.08 (3H, m), 7.26 (1H, dd), 7.32 (1H, d), 7.52 (1H, d), 7.81 (1H, d), 10.93 (1H, s); m/z ES⁺ [M+H]⁺ = 743.6.

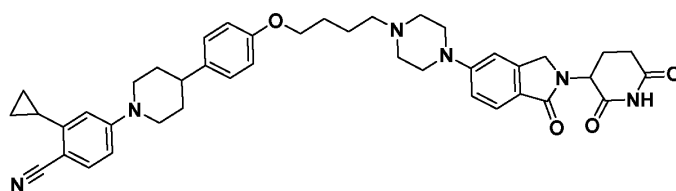
5

Example 42: 2-Cyclopropyl-4-{4-[4-{4-[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl}methyl]piperidin-1-yl}phenyl}piperidin-1-yl}benzonitrile

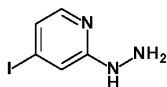


Intermediate 2b was reacted with Intermediate 3c using the general synthetic method illustrated by Example 1 to give the title compound after purification by preparative SFC (Column: Triart Diol-NP, 20*250mm, 5μm; Mobile Phase A:CO₂, Mobile Phase B:IPA (0.2% Et₂NH); Flow rate:50 mL/min; Gradient:40% B); ¹H NMR: 0.79-0.88 (2H, m), 0.97-1.08 (2H, m), 1.15-1.28 (3H, m), 1.49-1.74 (3H, m), 1.80 (4H, d), 1.96 (1H, d), 2.01-2.12 (1H, m), 2.21 (2H, d), 2.28-2.43 (1H, m), 2.52-2.67 (5H, m), 2.82-2.97 (3H, m), 3.23-3.32 (6H, m), 3.61 (2H, d), 4.02 (2H, d), 4.20 (1H, d), 4.33 (1H, d), 5.00-5.09 (1H, m), 6.45 (1H, d), 6.81-6.89 (3H, m), 7.02-7.10 (4H, m), 7.44-7.56 (2H, m), 10.95 (1H, s); m/z ES⁺ [M+H]⁺ = 726.5.

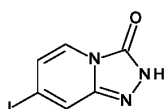
Example 43: 2-Cyclopropyl-4-{4-[4-(4-{4-[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl}butoxy)phenyl]piperidin-1-yl}benzonitrile



Intermediate 2c was reacted with Intermediate 14b using the general synthetic method illustrated by Example 5 to give the title compound after purification by flash C18-flash chromatography (gradient 0-37% MeCN in water) and further purification by preparative Prep-SFC (Column: GreenSep Basic; Mobile Phase A:CO₂, Mobile Phase B:MeOH (8mmol/L NH₃.MeOH)--HPLC; Flow rate:50 mL/min; Gradient:50% B); ¹H NMR: (300 MHz) 0.79-0.88 (2H, m), 1.00-1.09 (2H, m), 1.60 (2H, qd), 1.71-1.88 (6H, m), 1.92-2.14 (2H, m), 2.32-2.48 (2H, m), 2.56-2.78 (2H, m), 2.83-2.97 (4H, m), 3.09-3.24 (5H, m), 3.49-3.73 (2H, m), 3.92-4.10 (5H, m), 4.19-4.40 (2H, m), 5.07 (1H, dd), 6.46 (1H, d), 6.83-6.90 (3H, m), 7.11-7.19 (4H, m), 7.48 (1H, d), 7.59 (1H, d), 10.96 (1H, s); m/z ES⁺ [M+H]⁺ = 701.4.

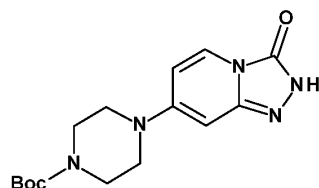
Intermediate 44a: 2-Hydrazineyl-4-iodopyridine

- Hydrazine monohydrate (1.23 g, 24.66 mmol) was added to 2-fluoro-4-iodopyridine (5.50 g, 24.66 mmol) in EtOH (50 mL) at RT under air and the mixture was stirred for 2 days. Water was then added and a solid collected by filtration to give the title compound (4.30 g, 74 %) as a pale yellow solid; ¹H NMR (300 MHz) 4.15 (2H, s), 6.85 (1H, dd), 7.11 (1H, d), 7.58 (1H, s), 7.65 (1H, d); *m/z* ES⁺ [M+H]⁺ = 236.

Intermediate 44b: 7-Iodo-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

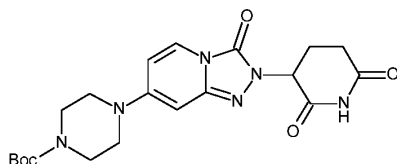
- CDI (4.45 g, 27.44 mmol) was added to 2-hydrazineyl-4-iodopyridine (4.30 g, 18.30 mmol) in MeCN (40 mL) at RT under air. The resulting solution was stirred at 60°C for 17h. The mixture was then filtered (with suction) and the solid was washed with MeCN to give the title compound (4.40 g, 92 %) as a pale yellow solid; ¹H NMR (300 MHz) 6.74 (1H, dd), 7.58 (1H, dd), 7.75 (1H, t), 12.47 (1H, s); *m/z* ES⁺ [M+H]⁺ = 262.

- Intermediate 44c: *tert*-Butyl 4-(3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridin-7-yl)piperazine-1-carboxylate**



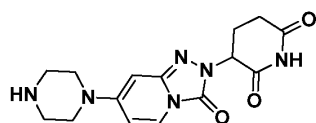
- RuPhos Pd G3 (0.481 g, 0.57 mmol) was added to 7-iodo-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one (1.5g, 5.75 mmol), *tert*-butyl piperazine-1-carboxylate (2.14 g, 11.49 mmol) and sodium 2-methylpropan-2-olate (1.66 g, 17.24 mmol) in *t*BuOH (10 mL) at RT under N₂. The resulting solution was stirred at 100°C for 3h then concentrated. Purification by FSC (gradient: 0-10% MeOH in DCM) gave the title compound (1.50 g, 82 %) as a yellow solid; ¹H NMR (300 MHz) 1.40 (9H, s), 3.20 (4H, dd), 3.41 (4H, t), 6.11 (1H, d), 6.58 (1H, dd), 7.63 (1H, d); *m/z* ES⁺ [M+H]⁺ = 320.

- Intermediate 44d: *tert*-Butyl 4-(2-(2,6-dioxopiperidin-3-yl)-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridin-7-yl)piperazine-1-carboxylate**



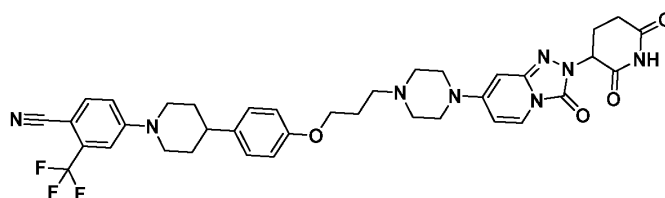
- NaH (0.095 g, 3.95 mmol)(60%) was added to *tert*-butyl 4-(3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-*a*]pyridin-7-yl)piperazine-1-carboxylate (1.05 g, 3.29 mmol) in DMF (10 mL) at RT under N₂. The resulting solution was stirred at 60°C for 0.5h. 3-Bromopiperidine-2,6-dione (0.631 g, 3.29 mmol) was then added and the solution was stirred at 60°C for 10h and then concentrated. Purification by flash C-18 chromatography (gradient: 10-80% MeCN in water) gave the title compound (0.600 g, 42 %) as a green solid; ¹H NMR (300 MHz) 1.40 (9H, s), 2.04-2.17 (1H, m), 2.48-2.62 (1H, m), 2.59-2.68 (1H, m), 2.87 (1H, ddd), 3.20-3.26 (4H, m), 3.37-3.45 (4H, m), 5.22 (1H, dd), 6.13 (1H, d), 6.66 (1H, dd), 7.72 (1H, d), 11.03 (1H, s); *m/z* ES⁺ [M+H]⁺ = 431.

Intermediate 44e: 3-(3-Oxo-7-(piperazin-1-yl)-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl)piperidine-2,6-dione



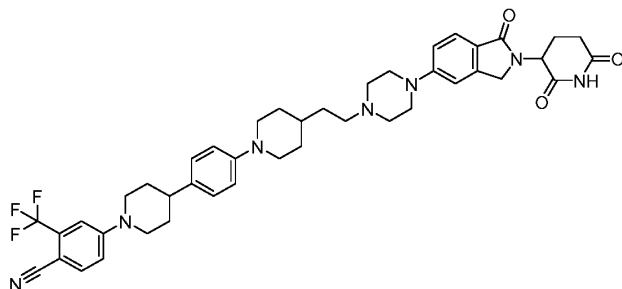
- tert*-Butyl 4-(2-(2,6-dioxopiperidin-3-yl)-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-*a*]pyridin-7-yl)piperazine-1-carboxylate (151 mg, 0.35 mmol) was added to HCl in 1,4-dioxane (3 mL, 12.00 mmol) at RT and the mixture was stirred for 2h. Concentration under reduced pressure then gave the title compound (0.120 g, 104 %) as a white solid; ¹H NMR (300 MHz) 2.06-2.16 (1H, m), 2.38-2.45 (1H, m), 2.61 (1H, dt), 2.88 (1H, ddd), 3.18 (4H, s), 3.50 (4H, s), 5.24 (1H, dd), 6.28 (1H, d), 6.67 (1H, dd), 7.78 (1H, d), 9.10 (1H, s), 11.04 (1H, s); *m/z* ES⁺ [M+H]⁺ = 331.1.

Example 44: 4-{4-[4-(3-{4-[2-(2,6-Dioxopiperidin-3-yl)-3-oxo-2,3-dihydro[1,2,4]triazolo[4,3-*a*]pyridin-7-yl]piperazin-1-yl}propoxy)phenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile



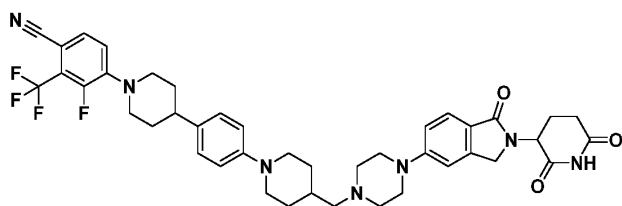
- Intermediate 13a was reacted with Intermediate 44e using the general synthetic method illustrated by Example 12 to give the title compound after purification by preparative TLC (eluent: DCM:MeOH, 10:1); ¹H NMR: 1.21-1.30 (5H, m), 1.61 (2H, qd), 1.79-1.99 (4H, m), 2.08-2.17 (1H, m), 2.62 (1H, dt), 2.77 (1H, ddt), 2.88 (1H, ddd), 3.04 (2H, td), 3.10-3.19 (1H, m), 3.19-3.28 (4H, m), 3.56-3.67 (1H, m), 3.99 (2H, t), 4.17 (2H, d), 5.23 (1H, dd), 6.11 (1H, d), 6.69 (1H, dd), 6.86 (2H, d), 7.15 (2H, d), 7.27 (1H, dd), 7.32 (1H, d), 7.71 (1H, d), 7.81 (1H, d), 11.03 (1H, s); *m/z* ES⁺ [M+H]⁺ = 717.4.

Example 45: 4-(4-{4-[4-(2-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazin-1-yl}ethyl)piperidin-1-yl]phenyl}piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



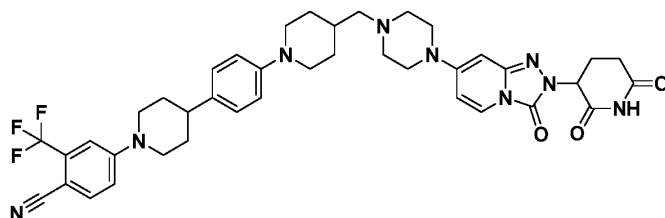
Intermediate 2c was reacted with Intermediate 15f using the general synthetic method illustrated by Example 2 to give the title compound after purification by preparative TLC (eluent: DCM:MeOH, 10:1); ¹H NMR: (300 MHz) 1.17-1.35 (2H, m), 1.45 (3H, s), 1.62 (2H, t), 1.80 (4H, dd), 1.90-2.02 (1H, m), 2.29-2.45 (4H, m), 2.53-2.79 (6H, m), 2.91 (1H, ddd), 3.04 (2H, t), 3.24-3.31 (5H, m), 3.61 (2H, d), 4.12-4.25 (3H, m), 4.34 (1H, d), 5.05 (1H, dd), 6.86 (2H, d), 7.03-7.13 (4H, m), 7.27 (1H, dd), 7.33 (1H, d), 7.53 (1H, d), 7.81 (1H, d), 10.95 (1H, s); *m/z* ES⁺ [M+H]⁺ = 768.5.

Example 46: 4-(4-{4-[4-(2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl}methyl)piperidin-1-yl}phenyl)piperidin-1-yl)-3-fluoro-2-(trifluoromethyl)benzonitrile



Intermediate 2c was reacted with Intermediate 6d using the general synthetic method illustrated by Example 2 to give the title compound after purification by HPLC (Column A, Eluent A, Basic Work-Up A); ¹H NMR: 1.19-1.27 (4H, m), 1.72 (3H, dd), 1.83 (4H, t), 1.93-2.01 (1H, m), 2.23 (2H, d), 2.39 (2H, td), 2.51-2.54 (4H, m), 2.58 (1H, dd), 2.64 (2H, d), 2.81-2.97 (1H, m), 3.04 (2H, t), 3.28-3.31 (4H, m), 3.63 (2H, d), 3.72 (2H, d), 4.22 (1H, d), 4.34 (1H, d), 5.05 (1H, dd), 6.88 (2H, d), 7.03-7.14 (4H, m), 7.46 (1H, t), 7.53 (1H, d), 7.80 (1H, d), 10.92 (1H, s); *m/z* ES⁺ [M+H]⁺ = 772.4.

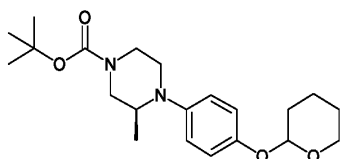
Example 47: 4-[4-(4-{4-[4-(2-(2,6-Dioxopiperidin-3-yl)-3-oxo-2,3-dihydro-1,2,4-triazolo[4,3-a]pyridin-7-yl]piperazin-1-yl}methyl)piperidin-1-yl}phenyl)piperidin-1-yl]-2-(trifluoromethyl)benzonitrile



Intermediate 4c was reacted with Intermediate 44e using the general synthetic method illustrated by Example 2 to give the title compound after purification by flash C18-flash chromatography (gradient: 0-40% MeCN in

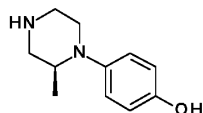
- water (0.1% formic acid)) to give white solid which was further purified by preparative TLC (eluent: DCM:MeOH, 10:1); ^1H NMR: 1.10-1.29 (4H, m), 1.52-1.69 (3H, m), 1.81 (4H, t), 2.09-2.18 (1H, m), 2.21 (2H, d), 2.41-2.49 (4H, m), 2.61 (3H, t), 2.89 (1H, ddd), 2.98-3.10 (2H, m), 3.23-3.28 (4H, m), 3.61 (2H, d), 4.17 (2H, d), 5.23 (1H, dd), 6.11 (1H, d), 6.69 (1H, dd), 6.82-6.90 (2H, m), 7.07 (2H, d), 7.26 (1H, dd), 7.32 (1H, d), 7.71 (1H, d), 7.81 (1H, d), 11.02 (1H, s); m/z ES^+ $[\text{M}+\text{H}]^+ = 756.4$.

Intermediate 48a: *tert*-Butyl (S)-3-methyl-4-(4-(((*RS*)-tetrahydro-2H-pyran-2-yl)oxy)phenyl)piperazine-1-carboxylate



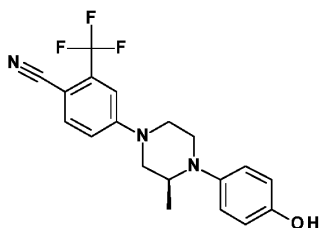
- 10 2-(4-Bromophenoxy)tetrahydro-2H-pyran (1.00 g, 3.89 mmol), *tert*-butyl (S)-3-methylpiperazine-1-carboxylate (1.17 g, 5.83 mmol), RuPhos (0.091 g, 0.19 mmol), RuPhos Pd G3 (0.163 g, 0.19 mmol) and potassium *tert*-butoxide (0.873 g, 7.78 mmol) were stirred in 1,4-dioxane (20 mL) and the mixture was degassed by bubbling N_2 . The mixture was then heated to 90°C for 2h. After cooling the mixture was partitioned between EtOAc and water. The organic solution was dried (Na_2SO_4) and concentrated. Purification
- 15 by FSC (gradient: 0-50% EtOAc in heptane) gave the title compound (1.10 g, 75 %) as a colourless oil; ^1H NMR (CDCl_3) 0.91 (3H, d), 1.30 (1H, dd), 1.48 (9H, s), 1.62-1.72 (2H, m), 1.84 (2H, dt), 2.00 (1H, ddt), 2.86-3.11 (2H, m), 3.43 (3H, s), 3.59 (2H, dtd), 3.70 (1H, s), 3.94 (1H, ddd), 5.32 (1H, q), 6.84-6.95 (2H, m), 6.95-7.06 (2H, m); m/z ES^+ $[\text{M}+\text{H}]^+ = 377.3$.

20 **Intermediate 48b: (S)-4-(2-Methylpiperazin-1-yl)phenol**



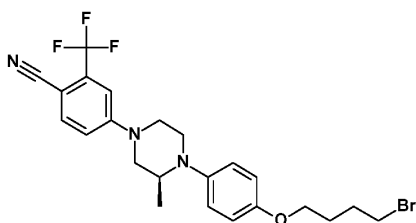
- 4M HCl in 1,4-dioxane (5.70 mL, 22.82 mmol) was added dropwise to a solution of *tert*-butyl (S)-3-methyl-4-(4-(((*RS*)-tetrahydro-2H-pyran-2-yl)oxy)phenyl)piperazine-1-carboxylate (1.10 g, 2.92 mmol) in DCM (20 mL) and the mixture was stirred overnight at RT. Et_2O (100 mL) was added and a precipitate was collected by
- 25 filtration under vacuum to give the title compound as a hydrochloride salt (0.696 g, 104 %) as a yellow solid; m/z ES^+ $[\text{M}+\text{H}]^+ = 193.1$.

Intermediate 48c: (S)-4-(4-(4-Hydroxyphenyl)-3-methylpiperazin-1-yl)-2-(trifluoromethyl)benzonitrile



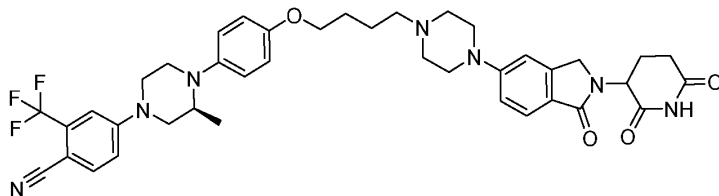
DIPEA (1.27 mL, 7.30 mmol), 4-fluoro-2-(trifluoromethyl)benzonitrile (0.552 g, 2.92 mmol) and (*S*)-4-(2-methylpiperazin-1-yl)phenol hydrochloride salt (0.668 g, 2.92 mmol) were dissolved in DMSO (5 mL) and the mixture was stirred at RT overnight. The mixture was then partitioned between water (25 mL) and EtOAc (25 mL). The organic solution was washed with brine, dried (MgSO₄) and concentrated. Purification by FSC (gradient: 0-60% EtOAc in heptane) gave the title compound (0.551 g, 52 %) as a yellow gum; ¹H NMR (CDCl₃) 1.00 (3H, d), 3.11 (1H, ddd), 3.14-3.2 (1H, m), 3.23 (1H, dd), 3.46 (1H, ddq), 3.5-3.59 (2H, m), 3.64 (1H, dd), 4.64 (1H, s), 6.75-6.84 (2H, m), 6.9-6.96 (2H, m), 6.98 (1H, dd), 7.14 (1H, d), 7.63 (1H, d); *m/z* ES⁺ [M+H]⁺ = 362.1.

Intermediate 48d: (*S*)-4-(4-(4-(4-Bromobutoxy)phenyl)-3-methylpiperazin-1-yl)-2-(trifluoromethyl)benzonitrile



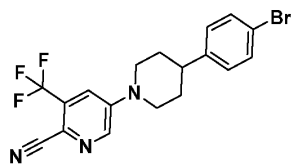
(*S*)-4-(4-(4-Hydroxyphenyl)-3-methylpiperazin-1-yl)-2-(trifluoromethyl)benzonitrile (0.244 g, 0.68 mmol), K₂CO₃ (0.112 g, 0.81 mmol) and 1,4-dibromobutane (0.161 mL, 1.35 mmol) were dissolved in anhydrous DMF (7 mL) under N₂. The mixture was stirred at 50°C for 16h. After cooling the mixture was diluted with EtOAc (50 mL), washed with sat. NaHCO₃ (50 mL) then sat. brine (50 mL), dried (MgSO₄) and concentrated. Purification by FSC (gradient: 0-40% EtOAc in heptane) gave the title compound (0.215 g, 64 %) as a yellow oil; ¹H NMR (CDCl₃) 1.00 (3H, d), 1.93 (2H, dq), 2-2.15 (2H, m), 3-3.33 (3H, m), 3.4-3.58 (5H, m), 3.64 (1H, dd), 3.97 (2H, t), 6.82-6.9 (2H, m), 6.93-7.02 (3H, m), 7.14 (1H, d), 7.63 (1H, d); *m/z* ES⁺ [M+H]⁺ = 498.2.

Example 48: 4-((3*S*)-4-[4-(4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazin-1-yl]butoxy)phenyl]-3-methylpiperazin-1-yl)-2-(trifluoromethyl)benzonitrile



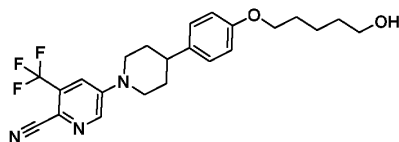
- Intermediate 2c was reacted with Intermediate 48d using the general synthetic method illustrated by Example 5 to give the title compound after purification by HPLC (Column A, Eluent A, Basic Work-Up A); ¹H NMR: 0.91 (3H, d), 1.62 (2H, q), 1.74 (2H, p), 1.89-2.01 (1H, m), 2.39 (3H, t), 2.51-2.54 (4H, m), 2.55-2.64 (1H, m), 2.90 (1H, ddd), 3.04-3.18 (2H, m), 3.26-3.29 (4H, m), 3.42-3.58 (2H, m), 3.61-3.69 (2H, m), 3.69-3.76 (1H, m), 3.94 (2H, q), 4.21 (1H, d), 4.33 (1H, d), 5.05 (1H, dd), 6.86 (2H, d), 6.94 (2H, d), 7.06 (2H, d), 7.28 (1H, dd), 7.34 (1H, d), 7.52 (1H, d), 7.84 (1H, d), 10.92 (1H, s); *m/z* ES⁺ [M+H]⁺ = 744.4.

Intermediate 49a: 5-(4-(4-Bromophenyl)piperidin-1-yl)-3-(trifluoromethyl)picolinonitrile



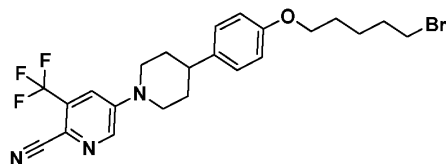
- 10 Cs₂CO₃ (4.07 g, 12.49 mmol) was added to 5-bromo-3-(trifluoromethyl)picolinonitrile (1.57 g, 6.25 mmol) and 4-(4-bromophenyl)piperidine (1.00 g, 4.16 mmol) in DMSO (10 mL) at RT. The resulting solution was stirred at 60°C for 10h. The mixture was then poured into water (100 mL) and extracted with EtOAc (3 × 50 mL). The combined organic solutions were dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-30% EtOAc in petroleum ether) gave the title compound (0.80 g, 47 %) as a yellow solid; ¹H NMR (300
- 15 MHz) 1.65 (2H, qd), 1.84 (2H, d), 2.85 (1H, tt), 3.10 (2H, t), 4.30 (2H, d), 7.23 (2H, d), 7.47 (2H, d), 7.63 (1H, d), 8.64 (1H, d); *m/z* ES⁺ [M+H]⁺ = 410.

Intermediate 49b: 5-(4-(4-((5-Hydroxypentyl)oxy)phenyl)piperidin-1-yl)-3-(trifluoromethyl)picolinonitrile



- 20 RockPhos Pd G3 (112 mg, 0.13 mmol) was added to pentane-1,5-diol (209 mg, 2.01 mmol), Cs₂CO₃ (1310 mg, 4.02 mmol) and 5-(4-(4-bromophenyl)piperidin-1-yl)-3-(trifluoromethyl)picolinonitrile (550 mg, 1.34 mmol) in 1,4-dioxane (7 mL) at RT under N₂. The resulting mixture was stirred at 100°C for 16h and then concentrated. Purification by FSC (gradient: 0-100% EtOAc in petroleum ether) gave the title compound
- 25 (0.120 g, 21%) as a white solid; ¹H NMR: 1.39-1.53 (4H, m), 1.60-1.75 (4H, m), 1.85 (2H, dd), 2.80 (1H, tt), 3.11 (2H, t), 3.41 (2H, q), 3.92 (2H, t), 4.30 (2H, d), 4.37 (1H, t), 6.85 (2H, d), 7.16 (2H, d), 7.64 (1H, d), 8.66 (1H, d); *m/z* ES⁺ [M+H]⁺ = 434.3.

Intermediate 49c: 5-(4-(4-((5-Bromopentyl)oxy)phenyl)piperidin-1-yl)-3-(trifluoromethyl)picolinonitrile



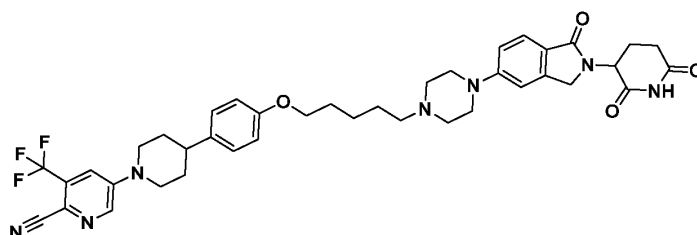
30

CBr₄ (153 mg, 0.46 mmol) was added to PPh₃ (121 mg, 0.46 mmol) and 5-(4-(4-((5-hydroxypentyl)oxy)-phenyl)piperidin-1-yl)-3-(trifluoromethyl)picolinonitrile (100 mg, 0.23 mmol) in DCM (1 mL) at RT and the mixture was stirred for 2h then concentrated. Purification by FSC (gradient: 0-50% EtOAc in petroleum ether) gave the title compound (0.110 g, 96 %) as a yellow oil; *m/z* ES⁺ [M+H]⁺ = 496.1.

5

Example 49: 5-(4-{4-[(5-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazin-1-yl}pentyl)oxy]phenyl}piperidin-1-yl)-3-(trifluoromethyl)pyridine-2-carbonitrile

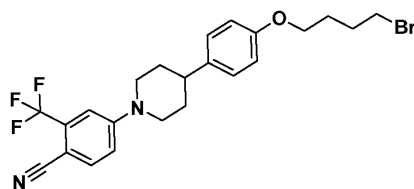
10



Intermediate 2c was reacted with Intermediate 49c using the general synthetic method illustrated by Example 5 to give the title compound after purification by FSC (gradient: 0-10% MeOH in DCM); ¹H NMR: 1.38-1.47 (2H, m), 1.47-1.58 (2H, m), 1.64 (2H, d), 1.67-1.77 (2H, m), 1.84 (2H, d), 1.90-2.00 (1H, m), 2.35-2.43 (2H, m), 2.58 (2H, d), 2.73-2.85 (1H, m), 2.90 (1H, ddd), 3.10 (2H, t), 3.24-3.29 (3H, m), 3.29-3.30 (5H, m), 3.93 (2H, t), 4.19-4.39 (4H, m), 5.04 (1H, dd), 6.85 (2H, d), 7.05 (2H, d), 7.16 (2H, d), 7.52 (1H, d), 7.63 (1H, d), 8.65 (1H, d), 10.94 (1H, s); *m/z* ES⁺ [M+H]⁺ = 744.3.

15

Intermediate 50a: 4-[4-[4-(4-Bromobutoxy)phenyl]-1-piperidyl]-2-(trifluoromethyl)benzonitrile



20

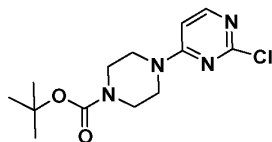
4-(4-(4-Hydroxyphenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (1.95 g, 5.63 mmol), K₂CO₃ (0.934 g, 6.76 mmol) and 1,4-dibromobutane (2.02 mL, 16.89 mmol) were suspended in MeCN (55 mL). The suspension was heated to 70°C. After 6h, starting material remained so further portions of K₂CO₃ (500 mg) and 1,4-dibromobutane (1 mL) were added and the mixture was stirred at 70°C overnight. A small amount of starting material remained so further portions of K₂CO₃ (500 mg) and 1,4-dibromobutane (1 mL) were added and the mixture was stirred at 70°C for 4h. The mixture was then cooled to RT and filtered (washing with MeCN). The filtrate was concentrated under reduced pressure. Purification by FSC (gradient: 0-50% EtOAc in heptane) gave the title compound (2.44 g, 90 %) as a yellow oil which solidified on standing; ¹H NMR (CDCl₃) 1.80 (2H, qd), 1.88-2.02 (4H, m), 2.02-2.12 (2H, m), 2.74 (1H, tt), 3.07 (2H, td), 3.48 (2H, t), 3.94-4.07 (4H, m), 6.82-6.89 (2H, m), 7.04 (1H, dd), 7.1-7.16 (2H, m), 7.19 (1H, d), 7.6-7.66 (1H, m); *m/z* ES⁺

25

30

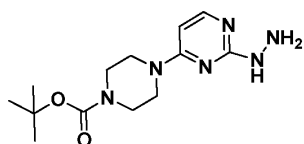
$[M+H]^+ = 481.2$.

Intermediate 50b: *tert*-Butyl 4-(2-chloropyrimidin-4-yl)piperazine-1-carboxylate



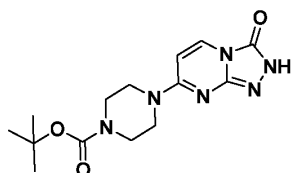
- 5 NEt_3 (2.77 mL, 19.87 mmol) was added to 2,4-dichloropyrimidine (1.48 g, 9.93 mmol) and *tert*-butyl piperazine-1-carboxylate (2.035 g, 10.93 mmol) in DMF (20 mL) at RT and the mixture was stirred for 2h. The mixture was then diluted with EtOAc, washed (water then sat. brine), dried (Na_2SO_4) and concentrated. Purification by FSC (gradient: 0-25% EtOAc in petroleum ether then 0-10% MeOH in DCM) gave the title compound (2.10 g, 71 %) as a white solid; ^1H NMR (300 MHz) 1.42 (9H, s), 3.39-3.44 (4H, m), 3.58-3.67 (4H, m), 6.83 (1H, d), 8.09 (1H, d); m/z ES^+ $[M+H]^+ = 299$.

Intermediate 50c: *tert*-Butyl 4-(2-hydrazineylpyrimidin-4-yl)piperazine-1-carboxylate



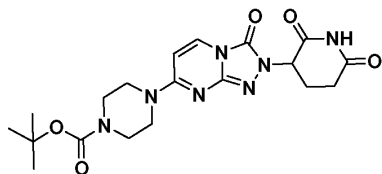
- 15 Hydrazine (1.641 mL, 33.47 mmol) was added to *tert*-butyl 4-(2-chloropyrimidin-4-yl)piperazine-1-carboxylate (2.00 g, 6.69 mmol) in EtOH (15 mL) and water (3 mL) at RT. The resulting mixture was stirred at 80°C for 16h and then concentrated. Trituration with water to give a solid which was collected by filtration and dried under vacuum to give the title compound (2.00 g, 101 %) as a white solid; m/z ES^+ $[M+H]^+ = 295$.

Intermediate 50d: *tert*-Butyl 4-(3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-*a*]pyrimidin-7-yl)piperazine-1-carboxylate



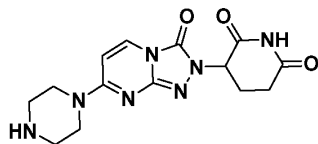
- 25 CDI (1.32 g, 8.15 mmol) was added to *tert*-butyl 4-(2-hydrazineylpyrimidin-4-yl)piperazine-1-carboxylate (2.00 g, 6.79 mmol) in THF (20 mL) at RT and the mixture was stirred for 1.5h, then concentrated. Trituration with MeCN and Et₂O gave a solid which was collected by filtration and dried under vacuum to give the title compound (1.93 g, 89 %) as a pale yellow solid; ^1H NMR: 1.43 (9H, s), 3.39-3.48 (4H, m), 3.66-3.80 (4H, m), 6.59 (1H, d), 7.98 (1H, d), 11.59 (1H, s); m/z ES^+ $[M+H]^+ = 321$.

Intermediate 50e: *tert*-Butyl 4-(2-(2,6-dioxopiperidin-3-yl)-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-*a*]pyrimidin-7-yl)piperazine-1-carboxylate



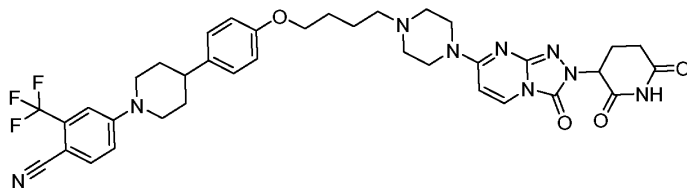
- NaH (0.233 g, 5.84 mmol) was added to *tert*-Butyl 4-(3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-*a*]pyrimidin-7-yl)piperazine-1-carboxylate (1.70 g, 5.31 mmol) in DMF (1 mL) at 0°C. The mixture was stirred at 0°C for 20 mins and warmed up to RT for further 20 mins. 3-Bromopiperidine-2,6-dione (1.223 g, 6.37 mmol) was then added and the mixture stirred at 60°C for 2h. After cooling, the mixture was diluted with DCM. This solution was washed (5% AcOH, water and then sat. brine), dried (Na₂SO₄) and concentrated. Purification by flash C18-flash chromatography (gradient: 0-30% MeCN in water (0.1% formic acid)) gave the title compound (0.586 g, 26 %) as a white solid; ¹H NMR: 1.42 (9H, s), 2.04-2.16 (1H, m), 2.35-2.48 (1H, m), 2.57-2.73 (1H, m), 2.87 (1H, ddd), 3.38-3.44 (4H, m), 3.65-3.80 (4H, m), 5.19 (1H, dd), 6.65 (1H, d), 8.06 (1H, d), 11.01 (1H, s); *m/z* ES⁺ [M+H]⁺ = 432.

Intermediate 50f: 3-(3-Oxo-7-piperazin-1-yl-[1,2,4]triazolo[4,3-*a*]pyrimidin-2-yl)piperidine-2,6-dione

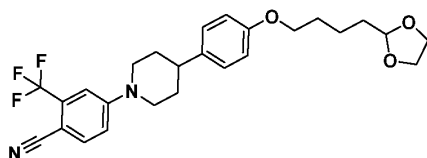


- HCl in 1,4-dioxane (1 mL, 4.00 mmol) was added to *tert*-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-*a*]pyridin-7-yl)piperazine-1-carboxylate (200 mg, 0.46 mmol) in DCM (1 mL) at RT and the mixture was stirred for 1h then concentrated. Trituration with Et₂O to give a solid which was collected by filtration and dried under vacuum to the title compound (0.180 g, 96 %) as a pale yellow solid; ¹H NMR: 2.06-2.17 (1H, m), 2.37-2.48 (1H, m), 2.57-2.70 (1H, m), 2.83-2.95 (1H, m), 3.14-3.22 (4H, m), 3.91-4.04 (4H, m), 5.21 (1H, dd), 6.70 (1H, d), 8.15 (1H, d), 9.22 (1H, br), 11.03 (1H, s).

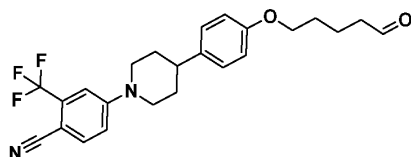
Example 50: 4-{4-[4-(4-{2-(2,6-Dioxopiperidin-3-yl)-3-oxo-2,3-dihydro[1,2,4]triazolo[4,3-*a*]pyrimidin-7-yl]piperazin-1-yl}butoxy)phenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile



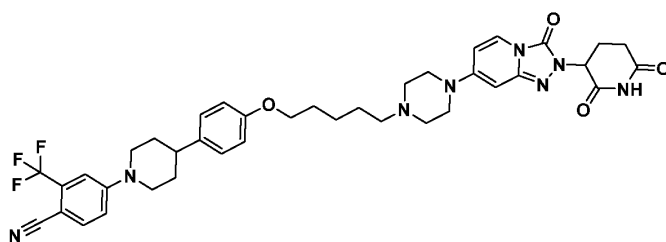
- Intermediate 50a was reacted with Intermediate 50f using the general synthetic method illustrated by Example 5 to give the title compound (as a formate salt) after purification by flash C18-flash chromatography (gradient: 0-40% MeCN in water (0.1% formic acid)); ¹H NMR: (300 MHz) 1.53-1.66 (4H, m), 1.65-1.79 (2H, m), 1.85 (2H, d), 2.04-2.17 (1H, m), 2.33-2.48 (7H, m), 2.54-2.66 (1H, m), 2.75-2.95 (2H, m), 3.05 (2H, t), 3.61-3.83 (4H, m), 3.96 (2H, t), 4.18 (2H, d), 5.19 (1H, dd), 6.67 (1H, d), 6.86 (2H, t), 7.16 (2H, t), 7.24-7.36 (2H, m), 7.82 (1H, d), 8.03 (1H, d), 11.03 (1H, s); *m/z* ES⁺ [M+H]⁺ = 732.3.

Intermediate 51a: 4-(4-(4-(4-(1,3-Dioxolan-2-yl)butoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile

- 5 K_2CO_3 (1.197 g, 8.66 mmol) was added to 4-(4-(4-hydroxyphenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (1.00 g, 2.89 mmol) and 2-(4-bromobutyl)-1,3-dioxolane (0.604 g, 2.89 mmol) in DMF (2 mL) at RT under air. The resulting solution was stirred at 80°C for 10h. Purification by FSC (gradient: 0-50% EtOAc in petroleum ether) gave the title compound (1.10 g, 80 %) as a yellow solid; m/z ES^+ $[M+H]^+ = 475$.

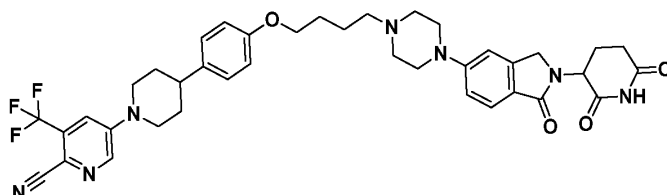
Intermediate 51b: 4-(4-(4-((5-Oxopentyl)oxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile

- 4-(4-(4-(4-(1,3-Dioxolan-2-yl)butoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (1.00 g, 2.11 mmol) was added to formic acid (10 mL) at RT and the mixture was stirred for 4h and then concentrated. Purification by FSC (gradient: 30-100% MeCN in water) gave the title compound (0.500 g, 55 %) as a purple oil; m/z ES^+ $[M+H]^+ = 431$.
- 15

Example 51: 4-(4-{4-[(5-{4-[2-(2,6-Dioxopiperidin-3-yl)-3-oxo-2,3-dihydro[1,2,4]triazolo[4,3-a]pyridin-7-yl]piperazin-1-yl}pentyl)oxy]phenyl}piperidin-1-yl)-2-(trifluoromethyl)benzonitrile

- 20 Intermediate 44e was reacted with Intermediate 51b using the general synthetic method illustrated by Example 2 to give the title compound after purification by preparative SFC (Column: Triart Diol-NP, 20*250mm, 5 μ m; Mobile Phase A:CO₂, Mobile Phase B:IPA(8mmol/L NH₃.MeOH)-HPLC; Flow rate:50 mL/min; Gradient:27% B; 254 nm; RT1:4.03; Injection Volumn:1.5 mL; Number Of Runs:10;); ¹H NMR: (300 MHz) 1.40-1.90 (12H, m), 2.10-2.25 (1H, m), 2.30-2.40 (3H, m), 2.55-2.65 (2H, m), 2.70-2.95 (3H, m), 3.01-3.12 (2H, m), 3.20-3.30 (4H, m), 3.90-4.00 (2H, m), 4.22 (2H, d), 5.24 (1H, d), 6.10-6.14 (1H, m), 6.69 (1H, d), 6.80-6.90 (2H, m), 7.10-7.21 (2H, m), 7.27- 7.33 (2H, m), 7.72 (1H, d), 7.82 (1H, d), 11.04 (1H, s); m/z ES^+ $[M+H]^+ = 745.4$.
- 25

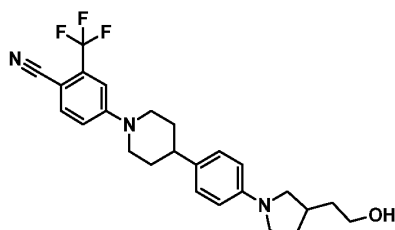
Example 52: 5-{4-[4-(4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl)butoxy]phenyl]piperidin-1-yl}-3-(trifluoromethyl)pyridine-2-carbonitrile



- 5 Intermediate 2c was reacted with Intermediate 11b using the general synthetic method illustrated by Example 5 to give the title compound after purification by preparative TLC (eluent: DCM:MeOH, 10:1); ¹H NMR: (300 MHz) 1.54-1.89 (8H, m), 1.90-2.02 (1H, m), 2.36-2.40 (4H, m), 2.52-2.65 (2H, m), 2.75-2.98 (2H, m), 3.11 (2H, t), 3.23-3.35 (6H, m), 3.97 (2H, t), 4.15-4.38 (4H, m), 5.05 (1H, dd), 6.86 (2H, d), 7.01-7.10 (2H, m), 7.17 (2H, d), 7.52 (1H, d), 7.64 (1H, d), 8.65 (1H, d), 10.94 (1H, s); *m/z* ES⁺ [M+H]⁺ = 730.3.

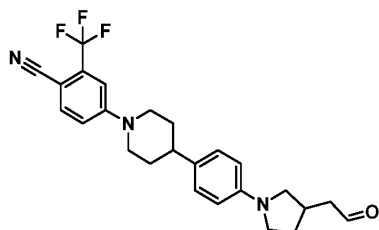
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Intermediate 53a: 4-[4-[4-[3-(2-Hydroxyethyl)pyrrolidin-1-yl]phenyl]-1-piperidyl]-2-(trifluoromethyl)-benzonitrile



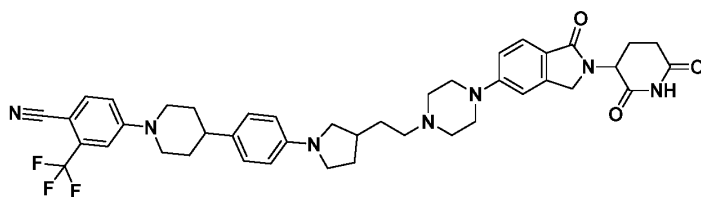
- 15 CuI (46.5 mg, 0.24 mmol) was added to 4-(4-(4-bromophenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (500 mg, 1.22 mmol), 2-(pyrrolidin-3-yl)ethan-1-ol (211 mg, 1.83 mmol), 2-((2,6-dimethylphenyl)amino)-2-oxoacetic acid (47.2 mg, 0.24 mmol) and K₃PO₄ (519 mg, 2.44 mmol) in DMSO (7 mL) under N₂. The resulting mixture was stirred at 115°C for 18h. The mixture was then cooled to RT and poured into water (50 mL) then extracted with EtOAc (3 × 50 mL). The combined organic solutions were washed with brine (50 mL), dried (MgSO₄) and concentrated. Purification by FSC (gradient: 0-50% EtOAc in heptane) gave the title
- 20 compound (0.347 g, 64 %) as a white solid; ¹H NMR (CDCl₃) 1.26 (1H, d), 1.63-1.82 (5H, m), 1.96 (2H, d), 2.18 (1H, dtd), 2.33-2.49 (1H, m), 2.69 (1H, dtd), 2.90-2.99 (1H, m), 3.04 (2H, td), 3.27 (1H, td), 3.35 (1H, td), 3.46 (1H, dd), 3.7-3.79 (2H, m), 4.01 (2H, d), 6.46-6.56 (2H, m), 6.98 (1H, dd), 7.02-7.12 (2H, m), 7.15 (1H, d), 7.60 (1H, d); *m/z*: ES⁺ [M+H]⁺ 444.3.

- 25 **Intermediate 53b: 4-[4-[4-[3-(2-Oxoethyl)pyrrolidin-1-yl]phenyl]-1-piperidyl]-2-(trifluoromethyl)-benzonitrile**



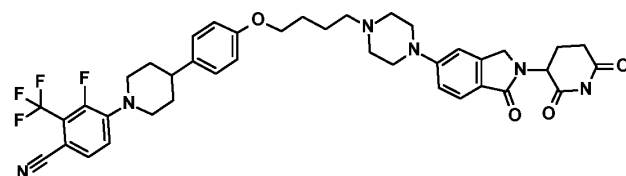
- Dess-Martin periodinane (184 mg, 0.43 mmol) was added to 4-[4-[3-(2-hydroxyethyl)pyrrolidin-1-yl]phenyl]-1-piperidyl]-2-(trifluoromethyl)benzonitrile (175 mg, 0.39 mmol) in DCM (5 mL) at 0°C. The resulting mixture was stirred at RT for 1h. The mixture was then diluted with DCM (15 mL) and poured into mixture of sat. NaHCO₃ (15 mL) and sodium thiosulfate solution (15 mL). The resulting suspension was stirred vigorously for 10 mins then the layers were separated. The organic solution was dried (Na₂SO₄) and concentrated to give the title compound as a red gum which was used without further purification; *m/z*: ES⁺ [M+H]⁺ 442.2.

- 10 **Example 53: 4-(4-{4-[3-(2-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazin-1-yl}ethyl)pyrrolidin-1-yl]phenyl}piperidin-1-yl)-2-(trifluoromethyl)benzonitrile**



- Intermediate 2c was reacted with Intermediate 53b using the general synthetic method illustrated by Example 2 to give the title compound after purification by HPLC (Column A, Eluent A, Basic Work-Up A); ¹H NMR: (CDCl₃) 1.75 (6H, ddd), 1.96 (2H, d), 2.19 (2H, ddq), 2.32 (2H, qd), 2.42-2.53 (2H, m), 2.59-2.66 (4H, m), 2.66-2.73 (1H, m), 2.82 (1H, td), 2.88 (1H, dd), 2.93 (1H, t), 2.99-3.1 (2H, m), 3.23-3.32 (1H, m), 3.35 (4H, q), 3.41-3.51 (1H, m), 4.01 (2H, d), 4.25 (1H, d), 4.41 (1H, d), 5.19 (1H, dd), 6.52 (2H, d), 6.88 (1H, s), 6.99 (2H, ddd), 7.08 (2H, d), 7.15 (1H, d), 7.60 (1H, d), 7.74 (1H, d), 7.93 (1H, s); *m/z* ES⁺ [M+H]⁺ = 754.4.

- 20 **Example 54: 4-(4-{4-[4-(4-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazin-1-yl}butoxy)phenyl]piperidin-1-yl}-3-fluoro-2-(trifluoromethyl)benzonitrile**

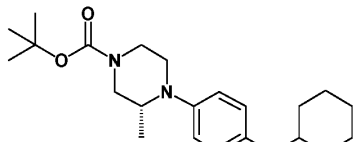


- Intermediate 2c was reacted with Intermediate 7b using the general synthetic method illustrated by Example 2 to give the title compound after purification by HPLC (Column A, Eluent A, Basic Work-Up A); ¹H NMR: 1.56-1.66 (2H, m), 1.76 (4H, dd), 1.86 (2H, d), 1.92-2.01 (1H, m), 2.37 (3H, d), 2.53 (4H, d), 2.59 (1H, d), 2.72 (1H, d), 2.83-2.96 (1H, m), 3.04 (2H, t), 3.28 (4H, s), 3.72 (2H, d), 3.98 (2H, t), 4.21 (1H, d), 4.33 (1H,

d), 5.05 (1H, dd), 6.88 (2H, d), 7.06 (2H, d), 7.18 (2H, d), 7.46 (1H, t), 7.52 (1H, d), 7.80 (1H, d), 10.92 (1H, s); m/z ES⁺ [M+H]⁺ = 747.4.

Intermediate 55a: *tert*-Butyl (*R*)-3-methyl-4-(4-(((*RS*)-tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)piperazine-1-carboxylate

5

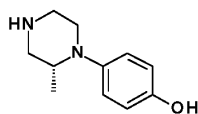


2-(4-Bromophenoxy)tetrahydro-2*H*-pyran (1.0 g, 3.89 mmol), *tert*-butyl (*R*)-3-methylpiperazine-1-carboxylate (1.168 g, 5.83 mmol), RuPhos (0.091 g, 0.19 mmol), RuPhos Pd G3 (0.163 g, 0.19 mmol) and potassium *tert*-butoxide (0.873 g, 7.78 mmol) were stirred in 1,4-dioxane (20 mL) and the mixture was degassed by bubbling

10 N₂. The mixture was then heated to 80 °C for 2h. After cooling, the mixture was partitioned between EtOAc (50 mL) and water (50 mL). The organic solution was dried and concentrated. Purification by FSC (gradient: 0-50% EtOAc in heptane) gave the title compound (0.859 g, 59%) as a colourless oil; ¹H NMR (CDCl₃) 0.91 (3H, d), 1.48 (9H, s), 1.66 (3H, dddd), 1.85 (2H, dq), 1.92-2.11 (1H, m), 2.99 (2H, d), 3.44 (3H, s), 3.60 (2H, ddt), 3.63-3.85 (1H, m), 3.94 (1H, ddd), 5.32 (1H, dt), 6.90 (2H, d), 6.96-7.03 (2H, m); m/z ES⁺ [M+H]⁺ = 377.3.

15

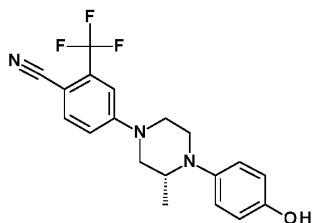
Intermediate 55b: (*R*)-4-(2-Methylpiperazin-1-yl)phenol



4M HCl in dioxane (5.7 mL, 22.82 mmol) was added dropwise to a solution of *tert*-butyl (*R*)-3-methyl-4-(4-(((*RS*)-tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)piperazine-1-carboxylate (859 mg, 2.28 mmol) in DCM (20 mL) and the mixture was stirred overnight at RT. Et₂O (100 mL) was added and the resulting precipitate was collected by filtration under vacuum to give the title compound as a hydrochloride salt (0.600 g, 115 %) as a yellow solid; m/z ES⁺ [M+H]⁺ = 193.1.

Intermediate 55c: (*R*)-4-(4-(4-Hydroxyphenyl)-3-methylpiperazin-1-yl)-2-(trifluoromethyl)benzonitrile

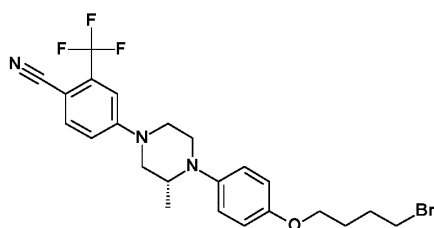
25



DIPEA (0.993 mL, 5.70 mmol), 4-fluoro-2-(trifluoromethyl)benzonitrile (0.431 g, 2.28 mmol) and (*R*)-4-(2-methylpiperazin-1-yl)phenol hydrochloride salt (0.521 g, 2.28 mmol) were dissolved in DMSO (5 mL) and the

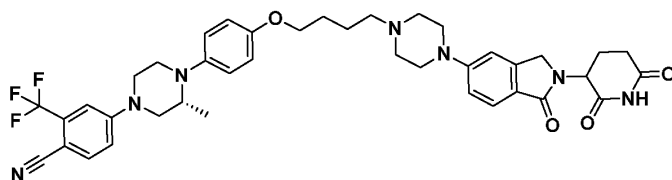
- mixture was stirred at RT overnight. The mixture was then partitioned between water (25 mL) and EtOAc (25 mL). The organic solution was washed with brine, dried (MgSO₄) and concentrated. Purification by FSC (gradient: 0-60% EtOAc in heptane) gave the title compound (0.610 g, 74 %) as a yellow gum; ¹H NMR (CDCl₃) 1.00 (3H, d), 3.11 (1H, ddd), 3.16-3.25 (2H, m), 3.41-3.6 (3H, m), 3.64 (1H, dd), 4.72 (1H, s), 6.73-6.85 (2H, m), 6.89-7.01 (3H, m), 7.14 (1H, d), 7.57-7.71 (1H, m); *m/z* ES⁺ [M+H]⁺ = 362.

Intermediate 55d: (R)-4-(4-(4-(4-Bromobutoxy)phenyl)-3-methylpiperazin-1-yl)-2-(trifluoromethyl)benzonitrile



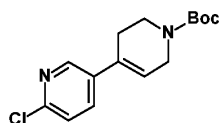
- 10 (R)-4-(4-(4-Hydroxyphenyl)-3-methylpiperazin-1-yl)-2-(trifluoromethyl)benzonitrile (0.184 g, 0.51 mmol), K₂CO₃ (0.084 g, 0.61 mmol) and 1,4-dibromobutane (0.122 mL, 1.02 mmol) were dissolved in anhydrous DMF (7 mL) under N₂. This mixture was stirred at 50°C for 16h. The mixture was then diluted with EtOAc (50 mL), washed with sat. NaHCO₃ (50 mL) then brine (50 mL), dried (MgSO₄) and concentrated. Purification by FSC (gradient: 0-40% EtOAc in heptane) gave the title compound (0.159 g, 63 %) as a yellow oil; ¹H NMR (CDCl₃) 1.00 (3H, d), 1.86-2 (2H, m), 2.02-2.15 (2H, m), 3.07-3.29 (3H, m), 3.49 (3H, t), 3.53 (2H, t), 3.64 (1H, dd), 3.97 (2H, t), 6.82-6.91 (2H, m), 6.93-7.02 (3H, m), 7.14 (1H, d), 7.57-7.72 (1H, m); *m/z* ES⁺ [M+H]⁺ = 496.2

Example 55: 4-((3R)-4-[4-(4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-indol-5-yl]piperazin-1-yl]butoxy)phenyl]-3-methylpiperazin-1-yl)-2-(trifluoromethyl)benzonitrile



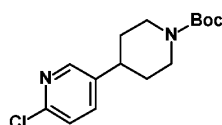
- Intermediate 2c was reacted with Intermediate 55d using the general synthetic method illustrated by Example 5 to give the title compound after purification by HPLC (Column A, Eluent A, Basic Work-Up A); ¹H NMR: 0.91 (3H, d), 1.54-1.68 (2H, m), 1.73 (2H, q), 1.97 (1H, dd), 2.35-2.43 (3H, m), 2.53 (4H, d), 2.59 (1H, d), 2.83-2.96 (1H, m), 3.04-3.17 (2H, m), 3.30 (4H, s), 3.42-3.56 (2H, m), 3.6-3.69 (2H, m), 3.69-3.8 (1H, m), 3.95 (2H, t), 4.21 (1H, d), 4.33 (1H, d), 5.04 (1H, dd), 6.86 (2H, d), 6.94 (2H, d), 7.06 (2H, d), 7.23-7.38 (2H, m), 7.52 (1H, d), 7.84 (1H, d), 10.92 (1H, s); *m/z* ES⁺ [M+H]⁺ = 744.4.

Intermediate 56a: tert-butyl 6-chloro-3',6'-dihydro-[3,4'-bipyridine]-1'(2'H)-carboxylate



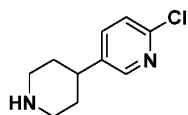
- 5 *tert*-Butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylate (50.0 g, 161 mmol), 5-bromo-2-chloro-pyridine (62.2 g, 323 mmol), K₂CO₃ (112 g, 808 mmol) and Pd(dppf)Cl₂ (5.92 g, 8.09 mmol) were added to 1,4-dioxane (350 mL) and H₂O (35.0 mL). The mixture was degassed and purged with N₂ three times. The mixture was then stirred at 95°C for 1h. H₂O (500 mL) and EtOAc (200 mL) were then added. The mixture was filtered and the filtrate was extracted with EtOAc (200 mL × 2). The combined organic solutions were dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: petroleum ether/EtOAc = 10/1 to 2/1) gave the title compound (34.2 g, 65%) as light yellow solid; ¹H NMR (CDCl₃) 1.49 (9H, s), 2.50 (1H, s), 3.65 (2H, t), 4.10 (2H, s), 6.09 (1H, s), 7.26 (1H, d), 7.62 (1H, dd), 8.40 (1H, s).
- 10

Intermediate 56b: *tert*-Butyl 4-(6-chloro-3-pyridyl)piperidine-1-carboxylate



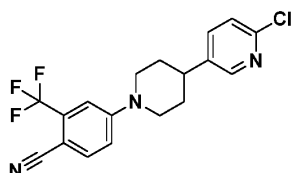
- MeOH (400.0 mL) was added to *tert*-butyl 6-chloro-3',6'-dihydro-[3,4'-bipyridine]-1'(2'H)-carboxylate (27.8 g, 94.3 mmol) and PtO₂ (4.29 g, 18.9 mmol). The resulting suspension was degassed and purged with H₂ three times. The mixture was then stirred at 15°C for 4.5h under H₂ (30 psi). The mixture was then filtered and the filtrate was concentrated. Purification by FSC (gradient: petroleum ether/EtOAc = 10/1 to 2/1) gave the title compound (13.09 g, 42%) as light yellow oil; ¹H NMR (CDCl₃) 1.49 (9H, s), 1.65-1.54 (2H, m), 1.82 (2H, d), 2.73-2.65 (2H, m), 2.82 (2H, t), 4.27 (2H, s), 7.28 (1H, d), 7.49 (1H, dd), 8.26 (1H, s);
- 15

20 **Intermediate 56c: 2-chloro-5-(4-piperidyl)pyridine**



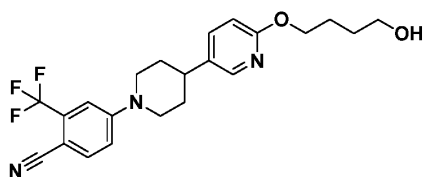
- 4N HCl in MeOH (130 mL) was added to *tert*-butyl 4-(6-chloro-3-pyridyl)piperidine-1-carboxylate (12.9 g, 43.4 mmol) and the mixture stirred at RT for 20 mins. Concentration of the mixture then gave the title compound as a hydrochloride salt (11.6 g, 43.0 mmol, 99%) as light yellow solid; ¹H NMR (CD₃OD) 1.96 (2H, m), 2.04-8.47 (1H, s), 2.14-2.11 (2H, m), 3.21-3.07 (3H, m), 3.54 (2H, d), 7.66 (1H, d), 8.03 (1H, dd).
- 25

Intermediate 56d: 4-[4-(6-Chloro-3-pyridyl)-1-piperidyl]-2-(trifluoromethyl)benzonitrile



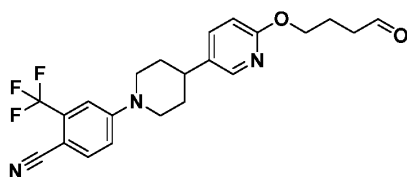
- 2-Chloro-5-(4-piperidyl)pyridine (10.0 g, 37.0 mmol), 4-fluoro-2-(trifluoromethyl)benzonitrile (14.0 g, 74.0 mmol), DIPEA (23.9 g, 185 mmol, 32.2 mL) were dissolved in DMSO (120.0 mL) and stirred at 50°C for 5.5h. The solution was then cooled to 0°C and hydrochloric acid (1 M, 50.0 mL) was added to the solution, (pH = 2). Sat NaHCO₃ (200.0 mL) solution was then added to the mixture to pH = 8. A solid was collected by
- 5 filtration and dried under vacuum. The solid was purified by recrystallization (petroleum ether/ EtOAc = 10/1) to give the title compound (5.50 g, 37% yield) as light yellow solid; ¹H NMR (CDCl₃) 1.84-1.77 (2H, m), 2.03-2.00 (2H, m), 2.87-2.81 (1H, m), 3.08 (2H, t), 4.05 (2H, d), 7.02-7.00 (1H, m), 7.17 (1H, s), 7.30 (1H, d), 7.51 (1H, dd), 7.63 (1H, d), 8.28 (1H, s); *m/z* ES⁺ [M+H]⁺ = 366.1.

10 **Intermediate 56e: 4-[4-[6-(4-Hydroxybutoxy)-3-pyridyl]-1-piperidyl]-2-(trifluoromethyl)benzonitrile**

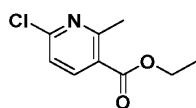


- Butane-1,4-diol (0.606 mL, 6.83 mmol) was dissolved in THF (10 mL) and cooled to 0°C (ice bath). NaH (60%, 0.137 g, 3.42 mmol) was added and the reaction brought to RT. 4-(4-(6-Chloropyridin-3-yl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (0.500 g, 1.37 mmol) was added in one portion and the mixture was heated
- 15 to 85°C for 16h. The mixture was then diluted with DMF (5.00 mL), additional NaH (0.137 g, 3.42 mmol) was added and the mixture was heated to 120°C for 16h. After cooling the mixture was diluted with EtOAc (50 mL). This solution was washed with water (50 mL), sat. NaHCO₃ (50 mL), and then sat. brine (50 mL). The solution was dried (MgSO₄) and concentrated. Purification by FSC (gradient 0-100% EtOAc in heptane) gave the title compound (0.413 g, 72 %) as a colourless oil; ¹H NMR (CDCl₃) 1.68 (1H, t), 1.71-1.73 (1H, m), 1.73-
- 20 1.82 (3H, m), 1.82-1.9 (2H, m), 1.98 (2H, d), 2.75 (1H, tt), 3.06 (2H, td), 3.73 (2H, q), 4.03 (2H, d), 4.32 (2H, t), 6.70 (1H, d), 6.99 (1H, dd), 7.16 (1H, d), 7.43 (1H, dd), 7.62 (1H, d), 8.01 (1H, d); *m/z* ES⁺ [M+H]⁺ = 420.0.

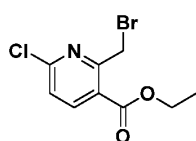
Intermediate 56f: 4-[4-[6-(4-Oxobutoxy)-3-pyridyl]-1-piperidyl]-2-(trifluoromethyl)benzonitrile



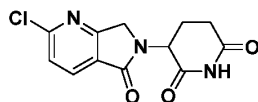
- Dess-Martin periodinane (228 mg, 0.54 mmol) was added to 4-(4-(6-(4-hydroxybutoxy)pyridin-3-yl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (205 mg, 0.49 mmol) in DCM (5 mL) at RT and the mixture was stirred for 1h. The mixture was then diluted with DCM (15 mL) and poured into mixture of sat. NaHCO₃ (25 mL) and sodium thiosulfate solution (25 mL). The resulting suspension was stirred vigorously for 10 mins and the
- 25 layers were separated. The organic portion was dried (Na₂SO₄) and concentrated to give the title compound (0.204 g, 100 %) as a yellow dry film, which was used without further purification; *m/z* ES⁺ [M+H]⁺ = 418.2.
- 30

Intermediate 56g: Ethyl 6-chloro-2-methylnicotinate

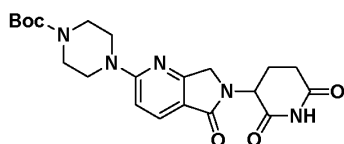
POCl₃ (61.7 mL, 662.28 mmol) was added to ethyl 2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (24 g, 132.46 mmol) at RT. The resulting solution was stirred at 100°C for 1h then concentrated. Purification by FSC (gradient: 0-20% EtOAc in petroleum ether) gave the title compound (23.00 g, 87 %) as a white solid; ¹H NMR (300 MHz) 1.32 (3H, t), 2.67 (3H, s), 4.31 (2H, q), 7.46 (1H, dd), 8.17 (1H, d); *m/z* ES⁺ [M+H]⁺ = 200.2.

Intermediate 56h: Ethyl 2-(bromomethyl)-6-chloronicotinate

AIBN (5.18 g, 31.56 mmol) was added to ethyl 6-chloro-2-methylnicotinate (21.0 g, 105.19 mmol) and NBS (28.1 g, 157.79 mmol) in CCl₄ (300 mL). The resulting mixture was stirred at 80°C for 16h and then concentrated. Purification by FSC (gradient: 0-10% EtOAc in petroleum ether) gave the title compound (28.0 g, 96 %) as a yellow oil; ¹H NMR (300 MHz) 1.34-1.38 (3H, m), 4.34-4.40 (2H, m), 4.93 (2H, s), 7.64 (1H, d), 8.29 (1H, d); *m/z* ES⁺ [M+H]⁺ = 278.

Intermediate 56i: 3-(2-Chloro-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione

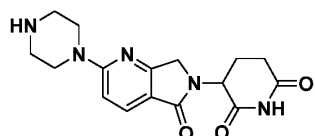
DIPEA (47.0 mL, 269.27 mmol) was added to ethyl 2-(bromomethyl)-6-chloronicotinate (25.00 g, 89.76 mmol) and 3-aminopiperidine-2,6-dione (9.20 g, 71.81 mmol) in DMF (250 mL). The resulting mixture was stirred at 40°C for 2h and then at 100°C for 16h before concentration under reduced pressure. Purification by FSC (gradient: 0-100% EtOAc in petroleum ether) gave material that was further purified by crystallisation from EtOAc to give the title compound (10.00 g, 40 %) as a purple solid; ¹H NMR: 1.96-2.08 (1H, m), 2.35-2.47 (1H, m), 2.56-2.66 (1H, m), 2.85-2.99 (1H, m), 4.39 (1H, d), 4.55 (1H, d), 5.17 (1H, dd), 7.67 (1H, d), 8.19 (1H, d), 11.02 (1H, s); *m/z* ES⁺ [M+H]⁺ = 280.1.

Intermediate 56j: *tert*-Butyl-4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)piperazine-1-carboxylate

DIPEA (1.40 mL, 7.79 mmol) was added to 3-(2-chloro-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-

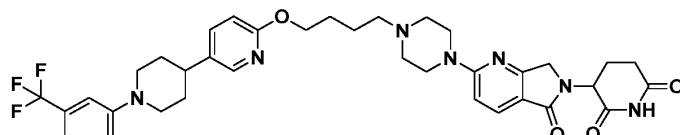
- 5 piperidine-2,6-dione (1.09 g, 3.90 mmol) and *tert*-butyl piperazine-1-carboxylate (0.726 g, 3.90 mmol) in DMSO (8 mL). The resulting mixture was stirred at 120°C for 3.5h in a microwave reactor. The mixture was then poured into ice water. A precipitate was collected by filtration and dried under vacuum for 2 days to give the title compound (0.950 g, 57 %) as a beige solid; ¹H NMR: 1.43 (9H, s), 1.97 (1H, dq), 2.34-2.44 (1H, m), 2.54-2.65 (1H, m), 2.83-2.98 (1H, m), 3.38-3.50 (4H, m), 3.57-3.74 (4H, m), 4.12 (1H, d), 4.29 (1H, d), 5.07 (1H, dd), 6.91 (1H, d), 7.80 (1H, d), 10.92 (1H, s); *m/z*: ES⁺ [M+H]⁺ 430.2.

Intermediate 56k: 3-(5-Oxo-2-(piperazin-1-yl)-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione



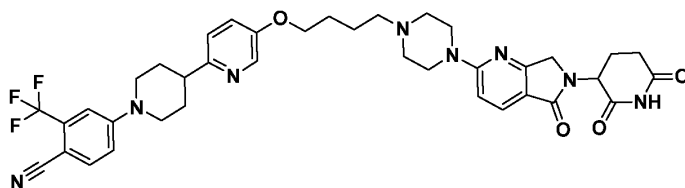
- 10 4M HCl in dioxane (8.7 mL, 34.93 mmol) was added in one portion to *tert*-butyl-4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-2-yl)piperazine-1-carboxylate (150 mg, 0.35 mmol) at RT and the mixture was stirred for 4h. The mixture was then concentrated to give the title compound as a bis-hydrochloride salt as a yellow solid that was used in the next step without further purification; ¹H NMR: 1.92-2.04 (1H, m), 2.39 (1H, dt), 2.62 (1H, s), 2.85-2.99 (1H, m), 3.20 (4H, br), 3.85-3.99 (4H, m), 4.15 (1H, d), 4.31 (1H, d), 5.09 (1H, dd), 7.01 (1H, d), 7.88 (1H, d), 9.13 (2H, s), 10.94 (1H, s); *m/z*: ES⁺ [M+H]⁺ 330.0.

Example 56: 4-{4-[6-(4-{4-[6-(2,6-Dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-2-yl]piperazin-1-yl}butoxy)pyridin-3-yl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile



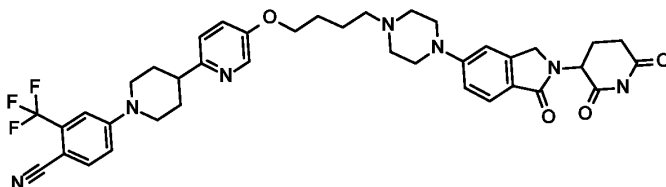
- 20 Intermediate 56f was reacted with Intermediate 56k using the general synthetic method illustrated by Example 2 to give the title compound after purification by HPLC (Column A, Eluent A, Basic Work-Up A); ¹H NMR: 1.54-1.62 (2H, m), 1.70 (2H, s), 1.71-1.78 (2H, m), 1.86 (2H, d), 1.93-2.01 (1H, m), 2.34-2.4 (3H, m), 2.42-2.47 (4H, m), 2.61 (1H, s), 2.86 (1H, s), 2.86-2.97 (1H, m), 3.05 (2H, t), 3.62 (4H, d), 4.11 (1H, d), 4.18 (2H, d), 4.22-4.35 (3H, m), 5.07 (1H, dd), 6.74 (1H, d), 6.90 (1H, d), 7.27 (1H, dd), 7.33 (1H, d), 7.61 (1H, dd), 7.77 (1H, d), 7.81 (1H, d), 8.04 (1H, d), 10.92 (1H, s); *m/z* ES⁺ [M+H]⁺ = 731.4.

Example 57: 4-{4-[5-(4-{4-[6-(2,6-Dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-2-yl]piperazin-1-yl}butoxy)pyridin-2-yl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile



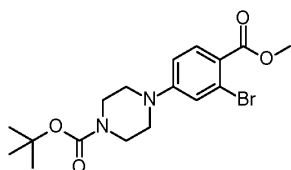
Intermediate 9e was reacted with Intermediate 56k using the general synthetic method illustrated by Example 5 to give the title compound (as a formate salt) after purification by flash C-18 chromatography (Eluent A: 0-11% MeCN in water (0.1% formic acid)); ¹H NMR: (300 MHz) 1.56-1.67 (2H, m), 1.67-1.84 (4H, m), 1.84-2.02 (3H, m), 2.32-2.50 (7H, m), 2.52-2.65 (1H, m), 2.82-3.00 (2H, m), 3.10 (2H, t), 3.62-3.65 (4H, m), 4.05 (2H, t), 4.10-4.22 (3H, m), 4.28 (1H, d), 5.07 (1H, dd), 6.90 (1H, d), 7.20-7.37 (4H, m), 7.79 (2H, dd), 8.20 (1H, d), 10.94 (1H, s); *m/z* ES⁺ [M+H]⁺ = 731.4.

Example 58: 4-{4-[5-(4-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl}butoxy)pyridin-2-yl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile



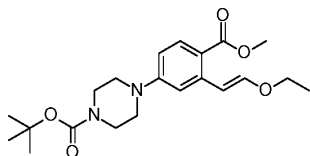
Intermediate 2c was reacted with Intermediate 9e using the general synthetic method illustrated by Example 5 to give the title compound (as a formate salt) after purification by flash C-18 chromatography (gradient: 0-21% MeCN in water (0.1% formic acid)); ¹H NMR: (300 MHz) 1.56-1.83 (6H, m), 1.83-2.03 (3H, m), 2.33-2.45 (4H, m), 2.52-2.65 (1H, m), 2.83-3.00 (2H, m), 3.09 (2H, t), 3.21-3.34 (7H, m), 4.06 (2H, t), 4.09-4.40 (4H, m), 5.05 (1H, dd), 7.06 (2H, d), 7.20-7.35 (4H, m), 7.50-7.56 (1H, m), 7.82 (1H, d), 8.20 (1H, d), 10.94 (1H, s); *m/z* ES⁺ [M+H]⁺ = 730.4.

Intermediate 59a: *tert*-Butyl 4-(3-bromo-4-(methoxycarbonyl)phenyl)piperazine-1-carboxylate



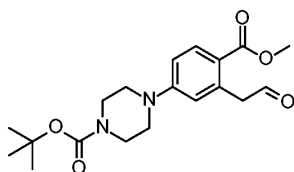
tert-Butyl piperazine-1-carboxylate (7.35 g, 39.48 mmol) was added to methyl 2-bromo-4-fluorobenzoate (9.2 g, 39.48 mmol) and DIPEA (6.90 mL, 39.48 mmol) in DMSO (180 mL) at RT. The resulting mixture was stirred at 120°C for 3h. The mixture was then poured into sat. brine (200 mL) and extracted with EtOAc (3 × 200 mL). The combined organic solutions were dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 10-40% EtOAc in petroleum ether) gave the title compound (8.10 g, 51%) as a yellow solid; *m/z* ES⁺ [M+H]⁺ = 399.

Intermediate 59b: *tert*-Butyl (*E*)-4-(3-(2-ethoxyvinyl)-4-(methoxycarbonyl)phenyl)piperazine-1-carboxylate



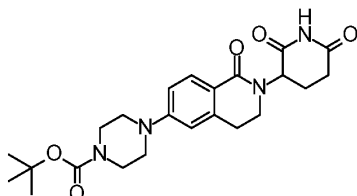
- 5 RuPhos Pd G3 (1.678 g, 2.00 mmol) was added to *tert*-butyl 4-(3-bromo-4-(methoxycarbonyl)phenyl)-piperazine-1-carboxylate (8.00 g, 20.04 mmol), (*E*)-2-(2-ethoxyvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7.94 g, 40.07 mmol) and Cs₂CO₃ (6.53 g, 20.04 mmol) in 1,4-dioxane (50 mL) and H₂O (50 mL) at RT under N₂. The resulting mixture was stirred at 80°C for 2h. The mixture was poured into sat. brine (300 mL) and extracted with EtOAc (3 × 300 mL). The combined organic solutions were dried (Na₂SO₄) and concentrated.
- 10 Purification by FSC (gradient: 10-40% EtOAc in petroleum ether) gave the title compound (7.68 g, 98 %) as a yellow oil; ¹H NMR: 1.27 (3H, t), 1.42 (9H, s), 3.28-3.30 (4H, m), 3.44-3.46 (4H, m), 3.74 (3H, s), 3.91 (2H, q), 6.75 (2H, t), 6.93 (1H, s), 7.16 (1H, d), 7.72 (1H, d); *m/z* ES⁺ [M+H]⁺ = 391.

Intermediate 59c: *tert*-Butyl 4-(4-(methoxycarbonyl)-3-(2-oxoethyl)phenyl)piperazine-1-carboxylate



- 15 *tert*-Butyl (*E*)-4-(3-(2-ethoxyvinyl)-4-(methoxycarbonyl)phenyl)piperazine-1-carboxylate (1.00 g, 2.56 mmol) was added to hydrochloric acid (1.5 mL, 1.50 mmol) in THF (10 mL) at RT. The resulting mixture was stirred at 40°C for 16h. The mixture was then poured into sat. NaHCO₃ solution (50 mL) and this mixture was extracted with EtOAc (2 × 100 mL). The combined organic solutions were dried (Na₂SO₄) and concentrated.
- 20 Purification by FSC (gradient: 20-50% EtOAc in petroleum ether) gave the title compound (0.47 g, 51%) as a pale yellow oil; ¹H NMR: 1.42 (9H, d), 3.30-3.47 (8H, m), 3.72 (3H, d), 3.98 (2H, s), 5.75 (1H, d), 6.84-6.94 (2H, m), 7.85 (1H, d), 9.64 (1H, s); *m/z* ES⁺ [M+H]⁺ = 363.

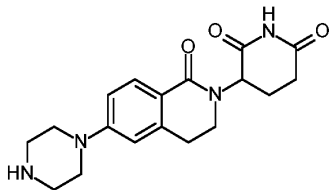
Intermediate 59d: *tert*-Butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)piperazine-1-carboxylate



- 25 *tert*-Butyl 4-(4-(methoxycarbonyl)-3-(2-oxoethyl)phenyl)piperazine-1-carboxylate (2.50 g, 6.90 mmol) was added to 3-amino-piperidine-2,6-dione hydrochloride salt (1.135 g, 6.90 mmol) in a mixture of IPA (15 mL)

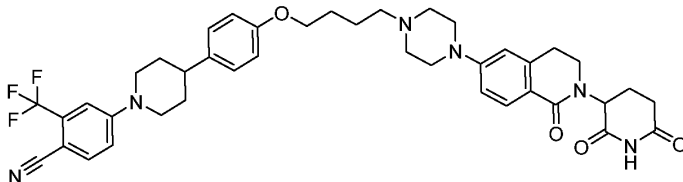
- and DCM (15 mL) at RT and the mixture was stirred for 1h. NaBH(OAc)₃ (2.92 g, 13.80 mmol) was then added and the mixture was stirred at 40°C for 16h then concentrated. Purification by FSC (gradient: 10-50% EtOAc in petroleum ether) gave the title compound (0.50 g, 16%) as a white solid; ¹H NMR: 1.42 (9H, s), 1.83-1.94 (1H, m), 2.37 (1H, ddd), 2.54 (1H, d), 2.86 (3H, dtd), 3.26-3.28 (4H, m), 3.34-3.52 (6H, m), 5.16 (1H, s), 6.78 (1H, s), 6.89 (1H, d), 7.70 (1H, d), 10.85 (1H, s); *m/z* ES⁺ [M+H]⁺ = 443.

Intermediate 59e: 3-(1-oxo-6-(piperazin-1-yl)-3,4-dihydroisoquinolin-2(1H)-yl)piperidine-2,6-dione



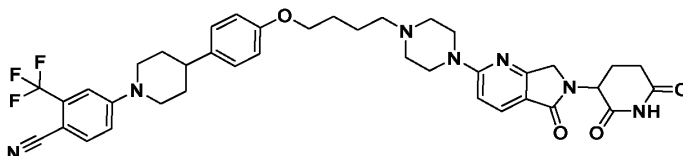
- tert*-Butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)piperazine-1-carboxylate (100 mg, 0.23 mmol) was added to HCl in 1,4-dioxane (3 mL, 12.00 mmol) at RT and the mixture was stirred for 1h. The crude mixture was triturated with Et₂O to give a solid which was collected by filtration and dried under vacuum to give the title compound (0.088 g, 114 %) as a white solid; ¹H NMR (300 MHz) 1.82-1.95 (1H, m), 2.30-2.44 (1H, m), 2.57 (1H, d), 2.71-3.02 (3H, m), 3.19-3.20 (4H, m), 3.36-3.61 (6H, m), 5.07-5.29 (1H, m), 6.86 (1H, d), 6.95 (1H, dd), 7.74 (1H, d), 9.21 (1H, br, s), 10.87 (1H, s) *m/z* ES⁺ [M+H]⁺ = 343.

Example 59: 4-{4-[4-(4-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl]piperazin-1-yl}butoxy)phenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile



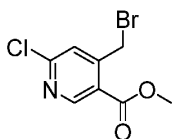
- Intermediate 50a was reacted with Intermediate 59e using the general synthetic method illustrated by Example 5 to give the title compound (as a formate salt) after purification by C-18 flash chromatography (Eluent: 5-50% MeCN in water (0.1% formic acid)); ¹H NMR: 1.53-1.68 (4H, m), 1.68-1.80 (2H, m), 1.79-1.97 (3H, m), 2.31-2.45 (2H, m), 2.53-2.69 (3H, m), 2.69-2.96 (5H, m), 3.04 (2H, t), 3.32-3.51 (8H, m), 3.97 (2H, t), 4.17 (2H, d), 5.16 (1H, s), 6.78 (1H, s), 6.87 (3H, t), 7.15 (2H, d), 7.26 (1H, d), 7.32 (1H, s), 7.69 (1H, d), 7.81 (1H, d), 10.84 (1H, s); *m/z* ES⁺ [M+H]⁺ = 743.3.

Example 60: 4-{4-[4-(4-{4-[6-(2,6-Dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl]piperazin-1-yl}butoxy)phenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile



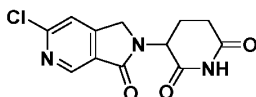
- Intermediate 50a was reacted with Intermediate 56k using the general synthetic method illustrated by Example 5 to give the title compound after purification by C-18 flash chromatography (Eluent: 0-40% MeCN in water (0.1% formic acid)); ^1H NMR: 1.54-1.67 (4H, m), 1.68-1.78 (2H, m), 1.84 (2H, d), 1.92-2.00 (1H, m), 2.31-2.42 (3H, m), 2.42-2.49 (4H, m), 2.54-2.69 (1H, m), 2.71-2.82 (1H, m), 2.83-2.97 (1H, m), 2.98-3.09 (2H, m), 3.57-3.71 (4H, m), 3.90-4.02 (2H, m), 4.05-4.32 (4H, m), 5.02-5.11 (1H, m), 6.82-6.93 (3H, m), 7.15 (2H, d), 7.26 (1H, d), 7.32 (1H, s), 7.73-7.84 (2H, m), 10.93 (1H, s); m/z ES^+ $[\text{M}+\text{H}]^+ = 730.5$.

Intermediate 61a: Methyl 4-(bromomethyl)-6-chloronicotinate



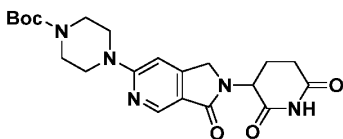
- 10 NBS (4.79 g, 26.94 mmol) was added to AIBN (0.885 g, 5.39 mmol) and methyl 6-chloro-4-methylnicotinate (5.00 g, 26.94 mmol) in CCl_4 (5 mL) at RT. The resulting mixture was stirred at 80°C for 4h then concentrated. Purification by flash C18-flash chromatography (gradient: 0-70% MeCN in water (0.1% formic acid)) gave the title compound (2.5 g, 35 %) as a white solid; m/z ES^+ $[\text{M}+\text{H}]^+ = 266$.

- 15 **Intermediate 61b: 3-(6-Chloro-3-oxo-1,3-dihydro-2H-pyrrolo[3,4-c]pyridin-2-yl)piperidine-2,6-dione**



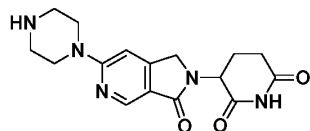
- DIPEA (4.95 mL, 28.4 mmol) was added to methyl 4-(bromomethyl)-6-chloronicotinate (2.50 g, 9.45 mmol) and 3-aminopiperidine-2,6-dione (1.82 g, 14.18 mmol) in DMF (10 mL) at RT under air. The resulting solution was stirred at 80°C for 15h then the mixture was then poured into water (20 mL). This mixture was extracted with EtOAc (3×20 mL), and the combined organic solutions were dried (Na_2SO_4) and concentrated. Purification by FSC (gradient: 0-100% EtOAc in petroleum ether) gave the title compound as a colourless solid which was used in the next step without further purification.

- 25 **Intermediate 61c: tert-Butyl 4-[2-(2,6-dioxo-3-piperidyl)-3-oxo-1-{H}-pyrrolo[3,4-c]pyridin-6-yl]piperazine-1-carboxylate**



- Pd-PEPPSI-*i*Pent (93 mg, 0.12 mmol) was added to 3-(6-chloro-3-oxo-1,3-dihydro-2H-pyrrolo[3,4-c]pyridin-2-yl)piperidine-2,6-dione (330 mg, 1.18 mmol), *tert*-butyl piperazine-1-carboxylate (330 mg, 1.77 mmol) and Cs_2CO_3 (1153 mg, 3.54 mmol) in 1,4-dioxane (3 mL) at RT under N_2 . The resulting solution was stirred at 100°C for 3h. Purification by FSC (gradient: 0-100% MeCN in water) gave the title compound (0.118 g, 23%) as a white solid; $[\text{M}+\text{H}]^+ = 430$.

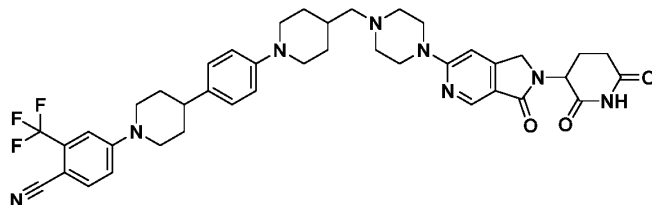
Intermediate 61d: 3-(3-Oxo-6-(piperazin-1-yl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridin-2-yl)piperidine-2,6-dione



5 *tert*-Butyl-4-(2-(2,6-dioxopiperidin-3-yl)-3-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)piperazine-1-carboxylate (118 mg, 0.27 mmol) was added to 4M HCl in 1,4-dioxane (2 mL) at RT under air and the mixture was stirred for 2h. The was then concentrated to give the title compound (0.110 g, 122 %) which was used in the next step without further purification; ¹H NMR (300 MHz) 1.90-2.01 (1H, m), 2.30-2.42 (1H, m), 2.55-2.65 (1H, m), 2.85-2.95 (1H, m), 3.17-3.19 (4H, m), 4.88-4.90 (4H, m), 4.38 (1H, d), 4.40 (1H, d), 5.08 (1H, d), 7.10 (1H, s), 8.50 (1H, s), 9.20-9.33 (2H, m), 11.00 (1H, s); *m/z* ES⁺, [M+H]⁺ = 330.

10

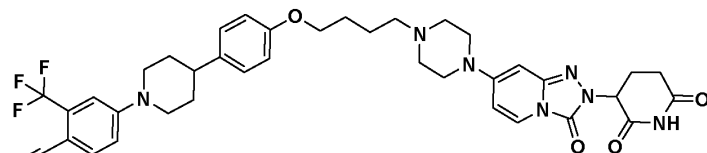
Example 61: 4-(4-{4-[4-{4-[2-(2,6-Dioxopiperidin-3-yl)-3-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl]-piperazin-1-yl}methyl]piperidin-1-yl}phenyl]piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



Intermediate 4c was reacted with Intermediate 61d using the general synthetic method illustrated by Example 2 to give the title compound after purification by preparative chiral-HPLC (Column: Viridis BEH 2-Ethylpyridine Prep OBD, 30*150mm, 5μm; Mobile Phase A: CO₂, Mobile Phase B: MeOH (8mmol/L NH₃.MeOH); Flow rate:50 mL/min; Gradient:28% B; 254 nm; RT1:6.18; Injection Volume:1 mL; Number Of Runs:10); ¹H NMR: (300 MHz) 1.11-1.41 (4H, m), 1.55-1.70 (2H, m), 1.70-2.00 (7H, m), 2.25-2.40 (3H, m), 2.60-2.80 (6H, m), 2.85-3.00 (2H, m), 3.02-3.15 (2H, m), 3.72 (4H, d), 4.13-4.31 (3H, m), 4.39 (1H, d), 5.06 (1H, dd), 6.88 (2H, d), 7.02-7.12 (3H, m), 7.22-7.38 (2H, m), 7.82 (1H, d), 8.49 (1H, s), 10.97 (1H, s); *m/z* ES⁺ [M+H]⁺ = 755.4.

20

Example 62: 4-{4-[4-(4-{4-[2-(2,6-Dioxopiperidin-3-yl)-3-oxo-2,3-dihydro[1,2,4]triazolo[4,3-a]pyridin-7-yl]-piperazin-1-yl}butoxy)phenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile

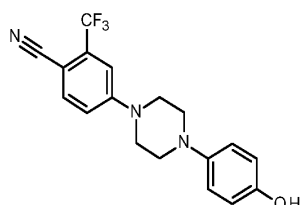


25

Intermediate 44e was reacted with Intermediate 50a using the general synthetic method illustrated by Example 12 to give the title compound after purification by HPLC (Column: DAICEL DCpak P4VP, 20mm*250mm, 5μm; Mobile Phase A:CO₂, Mobile Phase B:MeOH; Flow rate:50 mL/min; Gradient: 40% B; 254 nm; RT1:5.75; Injection Volume: 3 mL; Number Of Runs: 5; ¹H NMR: (300 MHz) 1.53-1.77 (6H, m), 1.84 (2H,

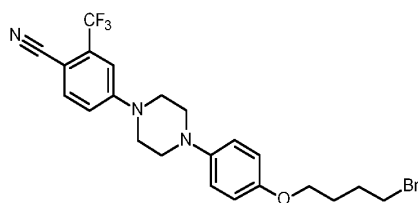
d), 2.07-2.18 (1H, m), 2.37 (2H, t), 2.42-2.50 (5H, m), 2.57-2.68 (1H, m), 2.69-2.97 (2H, m), 3.04 (2H, t), 3.20-3.27 (4H, m), 3.96 (2H, t), 4.18 (2H, d), 5.24 (1H, dd), 6.10 (1H, d), 6.69 (1H, dd), 6.86 (2H, d), 7.15 (2H, d), 7.27 (1H, dd), 7.33 (1H, d), 7.72 (1H, d), 7.82 (1H, d), 11.06 (1H, s); m/z ES⁺ [M+H]⁺ = 731.4.

5 Intermediate 63a: 4-(4-(4-Hydroxyphenyl)piperazin-1-yl)-2-(trifluoromethyl)benzonitrile



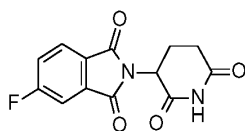
DIPEA (1.47 mL, 8.42 mmol), 4-fluoro-2-(trifluoromethyl)benzonitrile (1.06 g, 5.61 mmol) and 4-(piperazin-1-yl)phenol (1.00 g, 5.61 mmol) were dissolved in DMSO (5 mL). The mixture was stirred at RT overnight. Water (20 mL) was then added to give a suspension. The suspension was stirred at RT for 20 mins. A solid was collected by filtration, washed with water (50 mL) and hexanes (50 mL) to give the title compound (1.58 g, 81 %) as a cream solid; ¹H NMR (CDCl₃) 3.21 (4H, dd), 3.54 (4H, dd), 5.10 (1H, d), 6.77-6.84 (2H, m), 6.87-6.91 (2H, m), 7.01 (1H, dd), 7.18 (1H, d), 7.65 (1H, d); m/z : ES⁺ [M+H]⁺ 348.4.

15 Intermediate 63b: 4-[4-[4-(4-Bromobutoxy)phenyl]piperazin-1-yl]-2-(trifluoromethyl)benzonitrile



4-(4-(4-Hydroxyphenyl)piperazin-1-yl)-2-(trifluoromethyl)benzonitrile (0.520 g, 1.50 mmol), K₂CO₃ (0.248 g, 1.80 mmol) and 1,4-dibromobutane (0.358 mL, 2.99 mmol) were dissolved in anhydrous DMF (20 mL) under N₂ and the mixture was stirred for 18h. The mixture was then warmed to 50°C for 16h. The mixture was then diluted with EtOAc (50 mL), washed with sat. NaHCO₃ (50 mL) and brine (50 mL) and then dried (MgSO₄). Purification by FSC (gradient: 0-50% EtOAc in heptane) gave the title compound (0.214 g, 30 %) as a yellow oil; ¹H NMR (CDCl₃) 1.86-1.99 (2H, m), 2.02-2.14 (2H, m), 3.21-3.23 (4H, m), 3.48 (2H, t), 3.52-3.58 (4H, m), 3.97 (2H, t), 6.88 (2H, s), 6.89-6.95 (2H, m), 7.01 (1H, dd), 7.18 (1H, d), 7.65 (1H, d); m/z : ES⁺ [M+H]⁺ 483.9.

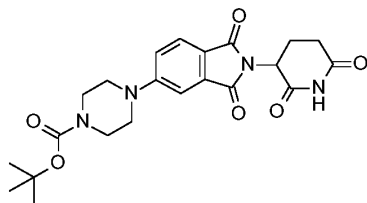
25 Intermediate 63c: 2-(2,6-dioxopiperidin-3-yl)-5-fluoroisindoline-1,3-dione



To a solution of 5-fluoroisobenzofuran-1,3-dione (7.50 g, 45.2 mmol) in AcOH (100 mL) was added sodium

acetate (7.41 g, 90.3 mmol) and 3-aminopiperidine-2,6-dione hydrochloride (7.43 g, 45.2 mmol). The resulting mixture was stirred at 120°C for 18h then concentrated. The residue was poured into water (200 mL) and stirred for 10 mins. A solid was collected by filtration, washed with water (2 × 50 mL) and dried under vacuum to give the title compound (11.8 g, 94 %) as a white solid; ¹H NMR: 2.03-2.12 (1H, m), 2.52-2.66 (2H, m), 2.90 (1H, ddd), 5.17 (1H, dd), 7.73 (1H, ddd), 7.85 (1H, dd), 8.01 (1H, dd), 11.12 (1H, s); *m/z*: ES- [M-H]⁻ 275.1.

Intermediate 63d: *tert*-Butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)piperazine-1-carboxylate

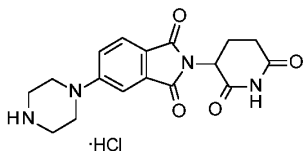


10

tert-Butyl piperazine-1-carboxylate (2.97 g, 15.9 mmol), 2-(2,6-dioxopiperidin-3-yl)-5-fluoroisindoline-1,3-dione (4.00 g, 14.5 mmol), DIPEA (7.80 mL, 43.4 mmol) and NMP (60 mL) were heated in a microwave reactor at 140°C for 2h. The mixture was then cooled to RT, diluted with water (100 mL) and extracted with EtOAc (2 × 100 mL). The combined organic solutions were washed with brine (2 × 50 mL), dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-100% EtOAc in heptane) gave the title compound (3.95 g, 62 %) as a yellow solid; ¹H NMR: 1.43 (9H, s), 2.03 (1H, ddd), 2.53-2.65 (2H, m), 2.77-2.97 (1H, m), 3.48 (8H, s), 5.08 (1H, dd), 7.25 (1H, dd), 7.35 (1H, d), 7.70 (1H, d), 11.06 (1H, s).

15

Intermediate 63e: 2-(2,6-Dioxopiperidin-3-yl)-5-(piperazin-1-yl)isindoline-1,3-dione



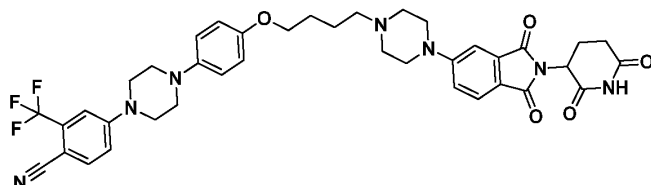
20

4M HCl in dioxane (22.3 mL, 89.3 mmol) was added to *tert*-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)piperazine-1-carboxylate (3.95 g, 8.93 mmol) in DCM (100 mL) at RT and the mixture was stirred for 18h. Concentration under reduced pressure then gave the title compound as a hydrochloride salt (3.40 g, 100 %) as a pale yellow solid; ¹H NMR: 2.04 (1H, ddd), 2.55-2.65 (2H, m), 2.90 (1H, ddd), 3.22 (4H, s), 3.67-3.73 (4H, m), 5.09 (1H, dd), 7.33 (1H, dd), 7.46 (1H, d), 7.75 (1H, d), 9.22 (2H, s), 11.07 (1H, s); *m/z*: ES⁺ [M+H]⁺ 343.2.

25

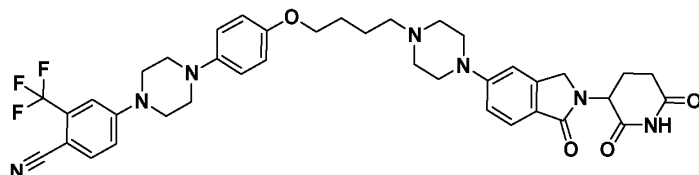
30

Example 63: 4-{4-[4-(4-[2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isindol-5-

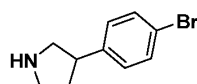
yl}piperazin-1-yl}butoxy)phenyl}piperazin-1-yl}-2-(trifluoromethyl)benzonitrile

Intermediate 63b was reacted with Intermediate 63e using the general synthetic method illustrated by Example 5 to give the title compound after purification by HPLC (Column A, Eluent A); ¹H NMR: (CDCl₃) 1.71 (2H, p), 1.78-1.9 (2H, m), 2.09-2.18 (1H, m), 2.43-2.49 (2H, m), 2.57-2.64 (4H, m), 2.66-2.94 (3H, m), 3.22 (4H, dd), 3.39-3.46 (4H, m), 3.51-3.59 (4H, m), 3.97 (2H, t), 4.93 (1H, dd), 6.85-6.9 (2H, m), 6.9-6.95 (2H, m), 7.03 (2H, ddd), 7.18 (1H, d), 7.28 (1H, d), 7.67 (2H, dd), 7.96 (1H, s); *m/z* (ES-) [M-H]⁻ = 742.1.

Example 64: 4-([4-[4-(2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl}butoxy)phenyl]piperazin-1-yl)-2-(trifluoromethyl)benzonitrile

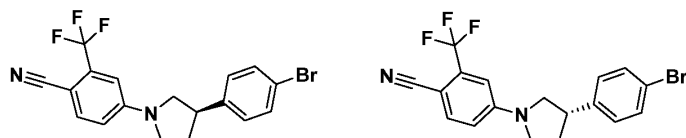


Intermediate 63b was reacted with Intermediate 2c using the general synthetic method illustrated by Example 5 to give the title compound (as a formate salt) after purification by HPLC (Column A, Eluent A); ¹H NMR: (CDCl₃) 1.81-1.87 (2H, m), 1.88 (1H, s), 2.21 (1H, ddq), 2.33 (1H, qd), 2.82 (1H, d), 2.85 (1H, s), 2.88-2.9 (2H, m), 2.93 (1H, s), 3.01-3.04 (4H, m), 3.22 (4H, dd), 3.47-3.52 (4H, m), 3.52-3.57 (4H, m), 3.96 (2H, t), 4.27 (1H, d), 4.42 (1H, d), 5.20 (1H, dd), 6.82-6.88 (2H, m), 6.89 (1H, s), 6.91-6.95 (2H, m), 7.00 (2H, ddd), 7.18 (1H, d), 7.65 (1H, d), 7.76 (1H, d), 8.03 (1H, s), 8.16 (2H, s); *m/z* ES⁺ [M+H]⁺ = 730.1.

Intermediate 65a: 3-(4-Bromophenyl)pyrrolidine

1-Bromopyrrolidine-2,5-dione (10.00 g, 56.18 mmol) was added to 3-phenylpyrrolidine (10.00 g, 67.93 mmol) and H₂SO₄ (53.00 g, 540.42 mmol) in water (53 mL) at RT. The resulting mixture was stirred at 70°C for 2h. The reaction was then quenched with sat. Na₂CO₃ solution. The resulting mixture was extracted with EtOAc and the combined extract solution were dried (Na₂SO₄) and concentrated to give the title compound as a brown liquid which was used in the next step without further purification; *m/z* ES⁺ [M+H]⁺ = 226.

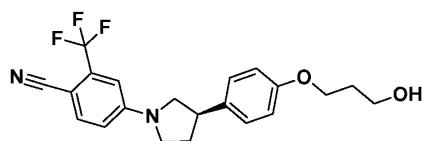
Intermediates 65b and 65c: 4-[(3*r*)-3-(4-Bromophenyl)pyrrolidin-1-yl]-2-(trifluoromethyl)benzonitrile and 4-[(3*s*)-3-(4-bromophenyl)pyrrolidin-1-yl]-2-(trifluoromethyl)benzonitrile (Absolute configurations not yet established)



- 5 Cs₂CO₃ (28.80 g, 88.45 mmol) was added to 4-fluoro-2-(trifluoromethyl)benzonitrile (12.55 g, 66.34 mmol) and 3-(4-bromophenyl)pyrrolidine (10.00 g, 44.22 mmol) in DMF (100 mL) at RT. The resulting mixture was stirred at 60°C for 2h. The mixture was then concentrated and diluted with EtOAc. The resulting solution was washed with water, dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-10% EtOAc in petroleum ether) gave material that was further purified by SFC (Column: CHIRALPAK AD-H SFC, 5*25cm, 5µm; Mobile Phase A:CO₂, Mobile Phase B:MeOH (2mM NH₃-MeOH); Flow rate:150 mL/min; Gradient:40% B; 220 nm; **65b** RT1:6.85 min; **65c** RT2:7.97 min) to give the title compounds: Intermediate **65b** (1.90 g, 11 %) as a pale yellow solid and Intermediate **65c** (2.200 g, 13 %) as a pale yellow solid.
- 10 Intermediate 65b: ¹H NMR: (300 MHz) 2.01-2.17 (1H, m), 2.35-2.46 (1H, m), 3.40-3.67 (4H, m), 3.82-3.94 (1H, m), 6.87 (1H, dd), 6.95 (1H, d), 7.33 (2H, d), 7.54 (2H, d), 7.80 (1H, d); 99% ee.
- Intermediate 65c: ¹H NMR (300 MHz) 2.01-2.14 (1H, m), 2.35-2.44 (2H, m), 3.43-3.65 (3H, m), 3.84-3.93 (1H, m), 6.88 (1H, dd), 6.95 (1H, d), 7.33 (2H, d), 7.54 (2H, d), 7.80 (1H, d); *m/z* ES⁺ [M+H]⁺ = 395; >99% ee.

15

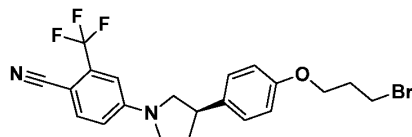
Intermediate 65d: (R)-4-(3-(4-(3-Hydroxypropoxy)phenyl)pyrrolidin-1-yl)-2-(trifluoromethyl)benzonitrile



- 20 RockPhos Pd G3 (63.6 mg, 0.08 mmol) was added to (*r*)-4-(3-(4-bromophenyl)pyrrolidin-1-yl)-2-(trifluoromethyl)benzonitrile (Intermediate 65b) (300 mg, 0.76 mmol), propane-1,3-diol (87 mg, 1.14 mmol) and Cs₂CO₃ (742 mg, 2.28 mmol) in 1,4-dioxane (5 mL) at RT under N₂. The resulting mixture was stirred at 100°C for 16h. Purification by FSC (gradient: 0-10% MeOH in DCM) gave material which was further purified by FSC (gradient 0-40% EtOAc in petroleum ether) to give the title compound (210 mg, 71%) as a yellow liquid; *m/z* ES⁺ [M+H]⁺ = 391.

25

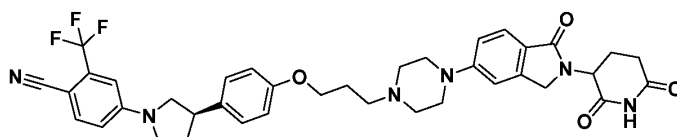
Intermediate 65e: (r)-4-(3-(4-(3-Bromopropoxy)phenyl)pyrrolidin-1-yl)-2-(trifluoromethyl)benzonitrile



- 30 PPh₃ (282 mg, 1.08 mmol) was added to CBr₄ (357 mg, 1.08 mmol) and (*r*)-4-(3-(4-(3-hydroxypropoxy)-phenyl)pyrrolidin-1-yl)-2-(trifluoromethyl)benzonitrile (210 mg, 0.54 mmol) in DCM (5 mL) at RT and the mixture was stirred for 16h. Purification by FSC (gradient: 0-30% EtOAc in petroleum ether) gave the title compound (135 mg, 55 %) as a yellow liquid. ¹H NMR (300 MHz) 2.01-2.17 (1H, m), 2.24 (2H, p), 2.32-2.43

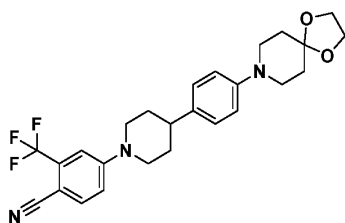
(1H, m), 3.32-3.44 (1H, m), 3.43-3.55 (2H, m), 3.60 (1H, d), 3.67 (2H, t), 3.86 (1H, dd), 4.07 (2H, t), 6.87 (1H, dd), 6.93 (2H, d), 6.95 (1H, s), 7.28 (2H, d), 7.80 (1H, d); m/z ES⁺ [M+H]⁺ = 453.

- 5 **Example 65: 4-((3*r*)-3-[4-(3-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazin-1-yl}propoxy)phenyl]pyrrolidin-1-yl)-2-(trifluoromethyl)benzonitrile** (Absolute configuration not yet established).



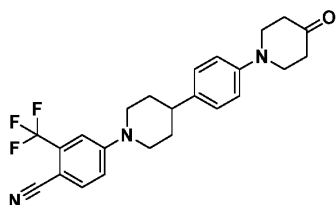
- 10 Intermediate 2c was reacted with Intermediate 65e using the general synthetic method illustrated by Example 5 to give the title compound after purification by C18-flash chromatography (gradient: 5-50% MeCN in water (0.1% formic acid)); ¹H NMR: (300 MHz) 1.85-2.15 (4H, m), 2.30-2.44 (2H, m), 2.52-2.67 (5H, m), 2.91 (1H, ddd), 3.31 (7H, d), 3.40-3.55 (2H, m), 3.55-3.68 (1H, m), 3.78-3.91 (1H, m), 4.02 (2H, t), 4.15-4.38 (2H, m), 5.05 (1H, dd), 6.83-6.98 (4H, m), 7.07 (2H, d), 7.26 (2H, d), 7.53 (1H, d), 7.80 (1H, d), 10.96 (1H, s); m/z ES⁺ [M+H]⁺ = 701.2.

- 15 **Intermediate 66a: 4-(4-(4-(1,4-Dioxo-8-azaspiro[4.5]decan-8-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile**



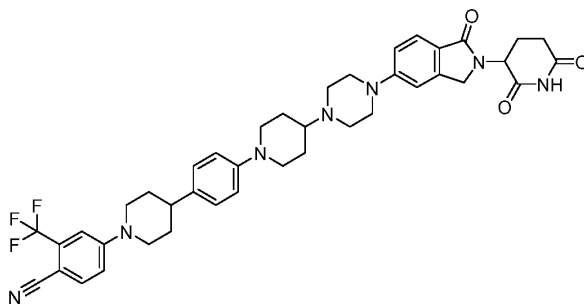
- 20 BrettPhos Pd G3 (177 mg, 0.20 mmol) was added to 4-(4-(4-bromophenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (800 mg, 1.95 mmol), 1,4-dioxo-8-azaspiro[4.5]decan-8-yl (420 mg, 2.93 mmol) and Cs₂CO₃ (1911 mg, 5.86 mmol) in 1,4-dioxane (30 mL) under N₂. The resulting mixture was stirred at 100°C for 3h. The mixture was concentrated and diluted with EtOAc (50 mL). This solution was washed with water (50 mL × 2), dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-10% MeOH in DCM) gave the title compound (750 mg, 81 %) as a yellow solid; ¹H NMR (CDCl₃) 1.77 (2H, dd), 1.80-1.89 (4H, m), 1.99 (2H, d), 2.64-2.79 (1H, m), 3.07 (2H, t), 3.28-3.38 (4H, m), 4.00-4.02 (4H, m), 4.05 (2H, s), 6.92 (2H, d), 7.00 (1H, dd), 7.11 (2H, d), 7.17 (1H, d), 7.63 (1H, d).
- 25

Intermediate 66b: 4-(4-(4-(4-Oxopiperidin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



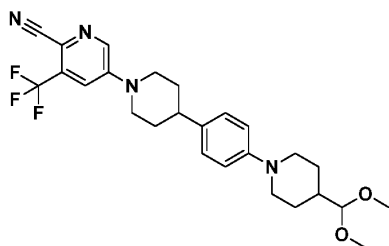
- Formic acid (17.08 mL, 445.36 mmol) was added to 4-(4-(4-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (700 mg, 1.48 mmol) in MeOH (20 mL). The resulting mixture was stirred at 60°C for 2 days and then concentrated. The residue was dissolved in EtOAc (50 mL). The resulting solution was washed with sat. NaHCO₃ (50 mL × 2), dried (Na₂SO₄) and concentrated to give the title compound (600 mg, 95 %) as a yellow gum; *m/z* ES⁺ [M+Na]⁺ = 450.

Example 66: 4-{4-[4-(4-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl]piperidin-1-yl]phenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile



- Intermediate 2c was reacted with Intermediate 66b using the general synthetic method illustrated by Example 2 to give the title compound after purification by C18-flash chromatography (0-100% MeCN in water); ¹H NMR: (300 MHz) 1.40-1.67 (4H, m), 1.73-2.02 (5H, m), 2.23-2.43 (3H, m), 2.54-2.78 (6H, m), 2.77-2.93 (1H, m), 3.02 (2H, t), 3.19-3.32 (5H, m), 3.61-3.72 (2H, m), 4.10-4.39 (4H, m), 5.03 (1H, dd), 6.86 (2H, d), 7.00-7.11 (4H, m), 7.25 (1H, dd), 7.31 (1H, d), 7.50 (1H, d), 7.79 (1H, d), 10.94 (1H, s); *m/z* ES⁺ [M+H]⁺ = 740.4.

Intermediate 67a: 5-(4-(4-(4-(Dimethoxymethyl)piperidin-1-yl)phenyl)piperidin-1-yl)-3-(trifluoromethyl)picolinonitrile

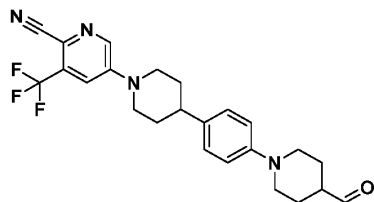


- Ruphos Pd G3 (65.3 mg, 0.08 mmol) was added to 5-(4-(4-bromophenyl)piperidin-1-yl)-3-(trifluoromethyl)picolinonitrile (320 mg, 0.78 mmol), 4-(dimethoxymethyl)piperidine (124 mg, 0.78 mmol), Cs₂CO₃ (254 mg, 0.78 mmol) and Ruphos (36.4 mg, 0.08 mmol) in 1,4-dioxane (5 mL) at RT under N₂. The resulting solution

was stirred at 100°C for 10h and then concentrated. Purification by FSC (gradient: 0-30% EtOAc in petroleum ether) gave the title compound (200 mg, 53%) as a yellow solid; ¹H NMR (300 MHz) 1.18-1.38 (2H, m), 1.55-1.72 (5H, m), 1.82 (2H, d), 2.50-2.59 (2H, m), 2.64-2.80 (1H, m), 3.08 (2H, t), 3.25 (6H, s), 3.61 (2H, d), 4.06 (1H, d), 4.19-4.32 (2H, m), 6.83 (2H, d), 7.06 (2H, d), 7.61 (1H, d), 8.63 (1H, d); *m/z* ES⁺ [M+H]⁺ = 489.

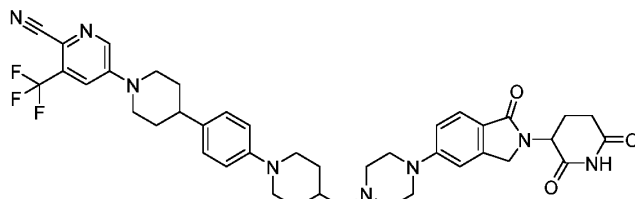
5

Intermediate 67b: 5-(4-(4-(4-Formylpiperidin-1-yl)phenyl)piperidin-1-yl)-3-(trifluoromethyl)picolinonitrile



- 10 5-(4-(4-(4-(Dimethoxymethyl)piperidin-1-yl)phenyl)piperidin-1-yl)-3-(trifluoromethyl)picolinonitrile (190 mg, 0.39 mmol) was stirred in formic acid (2 mL) at RT for 2h. The mixture was then concentrated to dryness and the resulting residue was dissolved in EtOAc (25 mL). This solution was washed with sat. NaHCO₃ (20 mL × 3) then sat. brine (20 mL × 2), dried (Na₂SO₄) and concentrated to give the title compound (140 mg, 81 %) which was used in the next step without further purification; *m/z* ES⁺ [M+H]⁺ = 443.2.

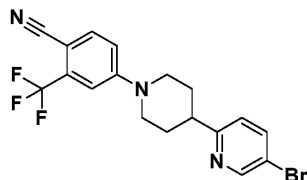
- 15 **Example 67: 5-(4-{4-[4-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazin-1-yl}methoxy]piperidin-1-yl}phenyl}piperidin-1-yl)-3-(trifluoromethyl)pyridine-2-carbonitrile**



- 20 Intermediate 2c was reacted with Intermediate 67b using the general synthetic method illustrated by Example 2 to give the title compound (as a formate salt) after purification preparative HPLC (Column: Sunfire prep C18 column, 30*150, 5um; Mobile Phase A: Water(0.1% formic acid), Mobile Phase B: MeCN; Flow rate: 60 mL/min; Gradient: 26 B to 40 B in 7 min; 254/220 nm; RT1: 5.55 and MeCN as eluents); ¹H NMR: (300 MHz) 1.29-1.46 (2H, m), 1.56-1.75 (2H, m), 1.80-1.92 (4H, m), 1.92-2.09 (2H, m), 2.26-2.47 (3H, m), 2.58-2.95 (5H, m), 3.04-3.30 (9H, m), 3.96-4.08 (2H, m), 4.21-4.42 (5H, m), 5.08 (1H, dd), 6.98 (2H, d), 7.12-7.23 (4H, m), 7.58-7.66 (2H, m), 8.66 (1H, d), 10.97 (1H, s); *m/z* ES⁺ [M+H]⁺ = 755.4.

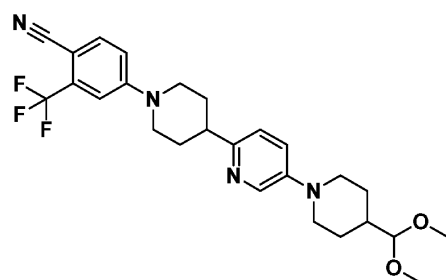
25

Intermediate 68a: 4-(4-(5-Bromopyridin-2-yl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



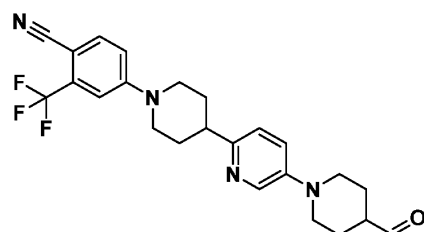
- 5-Bromo-2-(piperidin-4-yl)pyridine (486 mg, 2.02 mmol) was added to 4-fluoro-2-(trifluoromethyl)benzonitrile (400 mg, 2.12 mmol) and Cs_2CO_3 (1.723 g, 5.29 mmol) in DMSO (5 mL) at RT. The resulting mixture was stirred at 60°C for 16h. The mixture was then diluted with EtOAc (50 mL), washed with water (50 mL $\times$ 3) then sat. brine (50 mL $\times$ 2), dried (Na_2SO_4) and concentrated. Purification by FSC (gradient: 0-10% EtOAc in petroleum ether) gave the title compound (224 mg, 31%) as a white solid; m/z ES^+ $[\text{M}+\text{H}]^+ = 410$.

Intermediate 68b: 4-(4-(5-(4-(Dimethoxymethyl)piperidin-1-yl)pyridin-2-yl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



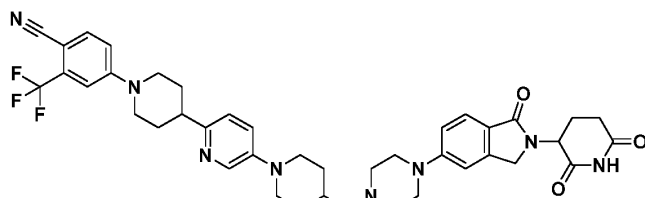
- 10 Ruphos Pd G3 (40.8 mg, 0.05 mmol) was added to 4-(dimethoxymethyl)piperidine (116 mg, 0.73 mmol), Cs_2CO_3 (477 mg, 1.46 mmol) and 4-(4-(5-bromopyridin-2-yl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (200 mg, 0.49 mmol) in dioxane (5 mL) at RT under N_2 . The resulting mixture was stirred at 100°C for 16h and then concentrated. Purification FSC (gradient: 0-80% EtOAc in petroleum ether) gave the title compound
- 15 (0.160 g, 67 %) as a yellow solid; ^1H NMR (300 MHz) 1.21-1.40 (2H, m), 1.59-1.77 (5H, m), 1.88 (2H, d), 2.61 (2H, dd), 2.83-2.98 (1H, m), 3.08 (2H, t), 3.26 (6H, s), 3.68 (2H, d), 4.08 (1H, d), 4.15 (2H, d), 7.10 (1H, d), 7.21-7.30 (2H, m), 7.31 (1H, d), 7.80 (1H, d), 8.17 (1H, d); m/z ES^+ $[\text{M}+\text{H}]^+ = 489$.

Intermediate 68c: 4-(4-(5-(4-formylpiperidin-1-yl)pyridin-2-yl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



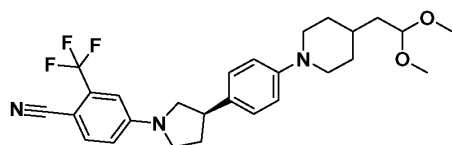
- 20 4-(4-(5-(4-(Dimethoxymethyl)piperidin-1-yl)pyridin-2-yl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (150 mg, 0.31 mmol) was added to formic acid (5 mL, 0.31 mmol) at RT and the mixture was stirred for 4h. The reaction was then quenched with sat. NaHCO_3 and extracted with EtOAc. The combined organic solutions
- 25 were dried (Na_2SO_4) and concentrated to give the title compound (0.160 g, 118 %) as yellow gum, which was used in the next step without further purification; ^1H NMR (300 MHz) 1.52-1.78 (6H, m), 1.84-1.93 (3H, m), 2.74-2.88 (2H, m), 3.08 (3H, t), 3.59 (2H, dt), 4.16 (2H, d), 7.11 (1H, d), 7.22-7.35 (3H, m), 7.81 (1H, d), 8.20 (1H, d), 9.63 (1H, s); m/z ES^+ $[\text{M}+\text{H}]^+ = 443$.

Example 68: 4-(4-{5-[4-({4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl)methyl]piperidin-1-yl}pyridin-2-yl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



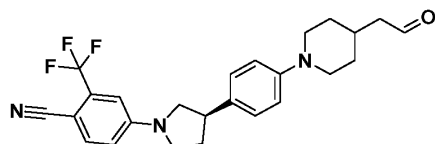
- 5 Intermediate 2c was reacted with Intermediate 68c using the general synthetic method illustrated by Example 2 to give the title compound after purification by HPLC (Column: Sunfire prep C18 column, 30*150, 5µm; Mobile Phase A: Water (0.1% formic acid), Mobile Phase B: MeCN; Flow rate:60 mL/min; Gradient:15 B to 25 B in 7 min; 254/220 nm; RT1:7.52); ¹H NMR: (300 MHz) 1.10-1.32 (2H, m), 1.66-1.97 (8H, m), 2.23 (2H, d), 2.37 (1H, dd), 2.59-2.77 (3H, m), 2.82-2.95 (2H, m), 3.09 (2H, t), 3.25-3.60 (8H, m), 3.69 (2H, d), 4.12-4.39 (4H, m), 5.06 (1H, dd), 7.04-7.15 (3H, m), 7.25-7.34 (3H, m), 7.53 (1H, d), 7.82 (1H, d), 8.20 (1H, d), 10.96 (1H, s); *m/z* ES⁺ [M+H]⁺ = 755.4.
- 10

Intermediate 69a: 4-[(3*r*)-3-[4-[4-(2,2-Dimethoxyethyl)-1-piperidyl]phenyl]pyrrolidin-1-yl]-2-(trifluoromethyl)benzonitrile



- 15 Ruphos Pd G3 (85 mg, 0.10 mmol) was added to Ruphos (47.2 mg, 0.10 mmol), 4-(2,2-dimethoxyethyl)-piperidine (259 mg, 1.49 mmol), Cs₂CO₃ (989 mg, 3.04 mmol) and 4-[(3*r*)-3-(4-bromophenyl)pyrrolidin-1-yl]-2-(trifluoromethyl)benzonitrile (Intermediate 65b) (400 mg, 1.01 mmol) in 1,4-dioxane (10 mL) at RT under N₂. The resulting mixture was stirred at 100°C for 16h and then concentrated. Purification by FSC
- 20 (gradient: 0-25% EtOAc in petroleum ether) gave the title compound (0.140 g, 28 %) as a yellow solid; ¹H NMR (300 MHz) 1.22-1.32 (3H, m), 1.46 (3H, d), 1.72 (2H, d), 1.99-2.10 (1H, m), 2.24-2.36 (1H, m), 2.49-2.63 (2H, m), 3.20 (6H, s), 3.36-3.51 (2H, m), 3.52-3.65 (3H, m), 3.74-3.86 (1H, m), 4.46 (1H, t), 6.80-6.93 (4H, m), 7.15 (2H, d), 7.77 (1H, d); *m/z* ES⁺, [M+H]⁺ = 488.

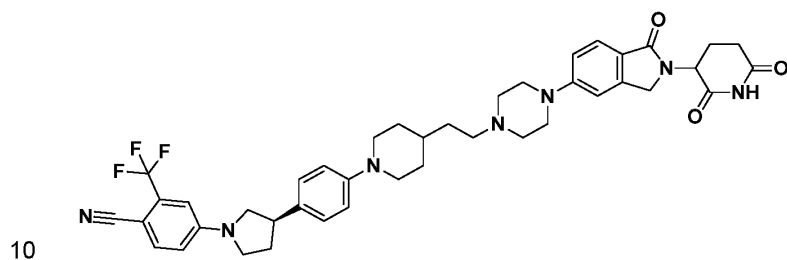
25 Intermediate 69b: (*r*)-4-(3-[4-(4-(2-Oxoethyl)piperidin-1-yl]phenyl)pyrrolidin-1-yl)-2-(trifluoromethyl)benzonitrile



4-[(3*r*)-3-[4-[4-(2,2-Dimethoxyethyl)-1-piperidyl]phenyl]pyrrolidin-1-yl]-2-(trifluoromethyl)benzonitrile (140 mg, 0.29 mmol) was added to formic acid (5 mL) at RT and the mixture was stirred for 2h. The reaction was

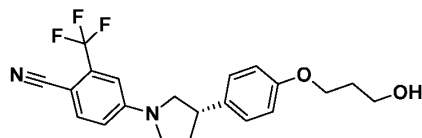
- then quenched with sat. NaHCO_3 and the resulting mixture was extracted with EtOAc. The combined organic solutions were dried (Na_2SO_4) and concentrated to give the title compound (0.157 g, 124 %) as yellow solid, which was used directly in the next step; ^1H NMR (300 MHz) 1.23-1.32 (2H, m), 1.72 (2H, d), 1.89-2.12 (2H, m), 2.24-2.38 (1H, m), 2.40 (2H, dd), 2.56-2.71 (2H, m), 3.35-3.53 (2H, m), 3.53-3.67 (3H, m), 3.76-3.88 (1H, m), 4.22 (1H, t), 6.83-6.95 (4H, m), 7.17 (2H, d), 7.78 (1H, d), 9.70 (1H, t); m/z ES^+ , $[\text{M}+\text{H}]^+ = 442$.

Example 69: 4-[(3*r*)-3-{4-[4-(2-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]-piperazin-1-yl}ethyl)piperidin-1-yl]phenyl}pyrrolidin-1-yl]-2-(trifluoromethyl)benzonitrile (Absolute stereochemistry not yet confirmed)



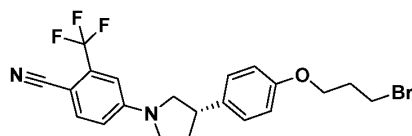
- Intermediate 2c was reacted with Intermediate 69b using the general synthetic method illustrated by Example 2 to give the title compound after purification by HPLC (Column: Sunfire prep C18 column, 30*150, 5 μm ; Mobile Phase A: Water (0.1% formic acid), Mobile Phase B: MeCN; Flow rate: 60 mL/min; Gradient: 20 B to 30 B in 7 min; 254/220 nm; RT: 8.33); ^1H NMR: 1.20-1.33 (2H, m), 1.30-1.50 (3H, m), 1.77 (2H, d), 1.91-2.01 (1H, m), 2.01-2.11 (1H, m), 2.29-2.44 (5H, m), 2.52-2.66 (4H, m), 2.91 (1H, ddd), 3.22-3.33 (8H, m), 3.40-3.80 (4H, m), 3.78-3.90 (1H, m), 4.21 (1H, d), 4.33 (1H, d), 5.05 (1H, dd), 6.82-6.96 (4H, m), 7.06 (2H, d), 7.17 (2H, d), 7.52 (1H, d), 7.79 (1H, d), 10.96 (1H, s); m/z ES^+ $[\text{M}+\text{H}]^+ = 754.3$.

- Intermediate 70a: (s)-4-(3-(4-(3-Hydroxypropoxy)phenyl)pyrrolidin-1-yl)-2-(trifluoromethyl)benzonitrile** (Absolute stereochemistry not yet confirmed)



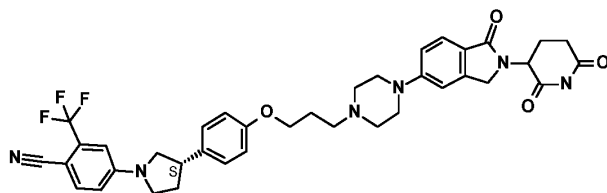
- RockPhos Pd G3 (63.6 mg, 0.08 mmol) was added to (s)-4-(3-(4-bromophenyl)pyrrolidin-1-yl)-2-(trifluoromethyl)benzonitrile (Intermediate 65c) (300 mg, 0.76 mmol), propane-1,3-diol (87 mg, 1.14 mmol) and Cs_2CO_3 (742 mg, 2.28 mmol) in 1,4-dioxane (5 mL) at RT under N_2 . The resulting mixture was stirred at 100°C for 16h and then concentrated. Purification by FSC (gradient: 0-30% EtOAc in petroleum ether) gave the title compound (120 mg, 41 %) as a white solid; ^1H NMR: 1.84 (2H, p), 2.06 (1H, ddd), 2.37 (1H, ddt), 3.32 (1H, s), 3.43-3.57 (4H, m), 3.60 (1H, ddd), 3.85 (1H, dd), 4.01 (2H, t), 4.53 (1H, t), 6.83-6.92 (3H, m), 6.94 (1H, d), 7.25 (2H, d), 7.79 (1H, d); m/z ES^+ $[\text{M}+\text{H}]^+ = 391$.

- Intermediate 70b: (s)-4-(3-(4-(3-Bromopropoxy)phenyl)pyrrolidin-1-yl)-2-(trifluoromethyl)benzonitrile**



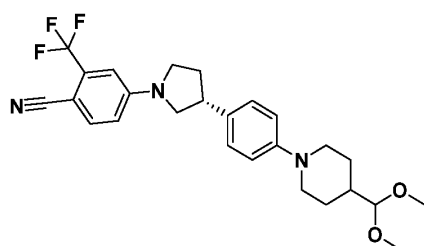
- 5 PPh₃ (134 mg, 0.51 mmol) was added to (S)-4-(3-(4-(3-hydroxypropoxy)phenyl)pyrrolidin-1-yl)-2-(trifluoromethyl)benzonitrile (100 mg, 0.26 mmol) and CBr₄ (170 mg, 0.51 mmol) in DCM (3 mL) at RT. The mixture was stirred for 1h, concentrated. Purification by FSC (gradient: 0-20% EtOAc in petroleum ether) gave the title compound (101 mg, 87 %) as a colourless gum; ¹H NMR: 2.01-2.14 (1H, m), 2.23 (2H, p), 2.37 (1H, dtd), 3.33-3.36 (1H, m), 3.41-3.56 (2H, m), 3.60 (1H, ddd), 3.66 (2H, t), 3.85 (1H, dd), 4.06 (2H, t), 6.87 (1H, dd), 6.91-6.96 (3H, m), 7.27 (2H, d), 7.79 (1H, d); *m/z* ES⁺ [M+H]⁺ = 453.

- 10 **Example 70: 4-((3S)-3-[4-(3-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl}propoxy)phenyl]pyrrolidin-1-yl)-2-(trifluoromethyl)benzonitrile** (Absolute stereochemistry not yet confirmed)



- Intermediate 2c was reacted with Intermediate 70b using the general synthetic method illustrated by Example 2 to give the title compound after purification by HPLC (Column: Sunfire prep C18 column, 30*150, 5μm; Mobile Phase A: Water(0.1% formic acid), Mobile Phase B: MeCN; Flow rate:60 mL/min; Gradient:30 B to 40 B in 7 min; 254/220 nm; RT1:5.23); ¹H NMR: (300 MHz) 1.84-2.05 (3H, m), 2.10 (1H, dd), 2.26-2.40 (3H, m), 2.51-2.65 (4H, m), 2.91 (1H, m), 3.25-3.48 (9H, m), 3.60 (1H, ddd), 3.85 (1H, dd), 4.02 (2H, t), 4.21-4.33 (2H, m), 5.06 (1H, dd), 6.82-6.94 (4H, m), 7.07 (2H, d), 7.22-7.31 (2H, m), 7.53 (1H, d), 7.79 (1H, d), 10.96 (1H, s); *m/z* ES⁺ [M+H]⁺ = 701.3.

- 20 **Intermediate 71a: (R)-4-(3-(4-(4-(Dimethoxymethyl)piperidin-1-yl)phenyl)pyrrolidin-1-yl)-2-(trifluoromethyl)benzonitrile**

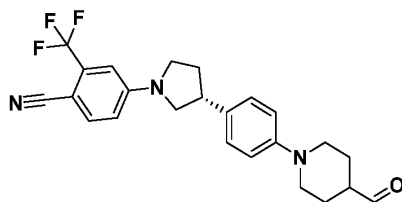


- 25 Ruphos Pd G3 (85 mg, 0.10 mmol) was added to Ruphos (47.2 mg, 0.10 mmol), 4-(dimethoxymethyl)-piperidine (259 mg, 1.49 mmol), Cs₂CO₃ (989 mg, 3.04 mmol) and (R)-4-(3-(4-Bromophenyl)pyrrolidin-1-yl)-2-(trifluoromethyl)benzonitrile (Intermediate 65b) (400 mg, 1.01 mmol) was added to 1,4-dioxane (10 mL) at RT. The resulting solution was stirred at 100°C for 16h. Purification by FSC (gradient: 0-20% EtOAc in

petroleum ether) gave the title compound (207 mg, 86 %) as a yellow solid; ^1H NMR (300 MHz) 0.85-0.97 (1H, m) 1.13-1.43 (3H, m), 1.70 (3H, d), 1.97-2.15 (1H, m), 2.36 (1H, d), 2.60 (1H, d), 3.27 (6H, s), 3.46 (1H, d), 3.54-3.67 (2H, m), 3.69 (1H, s), 3.77-3.89 (1H, m), 4.08 (1H, d), 6.85-6.91 (3H, m), 7.17 (2H, d), 7.79 (1H, d); m/z ES⁺ [M+H]⁺ = 474.

5

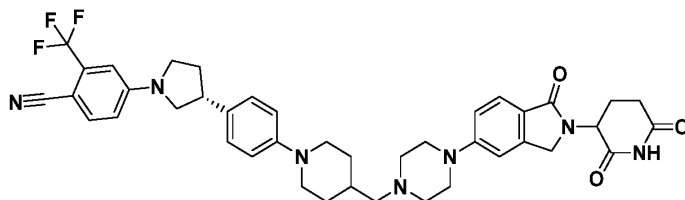
Intermediate 71b: (*r*)-4-(3-(4-(4-Formylpiperidin-1-yl)phenyl)pyrrolidin-1-yl)-2-(trifluoromethyl)benzonitrile



(*r*)-4-(3-(4-(4-(Dimethoxymethyl)piperidin-1-yl)phenyl)pyrrolidin-1-yl)-2-(trifluoromethyl)benzonitrile (180 mg, 0.38 mmol) was added to formic acid (5 mL) at RT and the mixture was stirred for 1h. The reaction was then quenched with sat. NaHCO₃. The resulting mixture was extracted with EtOAc, and the organic extract solution was dried (Na₂SO₄) and concentrated to give the title compound (204 mg, 126 %) as yellow gum, which was used in the next step without further purification; ^1H NMR (300 MHz) 1.48-1.71 (3H, m), 1.86-1.97 (2H, m), 1.96-2.12 (1H, m), 2.26-2.41 (1H, m), 2.74-2.85 (2H, m), 3.35-3.53 (2H, m), 3.56 (3H, dt), 3.76-3.88 (1H, m), 4.22 (1H, t), 6.81-6.95 (4H, m), 7.18 (2H, d), 7.78 (1H, d), 9.63 (1H, s); m/z ES⁺ [M+H]⁺ = 428.

15

Example 71: 4-[(3*r*)-3-{4-[4-{(4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]-piperazin-1-yl)methyl]piperidin-1-yl}phenyl]pyrrolidin-1-yl]-2-(trifluoromethyl)benzonitrile (Absolute stereochemistry not yet confirmed)

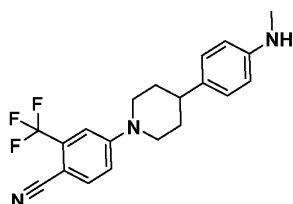


20

Intermediate 2c was reacted with Intermediate 71b using the general synthetic method illustrated by Example 2 to give the title compound after purification by HPLC (Column A, Eluent A); ^1H NMR: (300 MHz) 1.11-1.34 (2H, m), 1.65-1.88 (3H, m), 1.94-2.14 (2H, m), 2.22-2.43 (4H, m), 2.52-2.73 (6H, m), 2.82-3.00 (1H, m), 3.40-3.51 (7H, m), 3.54-3.74 (4H, m), 3.83 (1H, dd), 4.16-4.41 (2H, m), 5.06 (1H, dd), 6.83-6.97 (4H, m), 7.08 (2H, d), 7.18 (2H, d), 7.54 (1H, d), 7.79 (1H, d), 10.96 (1H, s); m/z ES⁺ [M+H]⁺ = 740.3.

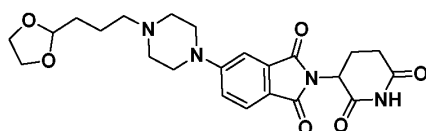
25

Intermediate 72a: 4-(4-(4-(Methylamino)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



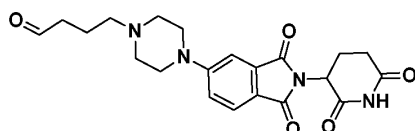
- 5 Cs₂CO₃ (1194 mg, 3.67 mmol) was added to 4-(4-(4-bromophenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (500 mg, 1.22 mmol) and methanamine 2M solution in THF (794 μL, 1.59 mmol) in 1,4-dioxane (5.3 mL). The reaction was degassed and BrettPhos Pd G3 (55.4 mg, 0.06 mmol) and BrettPhos (32.8 mg, 0.06 mmol) were added. The resulting mixture was stirred under N₂ at 80°C for 18h. The reaction was then quenched with water (50 mL). The resulting mixture was extracted with EtOAc (3 × 50 mL) and the combined organic solutions were dried (MgSO₄) and concentrated. Purification by FSC (gradient: 0-50% 3:1 EtOAc/EtOH in EtOAc) gave the title compound (318 mg, 72 %) as a beige solid; ¹H NMR: 1.58 (2H, qd), 1.82 (2H, d), 2.64 (3H, d), 2.65-2.7 (1H, m), 2.95-3.1 (2H, m), 4.15 (2H, d), 5.39 (1H, q), 6.47 (2H, d), 6.97 (2H, d), 7.26 (1H, dd), 7.31 (1H, d), 7.80 (1H, d); *m/z*: ES⁺ [M+H]⁺ 359.6.

Intermediate 72b: 5-(4-(3-(1,3-Dioxolan-2-yl)propyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione



- 15 2-(2,6-Dioxopiperidin-3-yl)-5-(piperazin-1-yl)isoindoline-1,3-dione hydrochloride salt (250 mg, 0.66 mmol), 2-(3-bromopropyl)-1,3-dioxolane (0.134 mL, 0.99 mmol), KI (329 mg, 1.98 mmol) and DIPEA (0.461 mL, 2.64 mmol) were dissolved in MeCN (10 mL) and stirred at 70°C for 4h. After cooling to RT, water (10 mL) was added. This mixture was extracted with DCM (2 × 50 mL) and the combined organic solutions were dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-10% MeOH in DCM) gave the title compound
- 20 (220 mg, 73 %) as a yellow solid; ¹H NMR (CDCl₃) 1.62-1.68 (2H, m), 1.69-1.76 (2H, m), 2.07-2.18 (1H, m), 2.40-2.49 (2H, m), 2.55-2.63 (4H, m), 2.67-2.8 (1H, m), 2.8-2.94 (2H, m), 3.40-3.46 (4H, m), 3.83-3.89 (2H, m), 3.95-4.01 (2H, m), 4.85-4.98 (2H, m), 7.05 (1H, dd), 7.28 (1H, d), 7.69 (1H, d), 8.00 (1H, s); *m/z*: ES⁺ [M+H]⁺ 457.4.

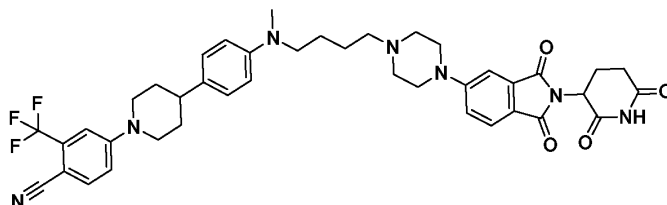
Intermediate 72c: 4-(4-(2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)piperazin-1-yl)butanal



- Formic acid (2 mL) was added to 5-(4-(3-(1,3-dioxolan-2-yl)propyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (125 mg, 0.27 mmol) at RT under air. The resulting solution was stirred at 40°C for 0.5h then diluted with toluene (3 mL). The solvent was removed under reduced pressure and the resulting
- 30 residue was dissolved in toluene (3 mL) and then concentrated again to give the title compound as a yellow

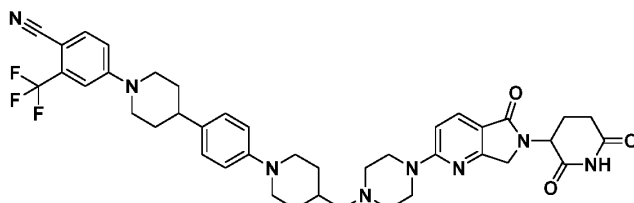
gum (assumed 100% yield) which was used in the next step without further purification; m/z : $ES^+ [M+H]^+$ 413.

5 **Example 72: 4-(4-{4-[4-(2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl}butyl)(methyl)amino]phenyl}piperidin-1-yl)-2-(trifluoromethyl)benzonitrile**



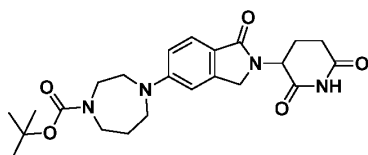
Intermediate 72a was reacted with Intermediate 72c using the general synthetic method illustrated by Example 2 to give the title compound (as a formate salt) after purification by HPLC (Column A, Eluent A). ^1H NMR: 1.52 (4H, d), 1.55-1.64 (2H, m), 1.83 (2H, d), 2.01 (1H, dd), 2.36 (2H, d), 2.50 (4H, s), 2.55-2.67 (1H, m), 2.67-2.74 (1H, m), 2.85 (3H, s), 2.86-2.94 (1H, m), 3.03 (2H, t), 3.30 (3H, t), 3.41-3.47 (4H, m), 4.15 (2H, d), 5.07 (1H, dd), 6.65 (2H, d), 7.04 (2H, d), 7.25 (2H, dd), 7.32 (2H, dd), 7.68 (1H, d), 7.80 (1H, d), 8.16 (2H, s), 11.06 (1H, s); m/z $ES^+ [M+H]^+ = 756.0$.

15 **Example 73: 4-(4-{4-[4-(6-(2,6-Dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl]piperazin-1-yl}methyl)piperidin-1-yl}phenyl}piperidin-1-yl)-2-(trifluoromethyl)benzonitrile**



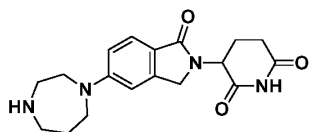
Intermediate 4c was reacted with Intermediate 56k using the general synthetic method illustrated by Example 2 to give the title compound after purification by HPLC (Column: Sunfire prep C18 column, 30*150, 5 μ m; Mobile Phase A: Water (0.1% formic acid), Mobile Phase B: MeCN; Flow rate: 60 mL/min; Gradient: 25 B to 35 B in 7 min; 254/220 nm; RT1: 6.95); ^1H NMR: (300 MHz) 1.22 (2H, q), 1.52-1.69 (3H, m), 1.77-1.87 (4H, m), 1.92-2.03 (1H, m), 2.21 (2H, d), 2.36 (1H, dd), 2.45 (3H, t), 2.52-2.77 (4H, m), 2.82-3.10 (3H, m), 3.64 (7H, m), 4.04-4.34 (4H, m), 5.08 (1H, dd), 6.89 (3H, dd), 7.08 (2H, d), 7.23-7.36 (2H, m), 7.80 (2H, dd), 10.96 (1H, s); m/z $ES^+ [M+H]^+ = 755.4$.

25 **Intermediate 74a: tert-Butyl-4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)-1,4-diazepane-1-carboxylate**



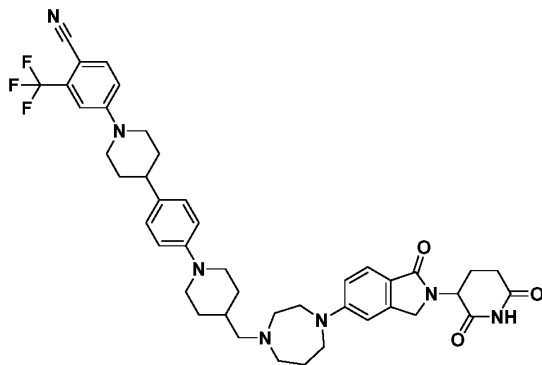
- 5 Pd-PEPPSI Ipent (0.123 g, 0.15 mmol) was added to 3-(5-bromo-1-oxoisindolin-2-yl)piperidine-2,6-dione (1.00 g, 3.09 mmol), *tert*-butyl 1,4-diazepane-1-carboxylate (0.806 g, 4.02 mmol) and Cs₂CO₃ (3.02 g, 9.28 mmol) in 1,4-dioxane (15 mL) at RT under N₂. The resulting mixture was stirred at 90°C for 16h. After cooling the mixture was poured into DCM (200 mL). The resulting solution was washed with 5% AcOH (200 mL) then water (200 mL), dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-10% EtOH in EtOAc) gave the title compound (0.400 g, 29 %) as a white solid; *m/z* ES⁺ [M+H]⁺ = 443.

Intermediate 74b: 3-(5-(1,4-Diazepan-1-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione



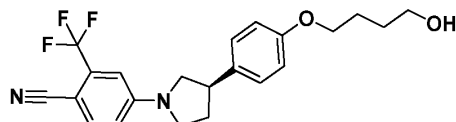
- 10 *tert*-Butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)-1,4-diazepane-1-carboxylate (390 mg, 0.88 mmol) was added to hydrochloric acid (0.134 mL, 4.41 mmol) in 1,4-dioxane (5 mL) at RT and the mixture was stirred for 2h. The mixture was then concentrated to give the title compound as a hydrochloride salt (300 mg, 99 %) as brown solid that was used in the next step without further purification; ¹H NMR (300 MHz)
- 15 1.90-1.98 (1H, m), 2.03-2.15 (2H, m), 2.35 (1H, qd), 2.57 (1H, d), 2.89 (1H, ddd), 2.99-3.11 (2H, m), 3.14-3.26 (2H, m), 3.59 (2H, t), 3.80 (2H, t), 4.18 (1H, d), 4.30 (1H, d), 5.02 (1H, dd), 6.85-6.93 (2H, m), 7.50 (1H, d), 9.27 (1H, s), 10.92 (1H, s); *m/z* ES⁺ [M+H]⁺ = 343.

Example 74: 4-(4-{4-[4-(2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isindol-5-yl)-1,4-diazepan-1-yl]methyl}phenyl)piperidin-1-yl}phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



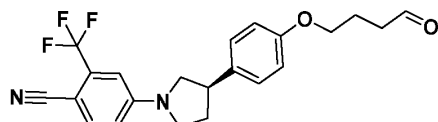
- 20 Intermediate 4c was reacted with Intermediate 74b using the general synthetic method illustrated by Example 2 to give the title compound after purification by HPLC (Column: Sunfire prep C18 column, 30*150, 5μm; Mobile Phase A: Water (0.1% formic acid), Mobile Phase B: MeCN; Flow rate: 60 mL/min; Gradient: 25 B to 35 B in 7 min; 254/220 nm; RT: 7.70); ¹H NMR: (300 MHz) 1.02-1.21 (2H, m), 1.46-2.00 (11H, m), 2.20-2.40
- 25 (4H, m), 2.49-2.61 (3H, m), 2.63-2.77 (3H, m), 2.82-3.07 (3H, m), 3.48-3.66 (6H, m), 4.15 (3H, d), 4.28 (1H, d), 5.01 (1H, dd), 6.76-6.85 (4H, m), 7.05 (2H, d), 7.20-7.34 (2H, m), 7.45 (1H, d), 7.79 (1H, d), 10.92 (1H, s); *m/z* ES⁺ [M+H]⁺ = 768.4.

Intermediate 75a: 4-[(3*r*)-3-[4-(4-Hydroxybutoxy)phenyl]pyrrolidin-1-yl]-2-(trifluoromethyl)benzonitrile



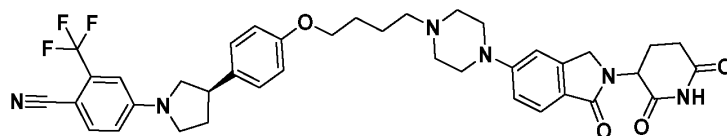
- Rockphos Pd G3 (83.8 mg, 0.10 mmol) was added to Cs₂CO₃ (975 mg, 2.99 mmol), butane-1,4-diol (135 mg, 1.50 mmol) and 4-[(3*r*)-3-(4-bromophenyl)pyrrolidin-1-yl]-2-(trifluoromethyl)benzonitrile (Intermediate 65b) (400 mg, 1.01 mmol) in dioxane (10 mL). The resulting mixture was stirred at 100°C for 16h and then concentrated. Purification by FSC (gradient: 0-25% EtOAc in petroleum ether) gave the title compound (0.204 g, 50 %) as a yellow liquid; ¹H NMR: 1.51-1.59 (2H, m), 1.69-1.77 (2H, m), 2.02-2.14 (1H, m), 2.31-2.43 (1H, m), 3.39-3.53 (5H, m), 3.61 (1H, t), 3.85 (1H, dd), 3.96 (2H, t), 4.23 (1H, t), 6.84-6.92 (3H, m), 6.94 (1H, d), 7.23-7.28 (2H, m), 7.80 (1H, d).

Intermediate 75b: (*r*)-4-(3-[4-(4-Oxobutoxy)phenyl]pyrrolidin-1-yl)-2-(trifluoromethyl)benzonitrile

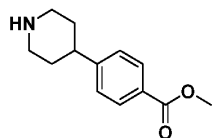


- Dess-Martin periodinane (450 mg, 1.06 mmol) was added to 4-[(3*r*)-3-[4-(4-hydroxybutoxy)phenyl]pyrrolidin-1-yl]-2-(trifluoromethyl)benzonitrile (203.8 mg, 0.50 mmol) in DCM (5 mL) at RT and the mixture was stirred for 1h. The mixture was then quenched with sat. NaHCO₃. The resulting mixture was extracted with DCM, and the organic extract solution was dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-25% EtOAc in petroleum ether) gave the title compound (0.094 g, 46 %) as a brown liquid; ¹H NMR: 1.91-2.02 (3H, m), 2.03-2.11 (1H, m), 2.37 (1H, dtd), 2.59 (2H, td), 3.41-3.55 (2H, m), 3.60 (1H, ddd), 3.84 (1H, dd), 3.96 (2H, t), 6.84-6.91 (3H, m), 6.94 (1H, d), 7.26 (2H, d), 7.79 (1H, d), 9.71 (1H, t); *m/z* ES⁺ [M+H]⁺ = 403.

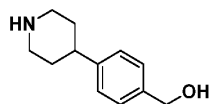
Example 75: 4-[(3*R*)-3-[4-(4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazin-1-yl)butoxy]phenyl]pyrrolidin-1-yl]-2-(trifluoromethyl)benzonitrile (Absolute stereochemistry not yet confirmed)



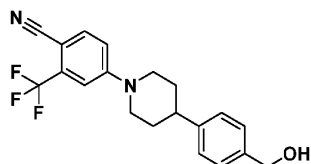
- Intermediate 2c was reacted with Intermediate 75b using the general synthetic method illustrated by Example 2 to give the title compound after purification by HPLC (Column A, Eluent A); ¹H NMR: 1.65-1.75 (4H, m), 1.92-2.08 (2H, m), 2.32-2.41 (5H, m), 2.57-2.61 (7H, m), 2.91 (1H, m), 3.48-3.61 (5H, m), 3.85 (1H, m), 3.99 (2H, t), 4.21 (1H, d), 4.33 (1H, d), 5.05 (1H, m), 6.83-6.95 (4H, m), 7.06-7.08 (2H, s), 7.22-7.30 (2H, m), 7.53 (1H, d), 7.80 (1H, d), 10.96 (1H, s); *m/z* ES⁺ [M+H]⁺ = 715.3.

Intermediate 76a: Methyl 4-(piperidin-4-yl)benzoate

- 5 SOCl₂ (24.15 g, 203.03 mmol) was added to 4-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)benzoic acid (12.40 g, 40.61 mmol) in MeOH (20 mL) at 0°C under air. The resulting solution was then stirred at 70°C for 15h and then concentrated to give the title compound (8.70 g, 39.7 mmol); ¹H NMR (CD₃OD) 1.86-2.04 (2H, m), 2.11 (2H, d), 3.02 (1H, tt), 3.17 (2H, t), 3.53 (2H, d), 3.91 (3H, s), 7.37-7.47 (2H, m), 7.95-8.05 (2H, m); *m/z* ES⁺, [M+H]⁺ = 220.

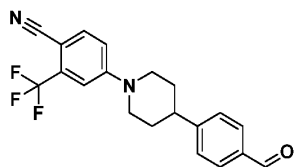
Intermediate 76b: 4-(Piperidin-4-yl)phenyl)methanol

- 10 LiAlH₄ (2.5M in THF, 176 mL, 198.35 mmol) was added to methyl 4-(piperidin-4-yl)benzoate (8.70 g, 39.67 mmol) in THF (90 mL) at 0°C. The mixture was then stirred at RT for 2h then quenched by addition of Na₂SO₄·H₂O. The mixture was then filtered and the filtrate was concentrated. Purification by FSC (gradient: 0-20% MeOH in DCM (containing 0.3% Et₃N)) gave the title compound (7.40 g, 97%) as a white solid; ¹H NMR (CD₃OD, 300 MHz) 1.67 (2H, qd), 1.76-1.87 (2H, m), 2.65 (1H, dt), 2.70-2.80 (2H, m), 3.15 (2H, dt), 4.58 (2H, s), 7.23 (2H, d), 7.30 (2H, d); *m/z* ES⁺, [M+H]⁺ = 192.
- 15

Intermediate 76c: 4-(4-(4-(Hydroxymethyl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile

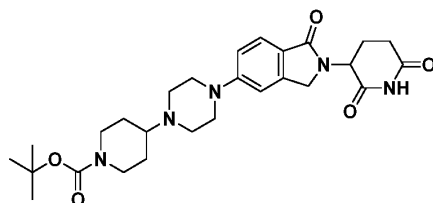
- 20 4-Fluoro-2-(trifluoromethyl)benzonitrile (6.72 g, 35.55 mmol) was added to Cs₂CO₃ (34.70 g, 106.65 mmol) and (4-(piperidin-4-yl)phenyl)methanol (6.80 g, 35.55 mmol) in DMF (50 mL) at RT under air and the mixture was stirred for 15h. The mixture was then diluted with EtOAc (150 mL), washed with sat. brine (100 mL × 3), dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-60% EtOAc in petroleum ether) gave the title compound (9.20 g, 72 %) as a white solid; ¹H NMR (CD₃OD, 300 MHz) 1.78 (2H, qd), 1.90-2.03 (2H, m), 2.76-2.91 (1H, m), 3.09 (2H, tt), 4.07-4.24 (2H, m), 4.58 (2H, s), 7.14-7.26 (3H, m), 7.27-7.35 (3H, m), 7.69 (1H, dd); *m/z* ES⁺, [M+H]⁺ = 361.
- 25

Intermediate 76d: 4-(4-(4-Formylphenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



Dess-Martin Periodinane (15.36 g, 36.21 mmol) was added to 4-(4-(4-(hydroxymethyl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (8.70 g, 24.14 mmol) in DCM (5 mL) at RT under air and the mixture was stirred for 3h. The mixture was then diluted with DCM (50 mL), washed with sat. brine (50 mL $\times$ 7), dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-50% EtOAc in petroleum ether) gave the title compound (5.30 g, 61 %) as a white solid; ¹H NMR (CD₃OD) 1.77-1.91 (2H, m), 2.01 (2H, ddd), 2.99 (1H, tt), 3.13 (2H, td), 4.20 (2H, dp), 7.23 (1H, dd), 7.32 (1H, d), 7.47-7.53 (2H, m), 7.72 (1H, d), 7.85-7.91 (2H, m), 9.96 (1H, s).

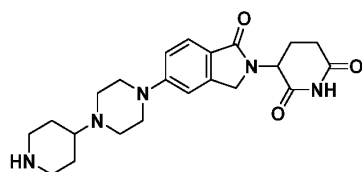
10 **Intermediate 76e: *tert*-Butyl 4-(4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazin-1-yl)piperidine-1-carboxylate**



NaBH(OAc)₃ (3.23 g, 15.23 mmol) was added to 3-(1-oxo-5-(piperazin-1-yl)isindolin-2-yl)piperidine-2,6-dione (1.0 g, 3.05 mmol), *tert*-butyl 4-oxopiperidine-1-carboxylate (0.607 g, 3.05 mmol) and Ti(OEt)₄ (1.389 g, 6.09 mmol) in 1,2-dichloroethane (50 mL) at RT and the mixture was stirred for 3h. The mixture was then poured into water (100 mL) and the resulting mixture was filtered through celite. The filtrate was extracted with DCM (2 $\times$ 100 mL), and the combined organic solutions were dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-10% MeOH in DCM) gave the title compound (0.500 g, 32 %) as a yellow solid; *m/z* ES⁺, [M+H]⁺ = 512.

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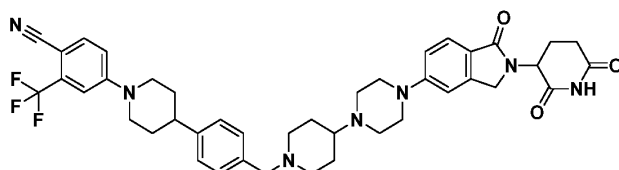
Intermediate 76f: 3-(1-Oxo-5-(4-(piperidin-4-yl)piperazin-1-yl)isindolin-2-yl)piperidine-2,6-dione



4M HCl in 1,4-dioxane (1.955 mL, 7.82 mmol) was added dropwise to *tert*-butyl 4-(4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazin-1-yl)piperidine-1-carboxylate (400 mg, 0.78 mmol) in DCM (20 mL) over a period of 2 mins and the mixture was stirred at RT for 2h. Concentration under reduced pressure then gave the title compound as a hydrochloride salt (300 mg, 79 %) as a white solid; *m/z* ES⁺, [M+H]⁺ = 412.

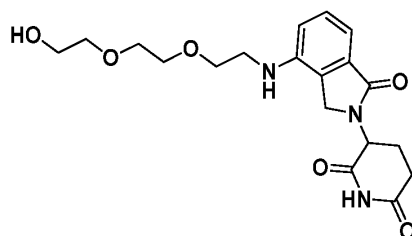
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Example 76: 4-(4-{4-[4-(4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isindol-5-yl]piperazin-1-

yl)piperidin-1-yl)methyl]phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile

- Intermediate 76d was reacted with Intermediate 76f using the general synthetic method illustrated by Example 2 to give the title compound (as a formate salt) after purification by HPLC (Column A, Eluent A). t: ¹H NMR: 1.43 (2H, q), 1.65 (2H, td), 1.75 (2H, d), 1.87 (2H, d), 1.91-2.01 (3H, m), 2.22 (1H, d), 2.36 (1H, qd), 2.62 (5H, t), 2.76-2.97 (4H, m), 3.00-3.11 (2H, m), 3.26 (4H, t), 3.45 (2H, s), 4.15-4.24 (3H, m), 4.32 (1H, d), 5.04 (1H, dd), 7.04 (2H, d), 7.21-7.27 (5H, m), 7.33 (1H, d), 7.48-7.54 (1H, m), 7.82 (1H, d), 8.16 (1H, s), 10.94 (1H, s); m/z ES⁺ [M+H]⁺ = 754.4.

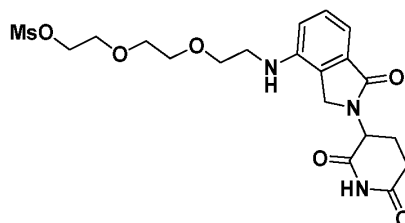
10 **Intermediate 77a: 3-(4-((2-(2-(2-Hydroxyethoxy)ethoxy)ethyl)amino)-1-oxoisindolin-2-yl)piperidine-2,6-dione**



- 3-(4-Amino-1-oxoisindolin-2-yl)piperidine-2,6-dione (100 mg, 0.39 mmol) and 2-(2-(2-bromoethoxy)-ethoxy)ethan-1-ol (100 mg, 0.47 mmol) was added to DIPEA (0.067 mL, 0.39 mmol) in NMP (0.5 mL). The resulting mixture was stirred at 130°C for 12h and was then concentrated to give the title compound as a brown dry film which was used in the next step without further purification; ¹H NMR: 2.00-2.07 (1H, m), 2.27-2.36 (1H, m), 2.57-2.66 (1H, m), 2.86-3.00 (1H, m), 3.33 (2H, t), 3.36-3.64 (11H, m), 3.70-3.78 (1H, m), 4.13 (1H, d), 4.25 (1H, d), 5.12 (1H, dd), 6.83 (1H, d), 6.96 (1H, d), 7.30 (1H, t), 11.02 (1H, s); m/z ES⁺ [M+H]⁺ = 392.

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Intermediate 77b: 2-(2-((2-(2-(2,6-Dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)amino)ethoxy)ethoxy)ethyl methanesulfonate



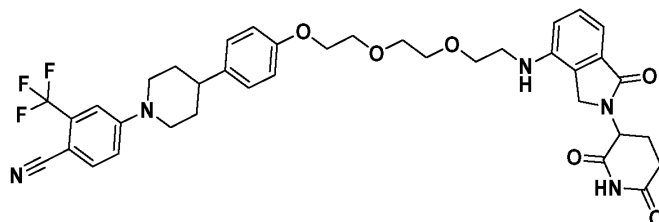
- Methanesulfonic anhydride (89 mg, 0.51 mmol) was added to 3-(4-((2-(2-(2-hydroxyethoxy)ethoxy)ethyl)-amino)-1-oxoisindolin-2-yl)piperidine-2,6-dione (100 mg, 0.26 mmol) and Et₃N (107 μL, 0.77 mmol) in

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DCM (10 mL) at 0°C. The resulting solution was stirred at RT for 1.5h. The mixture was then diluted with DCM (20 mL), washed with water (20 mL) then sat. brine (20 mL), dried (Na₂SO₄) and concentrated to give the title compound (120 mg, 100%) as a yellow gum which was used in the next step without further purification; *m/z* ES⁺ [M+H]⁺ = 470.

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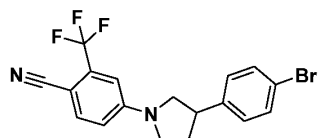
Example 77: 4-[4-(4-{2-[2-(2-{[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]amino}-ethoxy]ethoxy]ethoxy}phenyl)piperidin-1-yl]-2-(trifluoromethyl)benzonitrile



- 4-(4-(4-Hydroxyphenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (90 mg, 0.26 mmol) was added to NaH (31.2 mg, 0.78 mmol) in DMF (1 mL) and stirred at RT for 2h. 2-(2-(2-((2-(2,6-Dioxopiperidin-3-yl)-1-oxo-isoindolin-4-yl)amino)ethoxy)ethoxy)ethyl methanesulfonate (122 mg, 0.26 mmol) was then added and the mixture was stirred for 2h. Purification by preparative HPLC (SunFire Prep C18 OBD column, 30×150mm 5μm; Mobile Phase A: Water (0.1% formic acid), Mobile Phase B: MeCN) gave the title compound (10 mg, 5%) as a white solid. ¹H NMR: 1.54-1.68 (2H, m), 1.84 (2H, d), 2.27 (1H, td), 2.55-2.64 (1H, m), 2.75 (1H, d), 2.92 (1H, ddd), 3.04 (2H, t), 3.59 (6H, qd), 3.68-3.75 (2H, m), 4.00-4.06 (2H, m), 4.08-4.27 (4H, m), 5.11 (1H, dd), 5.60 (1H, q), 6.72-6.85 (1H, m), 6.81-6.91 (2H, m), 6.94 (1H, d), 7.10-7.18 (2H, m), 7.19-7.31 (2H, m), 7.33 (1H, d), 7.82 (1H, d), 11.02 (1H, s); *m/z* ES⁺ [M+H]⁺ = 720.3.

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Intermediates 78a: rac-4-(3-(4-Bromophenyl)pyrrolidin-1-yl)-2-(trifluoromethyl)benzonitrile

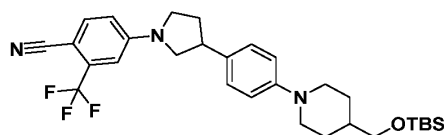


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- DIPEA (5.79 mL, 33.17 mmol) was added to racemic 3-(4-bromophenyl)pyrrolidine (2.50 g, 11.06 mmol) and 4-fluoro-2-(trifluoromethyl)benzonitrile (2.09 g, 11.06 mmol) in MeCN (50 mL). The resulting mixture was stirred at 50°C for 3h. The mixture was the concentrated to dryness and the residue was dissolved in EtOAc (100 mL). This solution was washed with water (100 mL × 2) then sat. brine (100 mL), then dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 1-20% EtOAc in petroleum ether) gave the title compound (2.20 g, 50%) as a colourless oil which solidified on standing; *m/z* ES⁺ [M+H]⁺ = 395.

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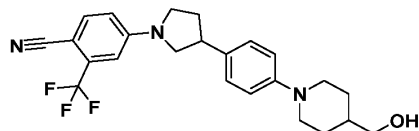
Intermediate 78b: 4-(3-(4-(4-(((*tert*-butyldimethylsilyl)oxy)methyl)piperidin-1-yl)phenyl)pyrrolidin-1-yl)-2-(trifluoromethyl)benzonitrile



5 RuPhos Pd G3 (85 mg, 0.10 mmol) was added to 4-(3-(4-bromophenyl)pyrrolidin-1-yl)-2-(trifluoromethyl)-benzonitrile (400 mg, 1.01 mmol), 4-(((*tert*-butyldimethylsilyl)oxy)methyl)piperidine (348 mg, 1.52 mmol), RuPhos (47.2 mg, 0.10 mmol) and Cs₂CO₃ (989 mg, 3.04 mmol) in 1,4-dioxane (5 mL) at RT under N₂. The resulting mixture was stirred at 100°C for 16h then concentrated. Purification FSC (0-100% EtOAc in heptane) gave the title compound (440 mg, 80 %) as a yellow liquid; ¹H NMR (300 MHz) 0.02 (6H, s), 0.85 (9H, s), 1.25 (2H, dd), 1.53 (1H, s), 1.70 (2H, d), 2.05 (1H, q), 2.33 (1H, s), 2.51-2.65 (2H, m), 3.43-3.45 (4H, m), 3.56 (1H, d), 3.64 (2H, d), 3.74-3.90 (1H, m), 6.80-6.96 (4H, m), 7.15 (2H, d), 7.30-7.37 (1H, m), 7.78 (1H, dd); *m/z* ES⁺ [M+H]⁺ = 544.

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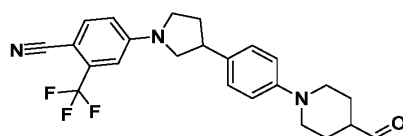
Intermediate 78c: 4-(3-(4-(4-(Hydroxymethyl)piperidin-1-yl)phenyl)pyrrolidin-1-yl)-2-(trifluoromethyl)benzonitrile



15 Tetra-*n*-butylammonium fluoride (in THF, 2.94 mL, 2.94 mmol) was added to 4-(3-(4-(((*tert*-butyldimethylsilyl)oxy)methyl)piperidin-1-yl)phenyl)pyrrolidin-1-yl)-2-(trifluoromethyl)benzonitrile (400 mg, 0.74 mmol) in THF (10 mL) at RT. The resulting solution was stirred at RT for 1.5h. The mixture was then diluted with EtOAc, washed with water then sat. brine, then dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-50% EtOAc in petroleum ether) gave the title compound (239 mg, 75 %) as a white solid; ¹H NMR (300 MHz) 1.22 (2H, qd), 1.55-1.43 (1H, m), 1.77-1.66 (2H, m), 2.07 (1H, q), 2.35 (1H, tt), 2.59 (3H, td), 3.28 (2H, dd), 3.45 (2H, td), 3.61-3.54 (1H, m), 3.64 (2H, dd), 3.82 (1H, dd), 4.47 (1H, t), 6.96-6.81 (4H, m), 7.21-7.12 (2H, m), 7.78 (1H, d); *m/z* ES⁺ [M+H]⁺ = 430.

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Intermediate 78d: 4-(3-(4-(4-Formylpiperidin-1-yl)phenyl)pyrrolidin-1-yl)-2-(trifluoromethyl)benzonitrile

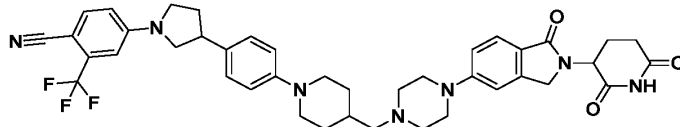


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30 Dess-Martin periodinane (415 mg, 0.98 mmol) was added to 4-(3-(4-(4-(hydroxymethyl)piperidin-1-yl)phenyl)pyrrolidin-1-yl)-2-(trifluoromethyl)benzonitrile (210 mg, 0.49 mmol) in DCM (5 mL) at RT. The resulting solution was stirred at RT for 1h. The mixture was then diluted with DCM, washed with sat. NaHCO₃, then sat. brine, dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-30% EtOAc in petroleum ether) gave the title compound (75 mg, 36 %) as a yellow solid; ¹H NMR (300 MHz) 1.57 (2H, dtd), 1.92 (2H, dd), 2.04 (1H, dd), 2.35 (1H, d), 2.54 (2H, s), 2.79 (2H, td), 3.27 (1H, s), 3.46 (3H, td), 3.56

(3H, dt), 3.82 (1H, dd), 6.96-6.81 (4H, m), 7.23-7.13 (2H, m), 7.78 (1H, d), 9.63 (1H, s); m/z ES⁺, [M+H]⁺ = 428.

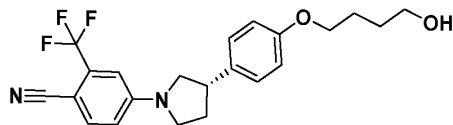
Example 78: 4-(3-{4-[4-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl}methoxy]piperidin-1-yl}phenyl}pyrrolidin-1-yl)-2-(trifluoromethyl)benzonitrile



Intermediate 2c was reacted with Intermediate 78d using the general synthetic method illustrated by Example 2 to give the title compound after purification by HPLC (Column: SunFire C18 OBD Prep Column, 100Å, 5 μm, 19 mm × 250 mm; Mobile Phase A: Water (0.1% formic acid), Mobile Phase B: MeCN; Flow rate: 25 mL/min; Gradient: 30 B to 45 B in 7 min; 254/220 nm; RT: 6.50); ¹H NMR: (300MHz) 1.14-1.38 (2H, m), 1.82 (3H, d), 1.92-2.14 (2H, m), 2.18-2.44 (8H, m), 2.60-2.68 (6H, m), 2.82-3.01 (1H, m), 3.45-3.49 (4H, m), 3.62-3.65 (3H, m), 3.78-3.89 (1H, m), 4.21 (1H, d), 4.35 (1H, d), 5.06 (1H, dd), 6.85-6.98 (4H, m), 7.08 (2H, d), 7.18 (2H, d), 7.54 (1H, d), 7.80 (1H, d), 10.96 (1H, s); m/z ES⁺ [M+H]⁺ = 740.4.

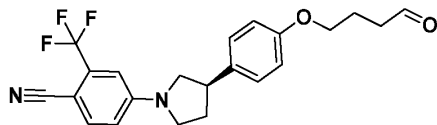
Intermediate 79a: (S)-4-(3-(4-(4-Hydroxybutoxy)phenyl)pyrrolidin-1-yl)-2-(trifluoromethyl)benzonitrile

(Absolute stereochemistry not yet confirmed)



RockPhos Pd G3 (85 mg, 0.10 mmol) was added to (S)-4-(3-(4-bromophenyl)pyrrolidin-1-yl)-2-(trifluoromethyl)benzonitrile (Intermediate 65c) (400 mg, 1.01 mmol), 1,4-butanediol (137 mg, 1.52 mmol) and Cs₂CO₃ (989 mg, 3.04 mmol) in 1,4-dioxane (10 mL) at RT under N₂. The resulting mixture was stirred at 100°C for 16h then concentrated. Purification by FSC (gradient: 0-25% EtOAc in petroleum ether) gave the title compound (177 mg, 43 %) as a yellow gum; ¹H NMR: 1.55 (2H, dq), 1.72 (2H, dq), 2.01-2.12 (1H, m), 2.29-2.42 (1H, m), 3.33-3.35 (1H, m), 3.41-3.53 (4H, m), 3.60 (1H, ddd), 3.84 (1H, dd), 3.95 (2H, t), 4.44 (1H, t), 6.83-6.93 (3H, m), 6.94 (1H, d), 7.25 (2H, d), 7.79 (1H, d).

Intermediate 79b: (S)-4-(3-(4-(4-Oxobutoxy)phenyl)pyrrolidin-1-yl)-2-(trifluoromethyl)benzonitrile

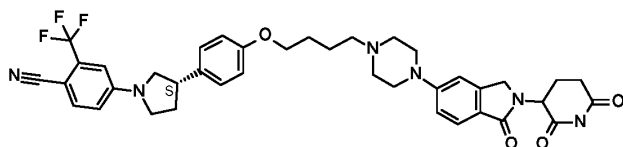


Dess-Martin periodinane (236 mg, 0.56 mmol) was added to (S)-4-(3-(4-(4-hydroxybutoxy)phenyl)pyrrolidin-1-yl)-2-(trifluoromethyl)benzonitrile (150 mg, 0.37 mmol) in DCM (5 mL) at RT. The resulting mixture was stirred at RT for 1h. The mixture was then diluted with DCM, washed with sat. NaHCO₃ then sat. brine, dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-30% EtOAc in petroleum ether) gave the title

compound (127 mg, 85 %) as a yellow gum; m/z ES⁺ [M+H]⁺ = 403.

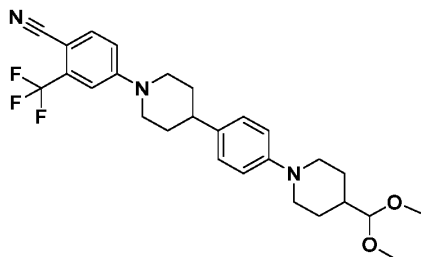
Example 79: 4-((3*S*)-3-[4-(4-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazin-1-yl}butoxy)phenyl]pyrrolidin-1-yl)-2-(trifluoromethyl)benzonitrile (Absolute

5 stereochemistry not yet confirmed)



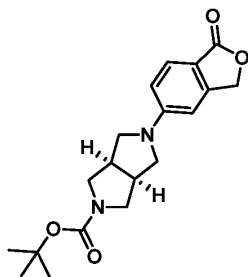
Intermediate 2c was reacted with Intermediate 79b using the general synthetic method illustrated by Example 2 to give the title compound after purification by HPLC (Column: SunFire C18 OBD Prep Column, 100Å, 5 μm, 19 mm × 250 mm; Mobile Phase A: Water (0.1% formic acid), Mobile Phase B: MeCN; Flow rate: 25 mL/min; Gradient: 42 % to 50 % in 7 min; 254/220 nm; RT1: 5.56); ¹H NMR: (300 MHz) 1.68-1.83 (4H, m), 1.90-2.11 (2H, m), 2.25-2.46 (5H, m), 2.51-2.65 (6H, m), 2.84-3.00 (2H, m), 3.41-3.66 (5H, m), 3.85 (1H, dd), 3.99 (2H, d), 4.22 (1H, d), 4.35 (1H, d), 5.06 (1H, dd), 6.83-6.98 (4H, m), 7.05-7.17 (2H, m), 7.27 (2H, d), 7.56 (1H, d), 7.80 (1H, d), 10.97 (1H, s); m/z ES⁺ [M+H]⁺ = 715.4.

Intermediate 80a: 4-(4-(4-(4-(Dimethoxymethyl)piperidin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



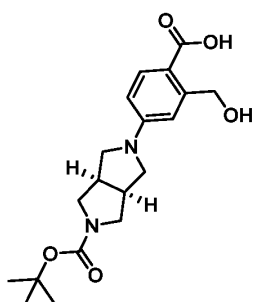
4-(4-(4-Bromophenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (1.00 g, 2.44 mmol), 4-(dimethoxymethyl)piperidine (0.467 g, 2.93 mmol), RuPhos G3 (0.153 g, 0.18 mmol), RuPhos (0.086 g, 0.18 mmol) and sodium *tert*-butoxide (0.704 g, 7.33 mmol) were dissolved in anhydrous 1,4-dioxane (24.4 mL). The mixture was degassed, under N₂ and stirred at 100°C overnight. The mixture was then cooled and concentrated. Water (10 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic solutions were dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-100% EtOAc in heptane) gave the title compound (0.393 g, 33 %) as a pale yellow solid; ¹H NMR (CDCl₃) 1.45 (2H, qd), 1.67-1.8 (3H, m), 1.8-1.89 (2H, m), 1.97 (2H, d), 2.55-2.77 (3H, m), 3.05 (2H, td), 3.37 (6H, s), 3.67 (2H, d), 4.01 (2H, d), 4.08 (1H, d), 6.88-6.92 (2H, m), 6.98 (1H, dd), 7.06-7.12 (2H, m), 7.15 (1H, d), 7.61 (1H, d); m/z : ES⁺ [M+H]⁺ 488.4.

Intermediate 80b: *tert*-Butyl (3*aR*,6*aS*)-5-(1-oxo-1,3-dihydroisobenzofuran-5-yl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate



- 5 *tert*-Butyl (3a*R*,6a*S*)-hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (4.19 g, 19.72 mmol) was added to 5-fluoroisobenzofuran-1(3*H*)-one (3.00 g, 19.72 mmol), DIPEA (10.33 mL, 59.16 mmol) in DMSO (3 mL). The resulting solution was stirred at 120°C for 40h. The reaction mixture was then poured into water. A precipitate was collected by filtration, washed with water (100 mL) and dried under vacuum. Purification by FSC (gradient: 0-40% EtOAc in DCM) gave the title compound (5.10 g, 75 %) as a white solid; ¹H NMR (300 MHz) 1.39 (9H, s), 3.02 (2H, m), 3.19-3.33 (4H, m), 3.51-3.63 (4H, m), 5.22 (2H, s), 6.61 (1H, d), 6.69 (1H, m), 7.58 (1H, d); *m/z* ES⁺, [M+H]⁺ = 345.1.

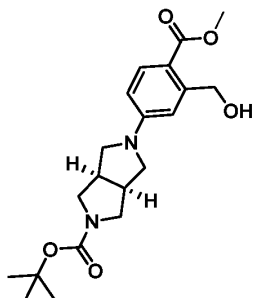
10 **Intermediate 80c: 4-((3a*R*,6a*S*)-5-(*tert*-Butoxycarbonyl)hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-2-(hydroxymethyl)benzoic acid**



- 15 NaOH (2.32 g, 58.07 mmol) was added to *tert*-butyl (3a*R*,6a*S*)-5-(1-oxo-1,3-dihydroisobenzofuran-5-yl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (5.00 g, 14.52 mmol) in THF (10 mL), MeOH (10 mL) and water (10 mL). The resulting solution was stirred at RT for 2h. The mixture was then diluted with water (50 mL) and washed with EtOAc (150 mL × 4). The combined organic solutions were dried (MgSO₄) and concentrated to give the title compound which was used in the next step without further purification; ¹H NMR (300 MHz) 1.39 (9H, s), 3.00 (2H, s), 3.15-3.24 (4H, m), 3.51-3.54 (4H, m), 4.78 (2H, s), 6.39-6.41 (1H, m), 6.84 (1H, d), 7.77 (1H, d); *m/z* ES⁺, [M+H]⁺ = 363.1.

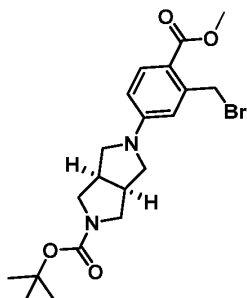
20

Intermediate 80d: *tert*-Butyl (3a*R*,6a*S*)-5-(3-(hydroxymethyl)-4-(methoxycarbonyl)phenyl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate



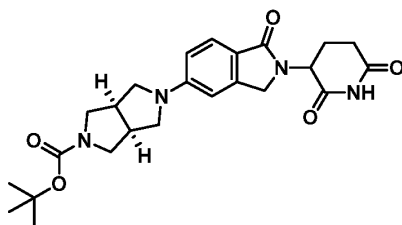
- Trimethylsilyldiazomethane (20.69 mL, 41.39 mmol) was added in one portion to 4-((3aR,6aS)-5-(*tert*-butoxycarbonyl)-hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-2-(hydroxymethyl)benzoic acid (5.00 g, 13.80 mmol) in MeOH (1 mL) and EtOAc (1 mL) at -10°C . The resulting solution was stirred at -10°C for 2h. The mixture was then quenched with water (600 mL) and extracted with EtOAc (3×300 mL). The combined organic solution were dried (MgSO_4) and concentrated to give the title compound (4.90 g, 94 %) as a brown oil which was used in the next step without further purification; m/z ES^+ , $[\text{M}+\text{H}]^+ = 377.1$.

10 **Intermediate 80e: *tert*-Butyl (3aR,6aS)-5-(3-(bromomethyl)-4-(methoxycarbonyl)phenyl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate**



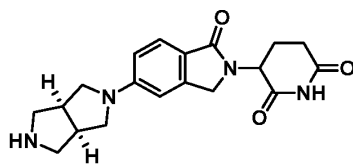
- PPh_3 (4.44 g, 16.92 mmol) was added in one portion to *tert*-butyl (3aR,6aS)-5-(3-(hydroxymethyl)-4-(methoxy-carbonyl)phenyl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (4.90 g, 13.02 mmol) and CBr_4 (5.61 g, 16.92 mmol) in THF (80 mL) at RT. The resulting solution was stirred at RT for 16h. The mixture was then filtered and the filtrate was concentrated. Purification by FSC (gradient: 0-40% EtOAc in DCM) gave the title compound (5.30 g, 93 %) as a white solid; m/z ES^+ , $[\text{M}+\text{H}]^+ = 439.0$.

20 **Intermediate 80f: *tert*-Butyl (3aR,6aS)-2-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-5-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-5-carboxylate**

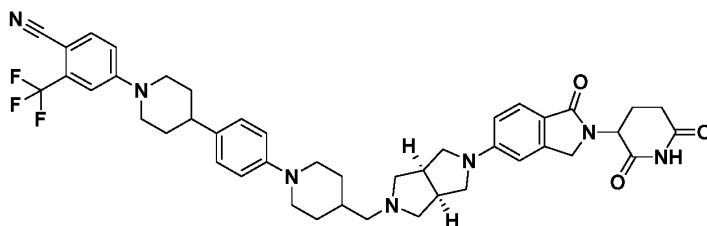


- DIPEA (5.02 mL, 28.76 mmol) was added in one portion to *tert*-butyl (3*aR*,6*aS*)-2-(1-(3-(bromomethyl)-4-(methoxycarbonyl)phenyl)piperidin-4-yl)octahydrocyclopenta[*c*]pyrrole-5-carboxylate (5.00 g, 9.59 mmol) and 3-aminopiperidine-2,6-dione hydrochloride salt (2.37 g, 14.38 mmol) in MeCN (100 mL) at RT. The resulting solution was stirred at 80°C for 35h. Purification by FSC (gradient: 0-60% EtOAc in DCM) gave the title compound (4.00 g, 92 %) as a green solid; *m/z* ES⁺, [M+H]⁺ = 455.0.

Intermediate 80g: 3-(5-((3*aR*,6*aS*)-Hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione



- 10 A solution of *tert*-butyl (3*aR*,6*aS*)-2-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isindolin-5-yl]-1,3,3*a*,4,6,6*a*hexahydropyrrolo[3,4-*c*]pyrrole-5-carboxylate (4.00 g, 8.80 mmol) in formic acid (20.4 mL) was stirred at RT for 16h. The solvent was then removed under reduced pressure to give the title compound (3.50 g, 89 %) as a black waxy solid which was used in the next step without further purification; *m/z* ES⁺, [M+H]⁺ = 355.1.
- 15 **Example 80: 4-{4-[4-(4-{[(3*aR*,6*aS*)-5-[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isindol-5-yl]hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl]methyl}piperidin-1-yl)phenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile**

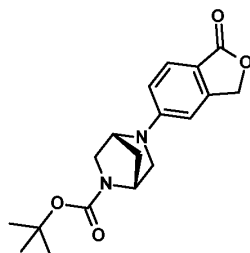


- Formic acid (3 mL) was added to 4-(4-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (70 mg, 0.14 mmol) and 3-(5-((3*aR*,6*aS*)-hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione (50.9 mg, 0.14 mmol) at RT under air. The resulting solution was stirred at 40°C for 0.5h and then diluted with toluene (3 mL). The resulting mixture was concentrated to dryness and the residue was azeotroped with toluene to dryness. The residue was then dissolved in DCM (2 mL) and IPA (1 mL) and NaBH(OAc)₃ (30.4 mg, 0.14 mmol) was added at RT. The resulting suspension was stirred for 0.5h under air at RT. The mixture was then diluted with EtOAc (20 mL), washed with sat. NaHCO₃ (2 × 5 mL) then sat. brine (5 mL), dried (MgSO₄) and concentrated. Purification by preparative HPLC (Column A, Eluent A) was carried out. Fractions containing the desired compound were concentrated to remove the MeCN and basified with sat. aq. NaHCO₃ to pH 9. This solution was then extracted with DCM (4 × 20 mL), the combined extracts were dried (MgSO₄) and concentrated to dryness to give the title compound (26.0 mg, 23 %) as a white solid; ¹H NMR (CDCl₃) 1.26 (1H, s), 1.28-1.38 (2H, m), 1.71 (1H, dd), 1.78 (1H, dd), 1.82-1.91 (2H, m), 1.92-1.99 (2H, m), 2.19 (1H, dtd), 2.28 (1H, dd), 2.34 (2H, dd), 2.54 (2H, d), 2.61-

2.67 (2H, m), 2.69 (2H, dt), 2.75 (1H, dd), 2.83 (1H, dd), 2.89 (1H, ddd), 2.94-3.09 (4H, m), 3.23 (2H, d), 3.57 (2H, t), 3.63 (2H, d), 4.01 (2H, d), 4.24 (1H, d), 4.39 (1H, d), 5.18 (1H, dd), 6.57 (1H, s), 6.68 (1H, dd), 6.85-6.92 (2H, m), 6.98 (1H, dd), 7.08 (2H, d), 7.15 (1H, d), 7.60 (1H, d), 7.71 (1H, d), 8.00 (1H, s); m/z ES⁺ [M+H]⁺ = 780.0.

5

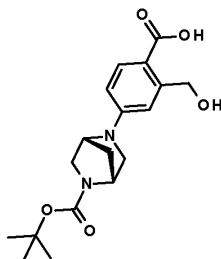
Intermediate 81a: *tert*-Butyl (1*R*,4*R*)-5-(1-oxo-1,3-dihydroisobenzofuran-5-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate



- DIPEA (10.33 mL, 59.16 mmol) was added to (1*R*,4*R*)-*tert*-butyl 2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (4.69 g, 23.66 mmol) and 5-fluoroisobenzofuran-1(3*H*)-one (3.00 g, 19.72 mmol) in DMSO (30 mL) at RT. The resulting mixture was stirred at 120°C for 16h. After cooling the mixture was poured into water (100 mL) and the resulting mixture was filtered to give the title compound (5.00 g, 77 %) as a white solid; ¹H NMR (300 MHz, CDCl₃) 1.44 (9H, d), 2.01 (2H, s), 3.29 (1H, s), 3.45 (2H, d), 3.56-3.65 (1H, m), 4.51 (1H, s), 4.63 (1H, d), 5.17 (2H, s), 6.46 (1H, d), 6.59-6.68 (1H, m), 7.70 (1H, d); m/z ES⁺, [M+H]⁺ = 331.1.

15

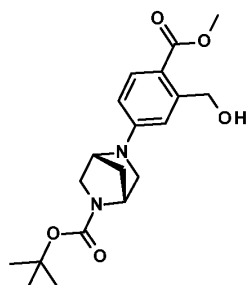
Intermediate 81b: 4-((1*R*,4*R*)-5-(*tert*-Butoxycarbonyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-2-(hydroxymethyl)benzoic acid



- NaOH (2.42 g, 60.54 mmol) was added to *tert*-butyl (1*R*,4*R*)-5-(1-oxo-1,3-dihydroisobenzofuran-5-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (5.00 g, 15.13 mmol) in a mixture of MeOH (20 mL), THF (20 mL) and water (20 mL) at RT and the mixture was stirred at RT for 16h. The solvent was removed under reduced pressure. The residue was acidified with 2M HCl. The mixture was then filtered to give the title compound (5.20 g, 99 %) as a white solid; m/z ES⁺, [M+H]⁺ = 349.1.

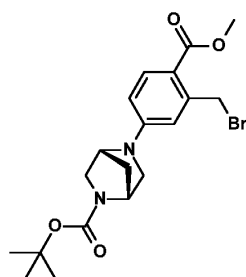
25

Intermediate 81c: *tert*-Butyl (1*R*,4*R*)-5-(3-(hydroxymethyl)-4-(methoxycarbonyl)phenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate



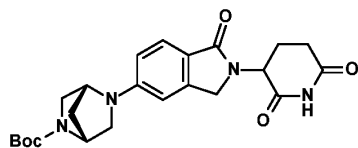
- Trimethylsilyldiazomethane (21.5 mL, 43.05 mmol) was added in one portion to 4-((1*R*,4*R*)-5-(*tert*-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-2-(hydroxymethyl)benzoic acid (5.00 g, 14.35 mmol) in MeOH (25 mL) and EtOAc (25 mL) at -10°C . The resulting solution was stirred at -10°C for 2h then water (600 mL) was added. This mixture was extracted with EtOAc (3×300 mL), the combined organic solutions were dried (MgSO_4) and concentrated to give the title compound (5.00 g, 96 %) as a brown oil which was used in the next step without further purification; m/z ES^+ , $[\text{M}+\text{H}]^+ = 363.2$.

10 **Intermediate 81d: *tert*-Butyl (1*R*,4*R*)-5-(3-(bromomethyl)-4-(methoxycarbonyl)phenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate**



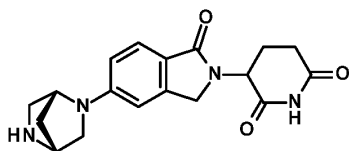
- Ph_3P (5.65 g, 21.53 mmol) was added to *tert*-butyl (1*R*,4*R*)-5-(3-(hydroxymethyl)-4-(methoxycarbonyl)-phenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (5.20 g, 14.35 mmol) and CBr_4 (7.14 g, 21.53 mmol) in THF (50 mL) at RT and the mixture was stirred at RT for 2h. The mixture was then filtered and the filtrate concentrated. Purification by FSC (gradient: 0-10% EtOAc in petroleum ether) gave the title compound (4.30 g, 71 %) as a white solid; ^1H NMR (300 MHz, CDCl_3) 1.44 (9H, d), 1.97 (2H, s), 3.16-3.47 (3H, m), 3.57 (1H, d), 3.87 (3H, s), 4.48 (1H, s), 4.96 (2H, s), 6.40-6.50 (1H, m), 6.54 (1H, d), 7.91 (1H, d); m/z ES^+ , $[\text{M}+\text{H}]^+ = 425.1$.

20 **Intermediate 81d: *tert*-Butyl (1*R*,4*R*)-5-[2-(2,6-dioxo-3-piperidyl)-1-oxo-isindolin-5-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate**



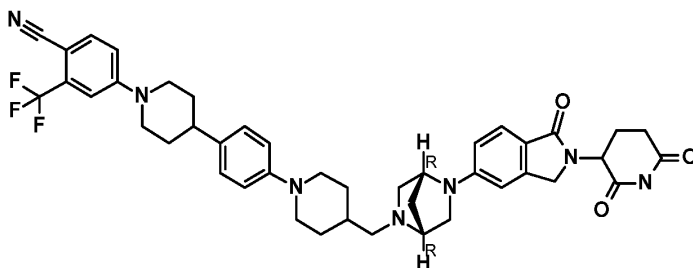
DIPEA (1.77 mL, 10.11 mmol) was added to *tert*-butyl (1*R*,4*R*)-5-(3-(bromomethyl)-4-(methoxycarbonyl)-phenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (4.30 g, 10.11 mmol) and 3-aminopiperidine-2,6-dione hydrochloride salt (2.50 g, 15.16 mmol) in MeCN (20 mL) at -10°C . The resulting solution was stirred at 80°C for 2h then concentrated. Purification by FSC (gradient: 0-50% EtOAc in DCM) gave the title compound (2.20 g, 49 %) as a green solid; ^1H NMR (300 MHz, CDCl_3) 1.44 (9H, d), 1.57 (2H, d), 2.20 (1H, s), 2.22-2.42 (1H, m), 2.72-2.96 (2H, m), 3.17-3.33 (1H, m), 3.43 (2H, d), 3.61 (1H, d), 4.24 (1H, d), 4.34-4.50 (2H, m), 4.61 (1H, d), 5.13-5.25 (1H, m), 6.53 (1H, d), 6.57-6.68 (1H, m), 7.70 (1H, d), 8.41 (1H, d); m/z ES^+ , $[\text{M}+\text{H}]^+ = 441.2$.

Intermediate 81e: 3-[5-[(1*R*,4*R*)-2,5-Diazabicyclo[2.2.1]heptan-2-yl]-1-oxo-isoindolin-2-yl]piperidine-2,6-dione



tert-Butyl (1*R*,4*R*)-5-(3-(bromomethyl)-4-(methoxycarbonyl)phenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (2.2 g, 4.99 mmol) was stirred in formic acid (30 mL) at RT for 2h. Concentration under reduced pressure then gave the title compound (1.50 g, 63 %) as a black solid; ^1H NMR (300 MHz) 1.97 (2H, d), 2.13 (1H, d), 2.28-2.48 (1H, m), 2.52-2.66 (1H, m), 2.82-3.00 (1H, m), 3.05-3.19 (1H, m), 3.27 (1H, d), 3.36 (1H, d), 3.53-3.70 (1H, m), 4.14-4.27 (1H, m), 4.27-4.40 (1H, m), 4.44 (1H, s), 4.74 (1H, s), 4.99-5.11 (1H, m), 6.70-6.84 (2H, m), 7.54 (1H, d), 8.26 (3H, s), 10.96 (1H, s); m/z ES^+ , $[\text{M}+\text{H}]^+ = 341.2$.

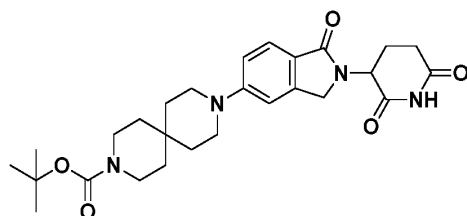
Example 81: 4-(4-{4-[4-[(1*R*,4*R*)-5-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]-2,5-diazabicyclo[2.2.1]heptan-2-yl]methyl]piperidin-1-yl]phenyl}piperidin-1-yl)-2-(trifluoromethyl)-benzonitrile



Formic acid (3 mL) was added to 4-(4-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (70 mg, 0.14 mmol) and 3-[5-[(1*R*,4*R*)-2,5-Diazabicyclo[2.2.1]heptan-2-yl]-1-

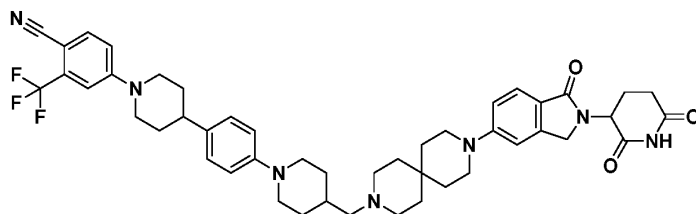
- oxo-isoindolin-2-yl]piperidine-2,6-dione (49 mg, 0.14 mmol) at RT under air. The resulting solution was stirred at 40°C for 0.5h and then diluted with toluene (3 mL). The resulting mixture was concentrated to dryness and the residue was azeotroped with toluene to dryness. The residue was then dissolved in DCM (2 mL) and IPA (1 mL) and NaBH(OAc)₃ (60.9 mg, 0.29 mmol) was added at RT. The resulting suspension was stirred for 18h under air at RT. The mixture was then diluted with EtOAc (20 mL), washed with sat. NaHCO₃ (2 × 5 mL) then sat. brine (5 mL), dried (MgSO₄) and concentrated. Purification by preparative HPLC (Column A, Eluent A, Basic Work-Up A) gave the title compound (41.0 mg, 37 %) as a white solid; ¹H NMR: (CDCl₃) 1.26 (2H, s), 1.32 (2H, td), 1.44 (1H, s), 1.71 (1H, dd), 1.75-1.8 (1H, m), 1.87 (2H, dd), 1.97 (2H, d), 2.19 (1H, dtd), 2.31 (1H, qd), 2.41 (2H, s), 2.55-2.67 (3H, m), 2.71 (1H, dt), 2.76-2.85 (1H, m), 2.85-2.95 (1H, m), 3.04 (3H, td), 3.31-3.46 (2H, m), 3.61 (3H, dt), 4.01 (2H, d), 4.19-4.32 (2H, m), 4.38 (1H, d), 5.19 (1H, ddd), 6.51 (1H, s), 6.61 (1H, dd), 6.88 (2H, d), 6.98 (1H, dd), 7.08 (2H, d), 7.15 (1H, d), 7.60 (1H, d), 7.69 (1H, d), 7.95 (1H, s); *m/z* ES⁺ [M+H]⁺ = 766.0.

Example 82a: *tert*-Butyl 9-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)-3,9-diazaspiro[5.5]undecane-3-carboxylate



- Pd-PEPPSI-IPent (0.110 g, 0.14 mmol) was added to *tert*-butyl 3,9-diazaspiro[5.5]undecane-3-carboxylate (0.850 g, 3.34 mmol), 3-(5-bromo-1-oxoisoindolin-2-yl)piperidine-2,6-dione (0.90 g, 2.79 mmol) and Cs₂CO₃ (2.72 g, 8.36 mmol) in 1,4-dioxane (30 mL) at RT under N₂. The resulting suspension was vacuum degassed, backfilling with N₂ and stirred at 110°C for 3h. The mixture was then cooled to RT, diluted with DCM (100 mL) and washed with 5% AcOH in water (50 mL), then brine (50 mL). The organic layer was dried (MgSO₄) and concentrated. Purification by FSC (gradient: 0-100% EtOAc in heptane then 10% EtOH in EtOAc) gave the title compound (0.397 g, 29 %) as a white solid. ¹H NMR (CDCl₃) 1.46 (13H, s), 1.62-1.68 (4H, m), 2.14-2.23 (1H, m), 2.32 (1H, qd), 2.72-3.04 (2H, m), 3.37 (8H, dt), 4.24 (1H, d), 4.40 (1H, d), 5.19 (1H, dd), 6.87 (1H, d), 6.98 (1H, dd), 7.72 (1H, d), 8.00 (1H, s); *m/z*: ES⁺ [M+H]⁺ 497.4.

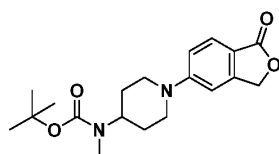
Example 82: 4-(4-{4-[4-(9-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]-3,9-diazaspiro[5.5]undecan-3-yl)methyl]piperidin-1-yl}phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



- Intermediate 80a was reacted with Intermediate 82a using the general synthetic method illustrated by Example

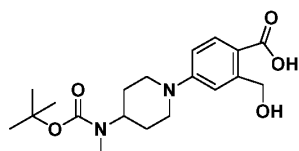
- 1 to give the title compound after purification by HPLC (Column A, Eluent A, Basic Work-Up A); ¹H NMR: (CDCl₃) 1.26-1.40 (4H, m), 1.28-1.4 (3H, m), 1.57 (3H, s), 1.63 (4H, s), 1.69-1.75 (1H, m), 1.79 (1H, d), 1.85 (2H, d), 1.94-2 (2H, m), 2.21 (2H, t), 2.26-2.35 (1H, m), 2.39 (3H, s), 2.6-2.74 (3H, m), 2.75-2.86 (1H, m), 2.86-2.95 (1H, m), 2.99-3.11 (2H, m), 3.25-3.37 (3H, m), 3.64 (2H, d), 4.01 (2H, d), 4.24 (1H, d), 4.40 (1H, d), 5.19 (1H, dd), 6.82-6.93 (3H, m), 6.95-7.01 (2H, m), 7.09 (2H, d), 7.15 (1H, d), 7.61 (1H, d), 7.71 (1H, d), 7.86 (1H, s); *m/z* ES⁺ [M+H]⁺ = 822.5.

Intermediate 83a: *tert*-Butyl methyl(1-(1-oxo-1,3-dihydroisobenzofuran-5-yl)piperidin-4-yl)carbamate



- 10 DIPEA (6.89 mL, 39.44 mmol) was added in one portion to 5-fluoroisobenzofuran-1(3*H*)-one (3.00 g, 19.72 mmol) and *tert*-butyl methyl(piperidin-4-yl)carbamate (6.34 g, 29.58 mmol) in DMSO (20 mL) at RT. The resulting solution was stirred at 120°C for 16h. The mixture was then poured into water (100 mL). This mixture was extracted with EtOAc (3 × 75 mL) and the combined organic solutions were dried (MgSO₄) and concentrated. Trituration with EtOAc and petroleum ether (1:5) to give a solid which was collected by
- 15 filtration and dried under vacuum to give the title compound (5.82 g, 85 %) as a white solid; ¹H NMR (CDCl₃) 1.50 (9H, s), 1.76-1.84 (4H, m), 2.75 (3H, s), 2.95-3.07 (2H, m), 3.95-4.03 (2H, m), 4.26 (1H, s), 5.22 (2H, s), 6.84 (1H, s), 6.98-7.05 (1H, m), 7.75 (1H, d); *m/z* ES⁺, [M+H]⁺ = 347.2.

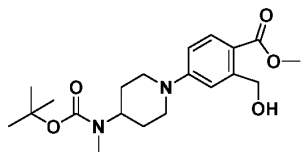
Intermediate 83b: 4-(4-((*tert*-Butoxycarbonyl)(methyl)amino)piperidin-1-yl)-2-(hydroxymethyl)benzoic acid



- NaOH (0.716 g, 17.90 mmol) was added in one portion to *tert*-butyl methyl(1-(1-oxo-1,3-dihydroisobenzofuran-5-yl)piperidin-4-yl)carbamate (6.20 g, 17.90 mmol) in a mixture of water (20 mL), MeOH (20 mL) and THF (20 mL) at -10°C. The resulting solution was stirred at -10°C for 2h then 1M HCl
- 25 (70 mL) was added. The mixture was extracted with EtOAc (3 × 300 mL) and the combined organic solutions were dried (MgSO₄) and concentrated to give the title compound (6.20 g, 95 %) as a brown oil which was used in the next step without further purification; ¹H NMR (300 MHz, CDCl₃) 1.48 (9H, s), 1.74-1.81 (4H, m), 2.74 (3H, s), 2.92-3.12 (2H, m), 3.93-4.11 (2H, m), 4.27 (1H, s), 4.81 (2H, s), 6.93 (2H, d), 7.98-8.07 (1H, m); *m/z* ES⁺, [M+H]⁺ = 365.2.

30

Intermediate 83c: Methyl 4-(4-((*tert*-butoxycarbonyl)(methyl)amino)piperidin-1-yl)-2-(hydroxymethyl)benzoate

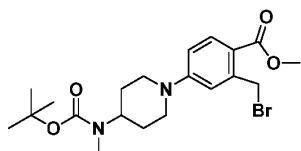


Trimethylsilyldiazomethane (25.5 mL, 51.04 mmol) was added in one portion to 4-((*tert*-butoxycarbonyl)-(methyl)-amino)piperidin-1-yl)-2-(hydroxymethyl)benzoic acid (6.20 g, 17.01 mmol) in MeOH (40 mL) and EtOAc (40 mL) at -10°C . The resulting solution was stirred at -10°C for 2h then water (600 mL) was added.

- 5 The mixture was extracted with EtOAc (3×300 mL) and the combined organic solutions were dried (MgSO_4) and concentrated to give the title compound (5.50 g, 85 %) as a brown oil which was used in the next step without further purification; ^1H NMR (300 MHz, CDCl_3) 1.47 (9H, s), 1.70-1.76 (4H, m), 2.71 (3H, s), 2.84-2.95 (1H, m), 2.95 (1H, d), 3.86 (3H, s), 3.88-4.04 (2H, m), 4.28 (1H, s), 4.72 (2H, s), 6.70-6.87 (1H, m), 6.87 (1H, d), 7.91 (1H, d); m/z ES^+ , $[\text{M}+\text{H}]^+ = 379.2$.

10

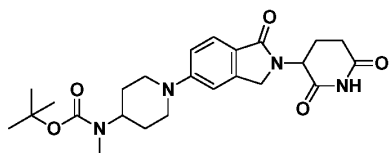
Intermediate 83d: Methyl 2-(bromomethyl)-4-((*tert*-butoxycarbonyl)(methyl)amino)piperidin-1-yl)benzoate



- 15 PPh_3 (4.96 g, 18.89 mmol) was added in one portion to methyl 4-((*tert*-butoxycarbonyl)(methyl)amino)-piperidin-1-yl)-2-(hydroxymethyl)benzoate (5.50 g, 14.53 mmol) and CBr_4 (6.27 g, 18.89 mmol) in THF (80 mL) at RT. The resulting solution was stirred at RT for 16h and then filtered and concentrated. Purification by FSC (gradient: 0-40% EtOAc in DCM) gave the title compound (5.00 g, 78 %) as a red oil; ^1H NMR (300 MHz, CDCl_3) 1.49 (9H, s), 1.67-1.83 (4H, m), 2.74 (3H, s), 2.74-2.99 (2H, m), 3.89 (3H, s), 3.97 (2H, d), 4.21 (1H, s), 4.98 (2H, s), 6.79-6.90 (1H, m), 6.91 (1H, d), 7.93 (1H, d); m/z ES^+ , $[\text{M}+\text{H}]^+ = 443.1$.

20

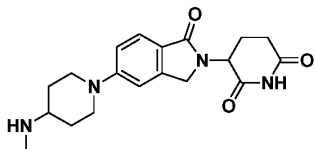
Intermediate 83e: *tert*-Butyl (1-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperidin-4-yl)-(methyl)carbamate



- 25 DIPEA (5.94 mL, 33.99 mmol) was added in one portion to methyl 2-(bromomethyl)-4-((*tert*-butoxycarbonyl)(methyl)amino)piperidin-1-yl)benzoate (5.00 g, 11.33 mmol) and 3-aminopiperidine-2,6-dione hydrochloride salt (2.80 g, 16.99 mmol) in MeCN (110 mL) at RT. The resulting solution was stirred at 80°C for 2 days then stirred overnight at RT. A precipitate was collected by filtration, washed with MeCN (100 mL) and dried under vacuum. Purification by FSC (gradient: 0-50% EtOAc in DCM) gave the title compound (3.30 g, 64 %) as a black solid; ^1H NMR (300 MHz) 1.41 (9H, s), 1.54-1.82 (4H, m), 1.89-2.03 (1H, m), 2.29-2.44 (1H, m), 2.54-2.64 (1H, m), 2.78-3.00 (3H, m), 3.08 (3H, s), 3.97 (3H, d), 4.21 (1H, d), 4.33 (1H, d), 5.00-
- 30

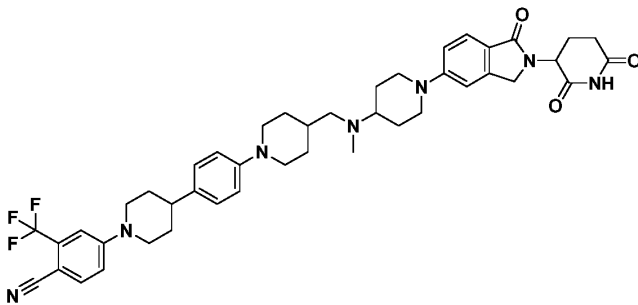
5.12 (1H, m), 7.02-7.11 (2H, m), 7.52 (1H, d), 10.95 (1H, s); m/z ES⁺, [M+H]⁺ = 457.2.

Intermediate 83f: 3-(5-(4-(Methylamino)piperidin-1-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione



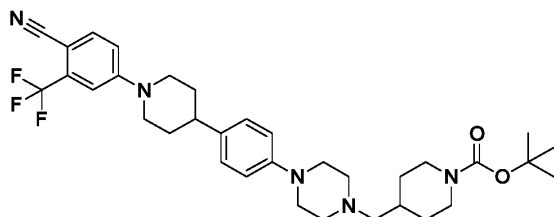
- 5 4M HCl in 1,4-dioxane (30 mL, 120.00 mmol) was added dropwise to butyl-(1-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperidin-4-yl)(methyl)carbamate (3.30 g, 7.23 mmol) in 1,4-dioxane (10 mL) at RT under N₂. The resulting mixture was stirred at RT for 16h. The mixture was then diluted with EtOAc (120 mL). A precipitate was collected by filtration, washed with EtOAc (300 mL) and dried under vacuum to give the title compound (2.90 g, 93 %) as a white solid; ¹H NMR (300 MHz) 1.73-1.93 (2H, m), 2.19 (2H, d), 2.32-2.45 (1H, m), 2.58 (2H, d), 2.79-2.98 (1H, m), 3.00-3.38 (3H, m), 3.56 (3H, s), 3.95 (2H, d), 4.25 (1H, d), 4.39 (1H, d), 5.01-5.13 (1H, m), 7.29-7.42 (2H, m), 7.62 (1H, d), 10.96 (1H, s); m/z ES⁺, [M+H]⁺ = 357.2.

Example 83: 4-((4-((1-(2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isindol-5-yl)piperidin-4-yl)(methylamino)methyl)piperidin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



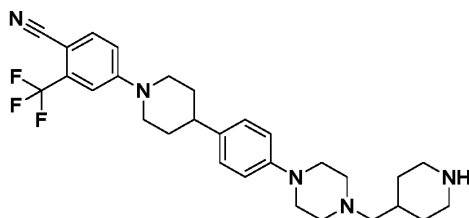
- 15 Intermediate 80a was reacted with Intermediate 83f using the general synthetic method illustrated by Example 2 to give the title compound after purification by HPLC (Column A, Eluent A, Basic Work-Up A); ¹H NMR: (CDCl₃) 0.85-0.90 (2H, m), 1.28-1.34 (3H, m), 1.69-1.75 (2H, m), 1.78 (2H, dd), 1.86 (3H, s), 1.97 (2H, d), 2.19 (1H, dtd), 2.33 (5H, dq), 2.57 (1H, d), 2.63-2.75 (3H, m), 2.85 (4H, tdd), 3.05 (2H, td), 3.65 (2H, d), 3.89 (2H, d), 4.01 (2H, d), 4.25 (1H, d), 4.40 (1H, d), 5.19 (1H, dd), 6.85-6.92 (3H, m), 6.98 (2H, d), 7.09 (2H, d), 7.15 (1H, d), 7.61 (1H, d), 7.72 (1H, d), 7.91 (1H, s); m/z ES⁺ [M+H]⁺ = 782.5.

Intermediate 84a: tert-Butyl 4-((4-(4-(1-(4-cyano-3-(trifluoromethyl)phenyl)piperidin-4-yl)phenyl)piperazin-1-yl)methyl)piperidine-1-carboxylate



BrettPhos Pd G3 (0.222 g, 0.24 mmol) was added to 4-(4-(4-bromophenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (2.00 g, 4.89 mmol), *tert*-butyl 4-(piperazin-1-ylmethyl)piperidine-1-carboxylate (1.524 g, 5.38 mmol) and Cs₂CO₃ (4.78 g, 14.66 mmol) in 1,4-dioxane (20 mL) at RT under N₂. The resulting solution was stirred at 100°C for 2h and then concentrated. Purification by FSC (gradient: 0-8% MeOH in DCM) gave the title compound (1.58 g, 53 %) as a yellow solid; *m/z* ES⁺, [M+H]⁺ = 612.

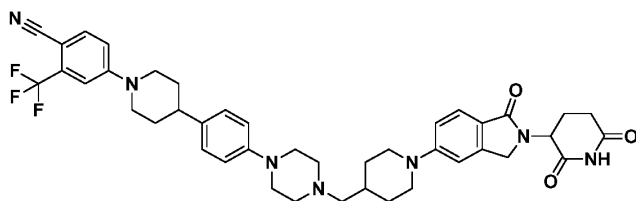
Intermediate 84b: 4-(4-(4-(4-(Piperidin-4-ylmethyl)piperazin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



10  4M HCl in 1,4-dioxane (12.26 mL, 49.04 mmol) was added slowly to *tert*-butyl 4-((4-(4-(1-(4-cyano-3-(trifluoromethyl)phenyl)piperidin-4-yl)phenyl)piperazin-1-yl)methyl)piperidine-1-carboxylate (1.50 g, 2.45 mmol) in DCM (50 mL). The resulting mixture was stirred at RT for 2h then concentrated. Purification by flash C18-flash chromatography (gradient: 0-100% MeCN in water (0.1 NH₄OH)) gave the title compound

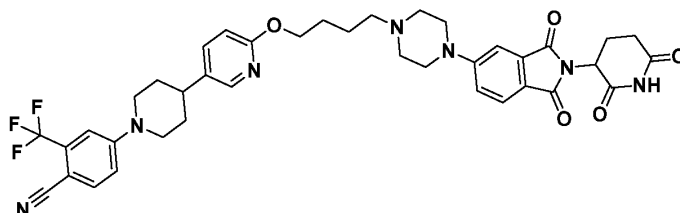
15 (0.950 g, 76 %) as a yellow solid; *m/z* ES⁺, [M+H]⁺ = 512.

Example 84: 4-(4-{4-[4-({1-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperidin-4-yl}methyl)piperazin-1-yl]phenyl}piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



- Pd-PEPPSI-IPent (107 mg, 0.14 mmol) was added to 4-(4-(4-(piperidin-4-ylmethyl)piperazin-1-yl)phenyl)-piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (700 mg, 1.37 mmol), 3-(5-bromo-1-oxoisindolin-2-yl)-piperidine-2,6-dione (442 mg, 1.37 mmol) and Cs_2CO_3 (892 mg, 2.74 mmol) in DMF (20 mL) under N_2 . The resulting mixture was stirred at 100°C for 15h. The mixture was then filtered through celite. Purification by
- 5 flash C18-flash chromatography (gradient: 0- 90% MeCN in water (containing 0.5% formic acid)) gave material that was further purified by preparative HPLC (Column: Xselect CSH OBD Column 30*150mm 5 μm ; Mobile Phase A:Water(0.1% formic acid), Mobile Phase B:MeCN; Flow rate:60 mL/min; Gradient: 34%B to 44%B in 7 min; 254 nm) to give the title compound as a formate salt (71.0 mg, 7%) as a yellow solid; ^1H NMR: 1.19 (2H, q), 1.53-1.67 (2H, m), 1.81 (5H, t), 1.91-1.99 (1H, m), 2.20 (2H, d), 2.32-2.43 (1H, m), 2.50-2.53 (2H, m), 2.54-2.59 (2H, m), 2.60-2.62 (1H, m), 2.65-2.75 (1H, m), 2.77-2.92 (3H, m), 2.98-3.11
- 10 (6H, m), 3.87 (2H, d), 4.13-4.23 (3H, m), 4.31 (1H, d), 5.04 (1H, dd), 6.86 (2H, d), 7.05-7.09 (4H, m), 7.26 (1H, dd), 7.32 (1H, d), 7.50 (1H, d), 7.81 (1H, d), 10.94 (1H, s); m/z ES^+ $[\text{M}+\text{H}]^+ = 754.4$.

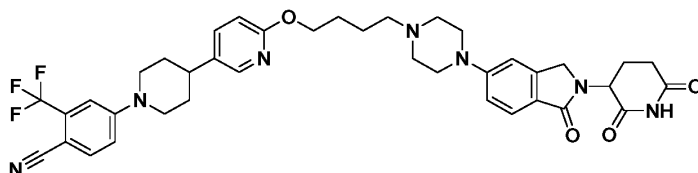
- Example 85: 4-{4-[6-(4-{4-[2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isindol-5-yl]piperazin-1-yl]butoxy}pyridin-3-yl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile**
- 15



- Intermediate 56f was reacted with Intermediate 63e using the general synthetic method illustrated by Example 2 to give the title compound after purification by HPLC (Column A, Eluent A, Basic Work-Up A); ^1H NMR: (CDCl_3) 1.65-1.73 (2H, m), 1.76 (2H, dd), 1.79-1.9 (2H, m), 1.97 (2H, d), 2.08-2.18 (1H, m), 2.43-2.51 (2H, m), 2.56-2.64 (4H, m), 2.67-2.74 (1H, m), 2.76 (1H, q), 2.77-2.86 (1H, m), 2.89 (1H, dd), 3.06 (2H, td), 3.3-
- 20 3.5 (4H, m), 4.03 (2H, d), 4.31 (2H, t), 4.93 (1H, dd), 6.70 (1H, d), 6.97-7.02 (1H, m), 7.05 (1H, dd), 7.16 (1H, d), 7.28 (1H, d), 7.43 (1H, dd), 7.62 (1H, d), 7.69 (1H, d), 7.95 (1H, s), 8.01 (1H, d); m/z ES^+ $[\text{M}+\text{H}]^+ = 744.0$.

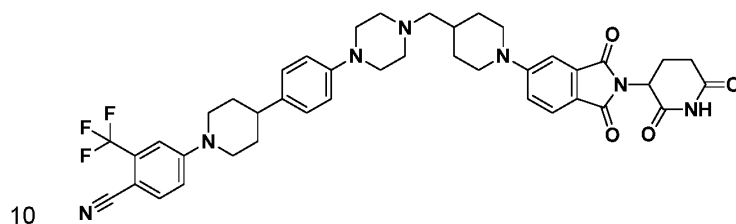
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- Example 86: 4-{4-[6-(4-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isindol-5-yl]piperazin-1-yl]butoxy}pyridin-3-yl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile**
- 30



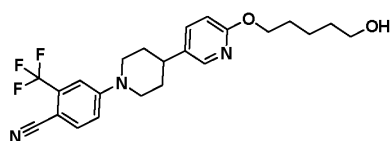
Intermediate 2c was reacted with Intermediate 56f using the general synthetic method illustrated by Example 2 to give the title compound after purification by HPLC (Column A, Eluent A, Basic Work-Up A); ¹H NMR: (CDCl₃) 1.50-1.90 (6H, m), 1.97 (2H, d), 2.19 (1H, dtd), 2.32 (1H, qd), 2.47 (2H, t), 2.61 (4H, s), 2.69-2.8 (1H, m), 2.8-2.87 (1H, m), 2.91 (1H, ddd), 3.06 (2H, td), 3.29-3.36 (4H, m), 4.03 (2H, d), 4.25 (1H, d), 4.30 (2H, t), 4.41 (1H, d), 5.19 (1H, dd), 6.70 (1H, d), 6.87 (1H, d), 6.99 (2H, dt), 7.16 (1H, d), 7.42 (1H, dd), 7.62 (1H, d), 7.73 (1H, d), 7.93 (1H, s), 8.01 (1H, d); *m/z* ES⁺ [M+H]⁺ = 730.5.

Example 87: 4-(4-{4-[4-{1-[2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isindol-5-yl]piperidin-4-yl}methyl]piperazin-1-yl}phenyl}piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



DIPEA (0.319 mL, 1.82 mmol) was added to 4-(4-(4-(piperidin-4-ylmethyl)piperazin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile hydrochloride salt (200 mg, 0.36 mmol) and 2-(2,6-dioxopiperidin-3-yl)-5-fluoroisindoline-1,3-dione (101 mg, 0.36 mmol) in DMF (5 mL). The resulting mixture was stirred at 100°C for 3h. The mixture was then diluted with EtOAc (50 mL), washed with water (50 mL) and then sat. brine (50 mL), dried (Na₂SO₄) and concentrated. Purification by preparative HPLC (Column A, Eluent A) gave the title compound (30.0 mg, 11 %) as a yellow solid; ¹H NMR: 1.11-1.24 (2H, m), 1.54-1.67 (2H, m), 1.77-1.89 (5H, m), 1.95-2.08 (1H, m), 2.12-2.26 (2H, m), 2.40-2.49 (2H, m), 2.52-2.63 (4H, m), 2.67-2.78 (1H, m), 2.80-2.90 (1H, m), 2.92-3.13 (8H, m), 4.05 (2H, d), 4.17 (2H, d), 5.06 (1H, dd), 6.87 (2H, d), 7.10 (2H, d), 7.20-7.30 (2H, m), 7.32 (2H, s), 7.65 (1H, d), 7.81 (1H, d), 11.07 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 768.4.

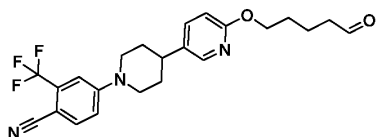
Intermediate 88a: 4-(4-(6-((5-Hydroxypentyl)oxy)pyridin-3-yl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



4-(4-(6-Chloropyridin-3-yl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (0.50 g, 1.37 mmol), Cs₂CO₃ (1.55 g, 4.78 mmol) and pentane-1,5-diol (0.72 mL, 6.83 mmol) were dissolved in toluene (15 mL) at degassed with N₂. Rockphos Pd G3 (0.057 g, 0.07 mmol) was then added and the mixture was heated at 90°C for 2h. The mixture was then diluted with EtOAc (100 mL), washed with water (100 mL) and then sat. brine (100 mL), dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-100% EtOAc in heptane) gave the title compound (0.375 g, 64 %) as a pale yellow oil; ¹H NMR (CDCl₃) 1.28 (1H, t), 1.53 (1H, s), 1.55-1.58 (1H, m), 1.61-1.7 (2H, m), 1.7-1.86 (4H, m), 1.92-2 (2H, m), 2.75 (1H, tt), 3.06 (2H, td), 3.62-3.75 (2H, m), 4.03 (2H, d), 4.28 (2H, t), 6.69 (1H, d), 6.99 (1H, dd), 7.16 (1H, d), 7.42 (1H, dd), 7.62 (1H, d), 8.01 (1H, d);

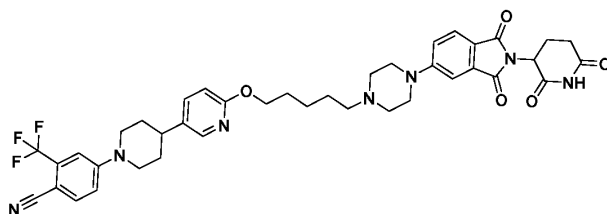
m/z : $ES^+ [M+H]^+$ 433.6.

Intermediate 88b: 4-(4-(6-((5-Oxopentyl)oxy)pyridin-3-yl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



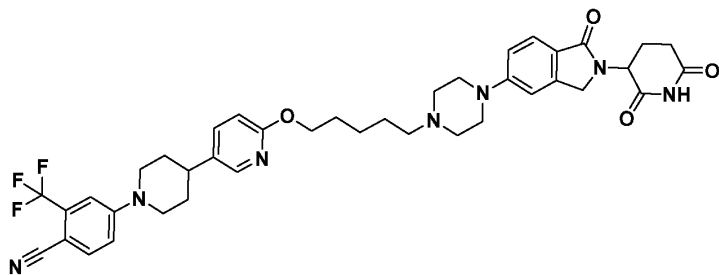
- 5 Dess-Martin periodinane (205 mg, 0.48 mmol) was added to 4-(4-(6-((5-hydroxypentyl)oxy)pyridin-3-yl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (190 mg, 0.44 mmol) in DCM (5 mL) at RT. The resulting mixture was stirred at RT for 1h. The mixture was then diluted with DCM (15 mL) and poured into mixture of sat. $NaHCO_3$ (25 mL) and sodium thiosulfate solution (25 mL). The resulting suspension was stirred vigorously for 10 mins and the layers were separated. The organic solution was dried (Na_2SO_4) and
- 10 concentrated to give the title compound (190 mg, 100 %) as a yellow dry film, which was used in the next step without further purification; ^1H NMR ($CDCl_3$) 1.75 (2H, td), 1.8-1.83 (3H, m), 1.98 (2H, d), 2.52 (2H, td), 2.75 (1H, ddt), 3.06 (2H, td), 3.93-4.09 (2H, m), 4.19-4.35 (2H, m), 6.69 (1H, d), 7.00 (1H, dd), 7.16 (1H, d), 7.42 (1H, dd), 7.62 (1H, d), 7.96-8.03 (2H, m), 9.79 (1H, t); m/z : $ES^+ [M+H]^+$ 432.2.

- 15 **Example 88: 4-(4-(6-((5-(4-(2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)piperazin-1-yl)pentyl)oxy)pyridin-3-yl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile**



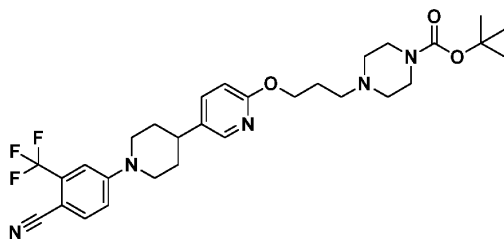
- Intermediate 63e was reacted with Intermediate 88b using the general synthetic method illustrated by Example 2 to give the title compound (as a formate salt) after purification by HPLC (Column A, Eluent A). ^1H NMR:
- 20 ($CDCl_3$) 1.51 (2H, p), 1.65-1.76 (3H, m), 1.76-1.86 (3H, m), 1.97 (2H, d), 2.14 (1H, ddq), 2.62-2.71 (2H, m), 2.71-2.74 (1H, m), 2.77 (1H, dd), 2.8-2.86 (1H, m), 2.89 (5H, dt), 3.06 (2H, td), 3.53-3.58 (4H, m), 3.71 (1H, s), 4.03 (2H, d), 4.27 (2H, t), 4.94 (1H, dd), 6.71 (1H, s), 7.00 (1H, dd), 7.07 (1H, dd), 7.16 (1H, d), 7.30 (1H, d), 7.43 (1H, dd), 7.62 (1H, d), 7.72 (1H, d), 8.01 (1H, d), 8.16 (2H, s); m/z : $ES^+ [M+H]^+$ = 758.5.

- 25 **Example 89: 4-(4-(6-((5-(4-(2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl)piperazin-1-yl)pentyl)oxy)pyridin-3-yl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile**



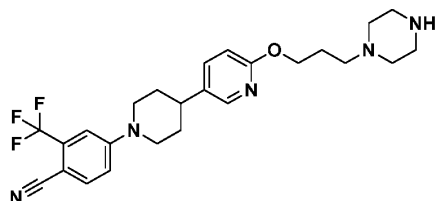
Intermediate 2c was reacted with Intermediate 88b using the general synthetic method illustrated by Example 2 to give the title compound (as a formate salt) after purification by HPLC (Column A, Eluent A). ¹H NMR: (CDCl₃) 1.53 (2H, p), 1.7-1.79 (2H, m), 1.82 (4H, dd), 1.97 (2H, d), 2.21 (1H, dt), 2.34 (1H, qd), 2.74 (1H, dt), 2.78-2.88 (3H, m), 2.92 (1H, ddd), 3.08 (6H, dd), 3.54-3.59 (4H, m), 4.03 (2H, d), 4.25-4.3 (3H, m), 4.43 (1H, d), 5.20 (1H, dd), 6.70 (1H, d), 6.90 (1H, d), 7.00 (2H, dd), 7.16 (1H, d), 7.43 (1H, dd), 7.62 (1H, d), 7.76 (1H, d), 8.01 (2H, d), 8.16 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 743.9.

Intermediate 90a: *tert*-Butyl 4-(3-((5-(1-(4-cyano-3-(trifluoromethyl)phenyl)piperidin-4-yl)pyridin-2-yl)oxy)propyl)piperazine-1-carboxylate



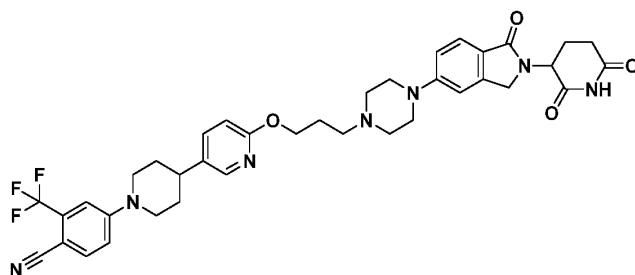
4-(4-(6-Chloropyridin-3-yl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (Intermediate 56d) (0.500 g, 1.37 mmol), Cs₂CO₃ (1.56 g, 4.78 mmol) and *tert*-butyl 4-(3-hydroxypropyl)piperazine-1-carboxylate (0.835 g, 3.42 mmol) were dissolved in toluene (15 mL) and degassed with N₂. Rockphos Pd G3 (0.057 g, 0.07 mmol) was added and the mixture was then heated at 90°C for 18h. The mixture was then diluted with EtOAc (100 mL), washed with water (100 mL) and then sat. brine (100 mL), dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-100% EtOAc in heptane) gave the title compound (0.285 g, 36 %) as a pale yellow solid; ¹H NMR (CDCl₃) 1.46 (9H, s), 1.76 (2H, qd), 1.92-1.99 (4H, m), 2.31-2.45 (4H, m), 2.46-2.55 (2H, m), 2.75 (1H, tt), 3.06 (2H, td), 3.37-3.46 (4H, m), 4.03 (2H, d), 4.32 (2H, t), 6.69 (1H, d), 6.93-7.02 (1H, m), 7.16 (1H, d), 7.42 (1H, dd), 7.62 (1H, d), 8.01 (1H, d); *m/z*: ES⁺ [M+H]⁺ = 574.0.

Intermediate 90b: 4-(4-(6-(3-(Piperazin-1-yl)propoxy)pyridin-3-yl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



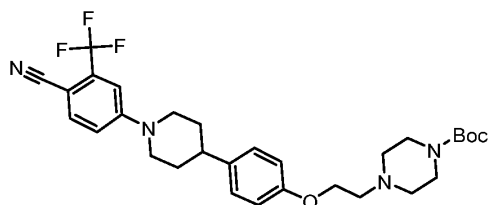
- 4M HCl in 1,4-dioxane (1.24 mL, 4.97 mmol) was added to *tert*-butyl 4-(3-((5-(1-(4-cyano-3-(trifluoromethyl)-phenyl)piperidin-4-yl)pyridin-2-yl)oxy)propyl)piperazine-1-carboxylate (285 mg, 0.50 mmol) in DCM (25 mL) and the mixture was stirred for 1h. Concentration under reduced pressure then gave the title compound as a bis-hydrochloride salt (255 mg, 101 %) as a white solid which was used directly in next step; ¹H NMR (CDCl₃) 1.76 (3H, qd), 1.97 (4H, d), 2.61 (2H, s), 2.72-2.78 (5H, m), 3.00-3.11 (2H, m), 3.15-3.22 (4H, m), 4.03 (2H, d), 4.32 (2H, t), 6.68 (1H, d), 7.00 (1H, dd), 7.16 (1H, d), 7.42 (1H, dd), 7.62 (1H, d), 8.00 (1H, d), 9.62 (1H, s); *m/z*: ES⁺ [M+H]⁺ 474.3.

10 Example 90: 4-(4-[6-(3-[4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazin-1-yl]propoxy)pyridin-3-yl]piperidin-1-yl]-2-(trifluoromethyl)benzonitrile



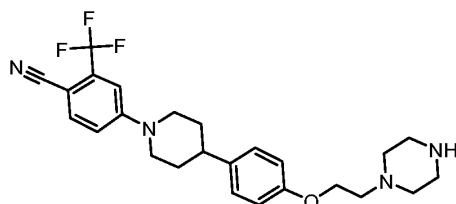
- CS₂CO₃ (466 mg, 1.43 mmol) and Pd-PEPPSI I-pent (18.89 mg, 0.02 mmol) were added in one portion to a degassed solution of 4-(4-(6-(3-(piperazin-1-yl)propoxy)pyridin-3-yl)piperidin-1-yl)-2-(trifluoromethyl)-benzonitrile (226 mg, 0.48 mmol) and 3-(5-bromo-1-oxoisindolin-2-yl)piperidine-2,6-dione (154 mg, 0.48 mmol) in 1,4-dioxane (8 mL) under N₂. The resulting mixture was stirred at 90°C for 5h. The mixture was then cooled to RT, diluted with DCM (50 mL), washed with 5% AcOH in water (50 mL), then water (50 mL), then dried (MgSO₄) and concentrated. Purification by preparative HPLC (Column A, Eluent A) was carried out. Fractions containing the desired compound were combined, diluted with water (150 mL) and extracted with DCM (3 × 100 mL). The combined organic solutions were washed with brine (100 mL), dried (MgSO₄) and concentrated. Further purification by preparative HPLC (Column A, Eluent A) gave the title compound as a formate salt (4.00 mg, 1 %) as a colourless gum. ¹H NMR: (CDCl₃) 1.76 (2H, qd), 1.98 (2H, d), 2.07 (2H, dt), 2.20 (1H, dtd), 2.33 (1H, qd), 2.73 (3H, dd), 2.77-2.81 (4H, m), 2.82-2.9 (2H, m), 2.93 (1H, dd), 2.98 (1H, s), 3.06 (3H, td), 3.34-3.45 (4H, m), 4.03 (2H, d), 4.26 (1H, d), 4.35 (2H, t), 4.42 (1H, d), 5.19 (1H, dd), 6.71 (1H, d), 6.88 (1H, d), 6.99 (2H, dd), 7.16 (1H, d), 7.43 (1H, dd), 7.62 (1H, d), 7.74 (1H, d), 8.01 (1H, d); *m/z*: ES⁺ [M+H]⁺ = 716.5.

Intermediate 91a: *tert*-Butyl 4-(2-(4-(1-(4-cyano-3-(trifluoromethyl)phenyl)piperidin-4-yl)phenoxy)-ethyl)piperazine-1-carboxylate



- RockPhos Pd G3 (0.102 g, 0.12 mmol) was added to 4-(4-(4-bromophenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (1.00 g, 2.44 mmol), *tert*-butyl 4-(2-hydroxyethyl)piperazine-1-carboxylate (0.844 g, 3.67 mmol) and Cs₂CO₃ (1.59 g, 4.89 mmol) in toluene (20 mL) under N₂. The resulting mixture was stirred overnight at 100°C then concentrated. Purification by FSC (gradient: 0-70% EtOAc in petroleum ether) gave the title compound (0.80 g, 59 %) as a yellow oil which solidified on standing; *m/z* ES⁺, [M+H]⁺ = 559.

Intermediate 91b: 4-(4-(4-(2-(Piperazin-1-yl)ethoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile

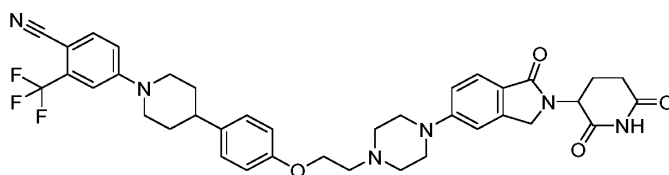


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4M HCl in dioxane (10 mL, 40.00 mmol) was added to *tert*-butyl 4-(2-(4-(1-(4-cyano-3-(trifluoromethyl)phenyl)piperidin-4-yl)phenoxy)ethyl)piperazine-1-carboxylate (750 mg, 1.34 mmol) in DCM (20 mL). The resulting mixture was stirred at RT for 2h. The solvent was removed under reduced pressure to give the title compound as a brown solid (assumed 100% yield); *m/z* ES⁺, [M+H]⁺ = 459.

15

Example 91: 4-(4-(4-(2-(4-(2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl)piperazin-1-yl)ethoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile

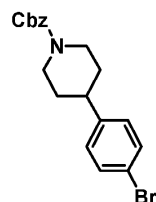


- Pd-PEPPSI-IPent (4.32 mg, 5.45 μmol) was added to 4-(4-(4-(2-(piperazin-1-yl)ethoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (50 mg, 0.11 mmol), 3-(5-bromo-1-oxoisindolin-2-yl)piperidine-2,6-dione (35.2 mg, 0.11 mmol) and Cs₂CO₃ (107 mg, 0.33 mmol) in DMF (3 mL) at RT under N₂. The resulting solution was stirred at 90°C for 16h. The mixture was then diluted with EtOAc (10 mL), washed with water (10 mL × 3) then sat. brine (10 mL × 2), dried (Na₂SO₄) and concentrated. Purification by preparative HPLC (Column: XBridge Shield RP18 OBD Column, 30*150mm, 5μm; Mobile Phase A: Water (10 mmol/L NH₄HCO₃+0.1% NH₃·H₂O), Mobile Phase B: MeCN) gave the title compound (11 mg, 14 %) as a white solid; ¹H NMR: 1.63 (2H, qd), 1.85 (2H, d), 1.92-2.00 (1H, m), 2.35-2.40 (1H, m), 2.56 (1H, s), 2.60-2.67 (3H, m), 2.71-2.81 (3H, m), 2.85-2.95 (1H, m), 3.05 (2H, t), 3.33 (5H, s), 4.10 (2H, t), 4.14-4.26 (3H, m), 4.33 (1H, d),

25

5.05 (1H, dd), 6.89 (2H, d), 7.07 (2H, d), 7.17 (2H, d), 7.28 (1H, dd), 7.33 (1H, d), 7.52 (1H, d), 7.82 (1H, d), 10.95 (1H, s); m/z : ES^+ $[M+H]^+ = 701.3$.

Intermediate 92a: Benzyl 4-(4-bromophenyl)piperidine-1-carboxylate



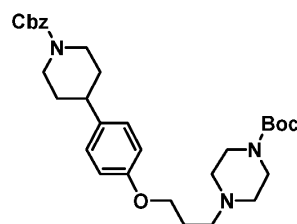
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Benzyl carbonochloridate (4.26 g, 24.99 mmol) was added dropwise to 4-(4-bromophenyl)piperidine (5.00 g, 20.82 mmol) and DIPEA (10.91 mL, 62.46 mmol) in DCM (100 mL) at 0°C over 5 mins. The resulting mixture was stirred at RT for 3h. The mixture was then diluted with DCM (100 mL), washed with water (200 mL $\times$ 2), dried (Na_2SO_4) and concentrated. Purification by FSC (gradient: 0-50% EtOAc in petroleum ether) gave the title compound (5.50 g, 71 %) as a yellow oil which solidified on standing; ^1H NMR ($CDCl_3$, 300 MHz) 1.37-1.72 (2H, m), 1.84 (2H, d), 2.54-2.75 (1H, m), 2.90 (2H, t), 4.34 (2H, br), 5.18 (2H, s), 7.04-7.24 (2H, m), 7.26-7.61 (7H, m); m/z : ES^+ $[M+H]^+ = 374$.

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Intermediate 92b: *tert*-Butyl 4-(3-(4-(1-((benzyloxy)carbonyl)piperidin-4-yl)phenoxy)propyl)piperazine-1-carboxylate

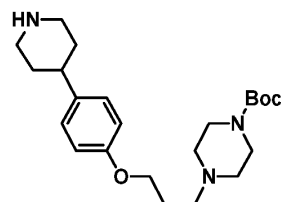
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RockPhos Pd G3 (0.336 g, 0.40 mmol) was added to benzyl 4-(4-bromophenyl)piperidine-1-carboxylate (3.00 g, 8.02 mmol), *tert*-butyl 4-(3-hydroxypropyl)piperazine-1-carboxylate (1.96 g, 8.02 mmol) and Cs_2CO_3 (5.22 g, 16.03 mmol) in toluene (60 mL) under N_2 . The resulting mixture was stirred at 100°C overnight and then concentrated. Purification by FSC (gradient: 0-70% EtOAc in petroleum ether) gave the title compound (2.30 g, 53 %) as a yellow oil which solidified on standing; m/z : ES^+ $[M+H]^+ = 538$.

Intermediate 92c: *tert*-Butyl 4-(3-(4-(Piperidin-4-yl)phenoxy)propyl)piperazine-1-carboxylate



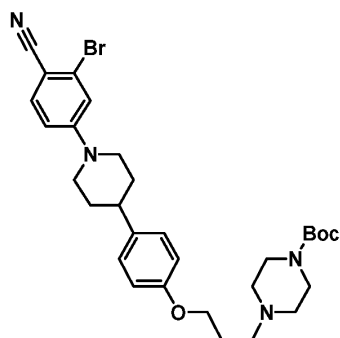
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tert-Butyl 4-(3-(4-(1-((benzyloxy)carbonyl)piperidin-4-yl)phenoxy)propyl)piperazine-1-carboxylate (2.800 g, 5.21 mmol) and $Pd(OH)_2$ (0.366 g, 0.26 mmol) in EtOAc (50 mL) were stirred under H_2 (with balloon) at RT

for 15h. The mixture was then filtered through celite and the filtrate was concentrated to dryness to give the title compound (1.80 g, 86 %) as a yellow solid; ^1H NMR (CDCl_3 , 300 MHz) 1.48 (9H, s), 1.66-2.07 (6H, m), 2.41-2.43 (4H, m), 2.49-2.63 (2H, m), 2.58-2.84 (2H, m), 2.82-2.34 (1H, m), 3.30 (2H, d), 3.44-3.46 (4H, m), 3.51 (3H, s), 4.02 (2H, t), 6.82-6.92 (2H, m), 7.15 (2H, d) m/z : $\text{ES}^+ [\text{M}+\text{H}]^+ = 404$.

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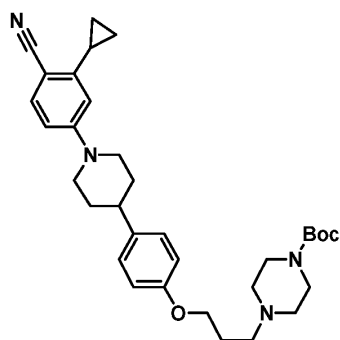
Intermediate 92d: *tert*-Butyl 4-(3-(4-(1-(3-bromo-4-cyanophenyl)piperidin-4-yl)phenoxy)propyl)piperazine-1-carboxylate



Cs_2CO_3 (1.45 g, 4.46 mmol) was added to *tert*-butyl 4-(3-(4-(piperidin-4-yl)phenoxy)propyl)piperazine-1-carboxylate (0.9 g, 2.23 mmol) and 2-bromo-4-fluorobenzonitrile (0.446 g, 2.23 mmol) in DMF (20 mL). The resulting mixture was stirred at 100°C for 15h. The mixture was then diluted with EtOAc (100 mL), washed with water (100 mL) then sat. brine (100 mL), dried (Na_2SO_4) and concentrated. Purification by FSC (gradient: 0-50% EtOAc in petroleum ether) gave the title compound (0.850 g, 65 %) as a yellow oil which solidified on standing; m/z : $\text{ES}^+ [\text{M}+\text{H}]^+ = 583$.

15

Intermediate 92e: *tert*-Butyl 4-(3-(4-(1-(4-cyano-3-cyclopropylphenyl)piperidin-4-yl)phenoxy)propyl)piperazine-1-carboxylate

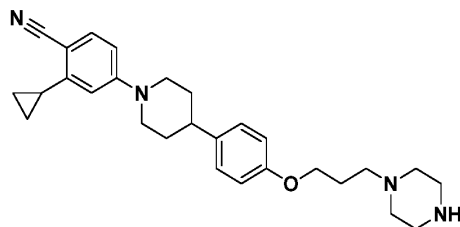


$\text{PdCl}_2(\text{dppf})$ (50.2 mg, 0.07 mmol) was added to a mixture of *tert*-butyl 4-(3-(4-(1-(3-bromo-4-cyanophenyl)piperidin-4-yl)phenoxy)propyl)piperazine-1-carboxylate (400 mg, 0.69 mmol), 2-cyclopropyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (173 mg, 1.03 mmol) and K_3PO_4 (291 mg, 1.37 mmol) in 1,4-dioxane (15 mL) under N_2 . The resulting mixture was stirred at 90°C for 15h. The mixture was then concentrated and the residue dissolved in EtOAc (50 mL). This solution was washed with water (50 mL) then sat. brine (50 mL), dried (Na_2SO_4) and concentrated. Purification by FSC (gradient: 0-50% EtOAc in petroleum ether) gave the

20

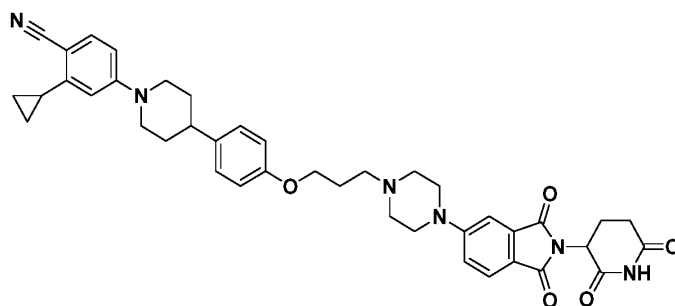
title compound (280 mg, 75 %) as a yellow solid; m/z : ES^+ $[M+Na]^+ = 567$.

Intermediate 92f: 2-Cyclopropyl-4-(4-(4-(3-(piperazin-1-yl)propoxy)phenyl)piperidin-1-yl)benzonitrile



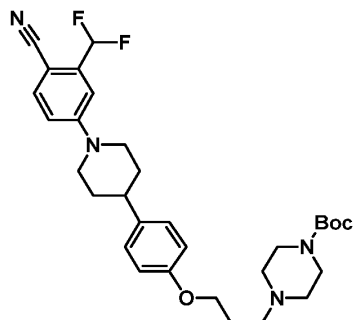
- 5 4M HCl in 1,4-dioxane (3.86 mL, 15.42 mmol) was added to *tert*-butyl 4-(3-(4-(1-(4-cyano-3-cyclopropyl-phenyl)piperidin-4-yl)phenoxy)propyl)piperazine-1-carboxylate (280 mg, 0.51 mmol) in DCM (20 mL). The resulting mixture was stirred at RT for 2h. The solvent was then removed under reduced pressure to give the title compound (220 mg, 89 %) as a yellow solid; m/z : ES^+ $[M+H]^+ = 445$.

- 10 **Example 92: 2-Cyclopropyl-4-{4-[4-(3-{4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazin-1-yl}propoxy)phenyl]piperidin-1-yl}benzonitrile**



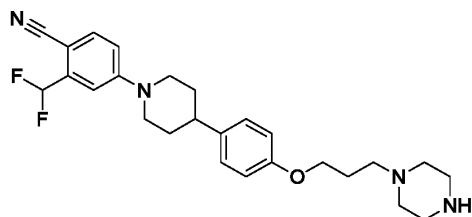
- Intermediate 63c was reacted with Intermediate 92f using the general synthetic method illustrated by Example 87 to give the title compound after purification by HPLC (Column A, Eluent A). ^1H NMR: 0.79-0.88 (2H, m), 0.98-1.08 (2H, m), 1.53-1.66 (2H, m), 1.81 (2H, d), 1.86-1.93 (2H, m), 1.98-2.12 (2H, m), 2.46 (3H, m), 2.51-2.70 (7H, m), 2.70-2.80 (1H, m), 2.88 (3H, t), 3.41-3.45 (4H, m), 3.95-4.06 (4H, m), 5.07 (1H, dd), 6.46 (1H, d), 6.81-6.90 (3H, m), 7.11-7.18 (2H, m), 7.26 (1H, dd), 7.34 (1H, d), 7.47 (1H, d), 7.68 (1H, d), 11.08 (1H, s); m/z : ES^+ $[M+H]^+ = 701.4$.

- 20 **Intermediate 93a: *tert*-Butyl 4-(3-(4-(1-(4-cyano-3-(difluoromethyl)phenyl)piperidin-4-yl)phenoxy)-propyl)piperazine-1-carboxylate**



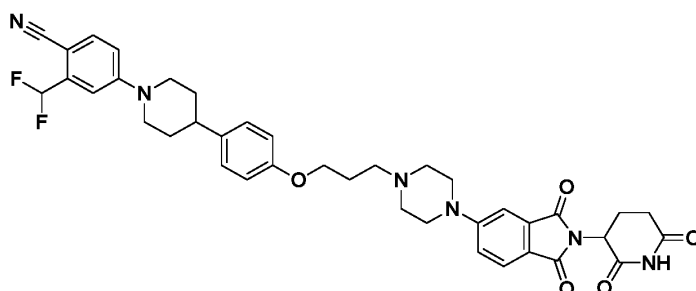
Bis(dibenzylideneacetone)palladium (39.4 mg, 0.07 mmol) was added to *tert*-butyl 4-(3-(4-(1-(3-bromo-4-cyanophenyl)piperidin-4-yl)phenoxy)propyl)piperazine-1-carboxylate (Intermediate 92d) (400 mg, 0.69 mmol), (oxydi-2,1-phenylene)bis(diphenylphosphine) (73.8 mg, 0.14 mmol) and (1,3-bis(2,6-diisopropylphenyl)imidazolidin-2-yl)(difluoromethyl)silver (377 mg, 0.69 mmol) in toluene (10 mL) under N₂. The resulting solution was stirred at 80°C for 18h. The mixture was then concentrated and diluted with EtOAc (50 mL). This solution was then washed with water (50 mL × 2) and sat. brine (50 mL), dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-50% EtOAc in petroleum ether) gave the title compound (311 mg, 82 %) as a yellow oil which solidified on standing; *m/z*: ES⁺ [M+H]⁺ = 555.

Intermediate 93b: 2-(Difluoromethyl)-4-(4-(4-(3-(piperazin-1-yl)propoxy)phenyl)piperidin-1-yl)benzonitrile



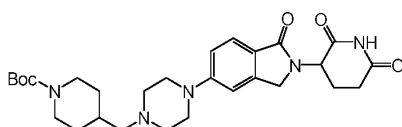
4M HCl in 1,4-dioxane (2.70 mL, 10.82 mmol) was added to *tert*-butyl 4-(3-(4-(1-(4-cyano-3-(difluoromethyl)-phenyl)piperidin-4-yl)phenoxy)propyl)piperazine-1-carboxylate (300 mg, 0.54 mmol) in DCM (10 mL) at RT. The resulting mixture was stirred at RT for 3h. The solvent was then removed under reduced pressure to give the title compound as a hydrochloride salt (253 mg, 95 %) as a yellow solid; *m/z*: ES⁺ [M+H]⁺ = 455.

Example 93: 2-(Difluoromethyl)-4-{4-[4-(3-[4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazin-1-yl}propoxy)phenyl]piperidin-1-yl}benzonitrile



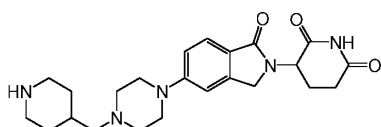
Intermediate 63c was reacted with Intermediate 93b using the general synthetic method illustrated by Example 87 to give the title compound after purification by HPLC (Column A, Eluent A). ¹H NMR: 1.55-1.69 (2H, m), 1.80-1.95 (4H, m), 1.98-2.05 (1H, m), 2.46 (2H, d), 2.51-2.63 (3H, m), 2.65 (1H, m), 2.77 (1H, d), 2.88 (1H, dd), 3.01 (2H, t), 3.30 (2H, m), 3.44 (4H, s), 3.99 (2H, t), 4.11 (2H, d), 5.07 (1H, dd), 6.86 (2H, d), 6.90-7.21 (4H, m), 7.22-7.41 (3H, m), 7.69 (2H, dd), 11.08 (1H, s); ¹⁹F NMR: (376 MHz) -110.7; *m/z*: ES⁺ [M+H]⁺ = 711.4.

Intermediate 94a: *tert*-Butyl 4-((4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazin-1-yl)methyl)piperidine-1-carboxylate



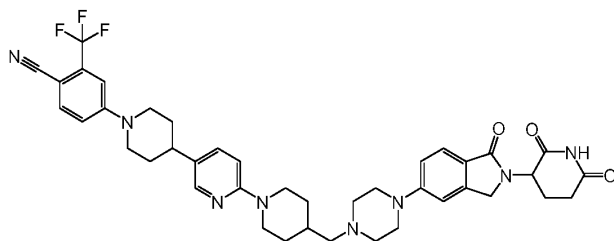
Sodium acetate (0.675 g, 8.22 mmol) was added in one portion to a stirred solution of *tert*-butyl 4-formylpiperidine-1-carboxylate (0.643 g, 3.02 mmol) and 3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride salt (1.00 g, 2.74 mmol) in DCM (100 mL) at RT under air. The resulting suspension was stirred for 1h at RT and then NaBH(OAc)₃ (0.871 g, 4.11 mmol) was added and the mixture was stirred at RT for 1h. The mixture was then diluted with water (20 mL). The organic phase was separated, washed with sat. NaHCO₃ solution (20 mL) and sat. brine (20 mL), dried (Na₂SO₄) and concentrated under reduced pressure to give the title compound (1.44 g, 100 %) which was used directly in the next step; *m/z*: ES⁺ [M-H]⁺ 524.2.

Intermediate 94b: 3-(1-Oxo-5-(4-(piperidin-4-ylmethyl)piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione



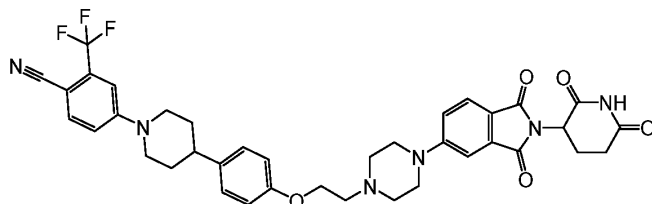
HCl (4M in 1,4-dioxane) (6.85 mL, 27.40 mmol) was added to *tert*-butyl 4-((4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazin-1-yl)methyl)piperidine-1-carboxylate (1.44 g, 2.74 mmol) in DCM (25 mL) and the mixture was stirred for 1h. Concentration under reduced pressure gave the title compound as a bis-HCl salt (1.40 g, 103 %) as a white solid, which was used directly in the next step; *m/z*: ES⁺ [M-H]⁺ 426.0.

Example 94: 4-[4-(6-{4-[(4-{2-[(3*R*)-2,6-Dioxopiperidin-3-yl]-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]-

piperazin-1-yl)methyl)piperidin-1-yl}pyridin-3-yl)piperidin-1-yl]-2-(trifluoromethyl)benzonitrile

- Anhydrous DMF (5mL) was added to a mixture of 4-(4-(6-chloropyridin-3-yl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (Intermediate 56d) (143 mg, 0.39 mmol), 3-(1-oxo-5-(4-(piperidin-4-ylmethyl)piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride salt (150 mg, 0.32 mmol), RuPhos (15.15 mg, 0.03 mmol), RuPhos Pd G3 (27.2 mg, 0.03 mmol) and sodium *tert*-butoxide (109 mg, 1.14 mmol). This mixture was degassed, under N₂, and stirred at 70°C for 1h. After cooling, the mixture was diluted with EtOAc (50 mL) and quenched with 5% AcOH in water (20 mL). The organics were separated, washed with sat. NaHCO₃ solution (50 mL) and brine (50 mL) then dried (Na₂SO₄) and concentrated. Preparative HPLC (Column A, Eluent A, Basic Work-Up A) gave the title compound (15.0 mg, 6 %) as a white solid; ¹H NMR: (CDCl₃) 1.30-1.45 (2H, m), 1.68-1.8 (3H, m), 1.85-1.99 (4H, m), 2.15-2.24 (1H, m), 2.27 (2H, d), 2.3-2.4 (1H, m), 2.53-2.64 (4H, m), 2.69 (1H, t), 2.76-2.87 (3H, m), 2.91 (1H, d), 3.05 (2H, t), 3.26-3.37 (4H, m), 4.01 (2H, d), 4.25 (3H, d), 4.41 (1H, d), 5.19 (1H, dd), 6.64 (1H, d), 6.88 (1H, s), 6.99 (2H, dd), 7.16 (1H, d), 7.31 (1H, dd), 7.62 (1H, d), 7.73 (1H, d), 7.84 (1H, s), 8.06 (1H, d); *m/z*: ES⁺ [M+H]⁺ = 755.0.

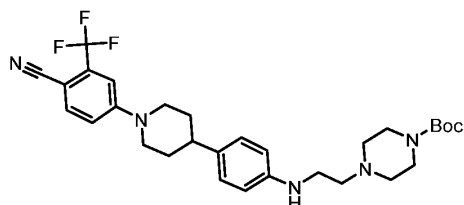
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Example 95: 4-{4-[4-(2-{4-[2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl}ethoxy)phenyl]piperidin-1-yl]-2-(trifluoromethyl)benzonitrile

- Intermediate 63c was reacted with Intermediate 91b using the general synthetic method illustrated by Example 87 to give the title compound after purification by HPLC (Column: Sunfire prep C18 column, 30*150, 5μm; Mobile Phase A: Water (0.1% formic acid), Mobile Phase B: MeCN; Flow rate:60 mL/min; Gradient: 30 B to 50 B in 7 min; 254/220 nm; RT1:6.62). ¹H NMR: (300 MHz) 1.55-1.75 (2H, m), 1.83 (2H, d), 1.93-2.05 (2H, m), 2.51-2.64 (5H, m), 2.69-2.77 (3H, m), 2.78-2.96 (1H, m), 3.03 (2H, t), 3.37-3.48 (4H, m), 4.08 (2H, t), 4.16 (2H, d), 5.05 (1H, dd), 6.88 (2H, d), 7.15 (2H, d), 7.25 (2H, d), 7.32 (2H, d), 7.66 (1H, d), 7.80 (1H, d), 11.06 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 715.4.

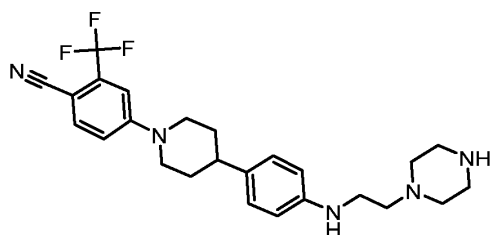
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Intermediate 96a: *tert*-Butyl 4-(2-((4-(1-(4-cyano-3-(trifluoromethyl)phenyl)piperidin-4-yl)phenyl)amino)ethyl)piperazine-1-carboxylate



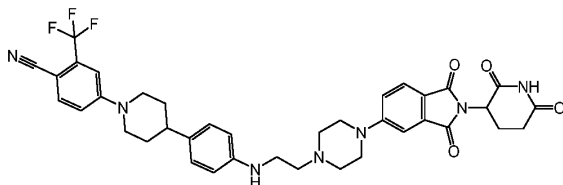
- Brettphos Pd G3 (0.222 g, 0.24 mmol) was added to 4-(4-(4-bromophenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (1.00 g, 2.44 mmol), *tert*-butyl 4-(2-aminoethyl)piperazine-1-carboxylate (0.62 g, 2.69 mmol) and Cs₂CO₃ (2.39 g, 7.33 mmol) in 1,4-dioxane (10 mL) at RT under N₂. The resulting mixture was stirred at 100°C for 15h under N₂. The mixture was then diluted with EtOAc (75 mL), and washed with sat. brine (50 mL × 3). The organic solution was dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 30-50% EtOAc in petroleum ether) gave the title compound (1.12 g, 82 %) as a white solid; ¹H NMR (300 MHz) 0.84 (1H, q), 1.39 (9H, s), 1.57 (2H, td), 1.81 (2H, d), 2.35-2.67 (4H, m), 2.46 (1H, s), 2.65 (1H, t), 2.95-3.15 (4H, m), 3.29 (2H, s), 4.15 (2H, d), 5.20 (1H, t), 6.51 (2H, d), 6.95 (2H, d), 7.25 (1H, dd), 7.31 (1H, d), 7.80 (1H, d); *m/z* ES⁺, [M+H]⁺ = 558.

Intermediate 96b: 4-(4-(4-(2-(Piperazin-1-yl)ethoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



- tert*-Butyl 4-(2-((4-(1-(4-cyano-3-(trifluoromethyl)phenyl)piperidin-4-yl)phenyl)amino)ethyl)piperazine-1-carboxylate (200 mg, 0.36 mmol) was added to 4M HCl solution in 1,4-dioxane (1.00 mL, 4.00 mmol) in MeOH (2 mL) at RT under air. The resulting mixture was stirred at RT for 3h. The solvent was removed under reduced pressure to give the title compound (159 mg, 97 %) as a white solid; ¹H NMR (300 MHz) 1.61 (2H, dd), 1.82 (2H, d), 2.69 (1H, d), 3.03 (2H, t), 3.32 (2H, d), 3.52-3.54 (10H, m), 4.16 (2H, d), 6.71 (2H, d), 7.06 (2H, d), 7.26 (1H, d), 7.31 (1H, d), 7.81 (1H, d), 9.76 (1H, s); *m/z* ES⁺, [M+H]⁺ = 458.

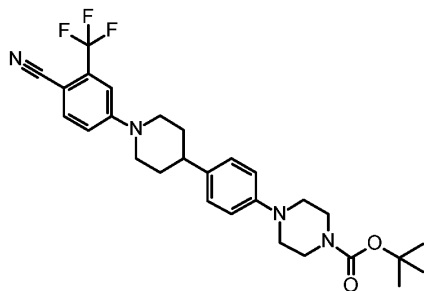
Example 96: 4-(4-{4-[(2-{4-[2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl}ethyl)amino]phenyl}piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



- Intermediate 63c was reacted with Intermediate 96b using the general synthetic method illustrated by Example 87 to give the title compound after purification by HPLC (Column B, Eluent A); ¹H NMR: 1.51-1.65 (2H, m),

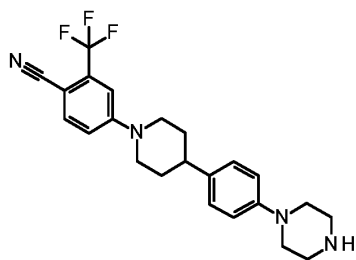
1.81 (2H, d), 1.95-2.07 (1H, m), 2.52-2.70 (8H, m), 2.88 (1H, ddd), 3.02 (2H, t), 3.14 (2H, t), 3.46 (4H, t), 4.15 (2H, d), 5.07 (1H, dd), 6.54 (2H, d), 6.96 (2H, d), 7.26 (2H, dt), 7.33 (2H, dd), 7.68 (1H, d), 7.80 (1H, d), 11.07 (1H, s); 2 protons underneath solvent peak; m/z : ES^+ $[M+H]^+ = 714.4$.

5 **Intermediate 97a: tert-Butyl 4-(4-(1-(4-cyano-3-(trifluoromethyl)phenyl)piperidin-4-yl)phenyl)piperazine-1-carboxylate**

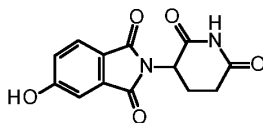


- 4-(4-(4-Bromophenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (0.573 g, 1.40 mmol), tert-butyl piperazine-1-carboxylate (1 eq), sodium *tert*-butoxide (0.404 g, 4.20 mmol), RuPhos Pd G3 (0.117 g, 0.14 mmol), RuPhos (0.065 g, 0.14 mmol) and anhydrous THF (14 mL) were added to a microwave tube. The mixture was degassed, the tube filled with N_2 , and the mixture stirred at 60°C overnight. After cooling and concentrating to dryness, water (10 mL) was added. This mixture was extracted with EtOAc (3×20 mL). The combined organic solutions were dried (Na_2SO_4) and concentrated. Purification by FSC (gradient: hexanes to 100% EtOAc) gave the title compound (0.614 g, 85 %) white solid; ^1H NMR (500 MHz, $CDCl_3$) 1.49 (9H, s), 1.70-1.85 (2H, m), 1.96-2.03 (2H, m), 2.65-2.80 (1H, m), 3.01-3.20 (6H, m), 3.48-3.77 (4H, m), 4.03 (2H, br d), 6.84-6.97 (2H, m), 7.00 (1H, dd), 7.10-7.19 (3H, m), 7.62 (1H, d); m/z : ES^+ , $[M+H]^+ = 515$.

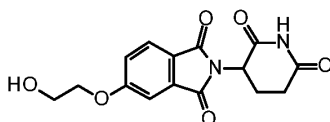
Intermediate 97b: 4-(4-(4-(Piperazin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



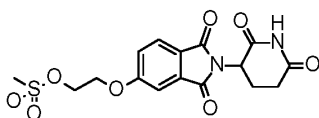
- 4 *tert*-Butyl 4-(4-(1-(4-cyano-3-(trifluoromethyl)phenyl)piperidin-4-yl)phenyl)piperazine-1-carboxylate (1.71 g, 3.32 mmol) was dissolved in DCM (8 mL) and TFA (4 mL). The mixture was stirred at RT for 3h. After concentrating, DCM (20 mL) was added and the mixture was washed with sat. $NaHCO_3$ (2×5 mL), dried (Na_2SO_4) and concentrated to dryness to give the title compound (1.37 g, 99 %) as a dry film; ^1H NMR (500 MHz, $CDCl_3$) 1.77 (2H, qd), 1.98 (2H, br d), 2.73 (2H, tt), 3.01-3.14 (6H, m), 3.20 (4H, dd), 4.03 (2H, br d), 6.90 (2H, d), 7.00 (1H, dd), 7.10-7.19 (3H, m), 7.62 (1H, d); m/z : ES^+ , $[M+H]^+ = 415$.

Intermediate 97c: 2-(2,6-Dioxopiperidin-3-yl)-5-hydroxyisoindoline-1,3-dione

- NaOAc (0.50 g, 6.09 mmol) was added to 5-hydroxyisobenzofuran-1,3-dione (0.50 g, 3.05 mmol) and 3-aminopiperidine-2,6-dione (0.39 g, 3.05 mmol) in AcOH (3 mL) at RT. The resulting mixture was stirred at 120°C for 3h then at RT overnight. A precipitate was then collected by filtration, washed with water (10 mL) and Et₂O (10 mL) and dried at 50°C to give the title compound (0.60 g, 72 %); ¹H NMR (500MHz) 2.08 (1H, dtd), 2.53-2.70 (2H, m), 2.90 (1H, ddd), 5.17 (1H, dd), 7.66-7.79 (1H, m), 7.86 (1H, dd), 8.02 (1H, dd), 11.21(1H,s); *m/z*: ES⁺, [M+H]⁺ = 275.

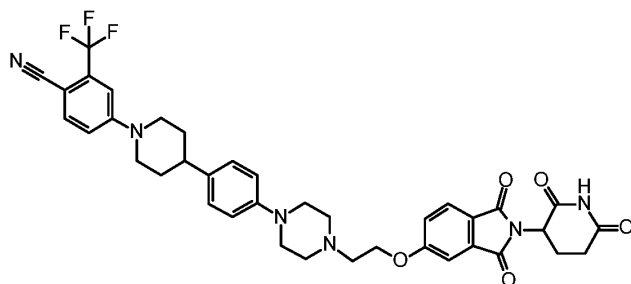
10 Intermediate 97d: 2-(2,6-Dioxopiperidin-3-yl)-5-(2-hydroxyethoxy)isoindoline-1,3-dione

- DMF (0.5 mL) was added to a mixture of 2-bromoethan-1-ol (114 mg, 0.91 mmol), K₂CO₃ (139 mg, 1.00 mmol) and 2-(2,6-dioxopiperidin-3-yl)-5-hydroxyisoindoline-1,3-dione (250 mg, 0.91 mmol). The resulting suspension was stirred at 50°C for 5h then concentrated. Water (10 mL) was added and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic solutions were dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: hexanes to EtOAc) gave the title compound (34 mg, 12 %); ¹H NMR (500 MHz, CDCl₃) 1.63-1.74 (1H, m), 2.13-2.20 (1H, m), 2.75-2.87 (2H, m), 4.01-4.09 (2H, m), 4.22 (2H, br d), 4.97 (1H, br dd), 7.25 (1H, d), 7.38 (1H, s), 7.81 (1H, br d), 8.02 (1H, s); *m/z*: ES⁺, [M+H]⁺ = 319.

20 Intermediate 97e: 2-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)ethyl methanesulfonate

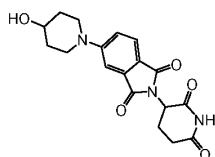
- Et₃N (0.030 mL, 0.21 mmol) was added to a mixture of methanesulfonic anhydride (22.33 mg, 0.13 mmol) and 2-(2,6-dioxopiperidin-3-yl)-5-(2-hydroxyethoxy)isoindoline-1,3-dione (34 mg, 0.11 mmol) in anhydrous CH₂Cl₂ (1 mL) at 0°C then stirred at RT overnight. The mixture was then diluted with DCM (10 mL), washed with water (10 mL), dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: hexanes to EtOAc) gave the title compound (15 mg, 35 %); ¹H NMR (500 MHz, CDCl₃) 2.14-2.20 (1H, m), 2.72-2.93 (3H, m), 3.11 (3H, s), 4.37-4.43 (2H, m), 4.59-4.66 (2H, m), 4.97 (1H, dd), 7.19-7.25 (1H, m), 7.37 (1H, d), 7.82 (1H, d), 8.11-8.25 (1H, m); *m/z*: ES⁺, [M+H]⁺ = 397.

30 Example 97: 4-(4-{4-[4-(2-{2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl}oxy)ethyl]piperazin-1-yl}phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



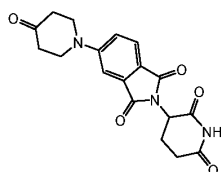
- DMF (0.5 mL) was added to a mixture of NaI (6 mg, 0.04 mmol), DIPEA (0.020 mL, 0.11 mmol), 4-(4-(piperazin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (16 mg, 0.04 mmol) and 2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)oxy)ethyl methanesulfonate (15 mg, 0.04 mmol). The resulting solution was stirred at 60-90°C for 3h then concentrated. DCM (10 mL) was added and the resulting solution was washed with water, sat. NaHCO₃ (2 mL), then dried (Na₂SO₄) and concentrated. Purification by FSC (hexanes to EtOAc) gave the title compound (7 mg, 23 %); ¹H NMR: (500 MHz) 1.55-1.64 (2H, m), 1.79-1.85 (2H, m), 2.01-2.05 (1H, m), 2.55-2.65 (6H, m), 2.70 (1H, s), 2.82 (2H, s), 2.84-2.93 (1H, m), 2.99-3.06 (2H, m), 3.06-3.11 (4H, m), 4.16 (2H, br d), 4.33 (2H, t), 5.11 (1H, dd), 6.86 (2H, d), 7.08 (2H, d), 7.25 (1H, dd), 7.31 (1H, d), 7.37 (1H, dd), 7.47 (1H, d), 7.81 (2H, dd), 11.09 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 715.3.

Intermediate 98a: 2-(2,6-Dioxopiperidin-3-yl)-5-(4-hydroxypiperidin-1-yl)isoindoline-1,3-dione



- 2-(2,6-Dioxopiperidin-3-yl)-5-fluoroisoindoline-1,3-dione (0.200 g, 0.72 mmol) was dissolved in DMA (1 mL). DIPEA (0.253 mL, 1.45 mmol) and piperidin-4-ol (0.081 g, 0.80 mmol) were then added. The mixture was then stirred at 100°C for 18h then concentrated. Purification by FSC (gradient: hexanes to EtOAc) gave the title compound (0.200 g, 77 %); ¹H NMR (500 MHz) 1.36-1.47 (2H, m), 1.73-1.84 (2H, m), 1.99-2.06 (1H, m), 2.52-2.63 (2H, m), 2.81-2.90 (1H, m), 3.18 (2H, ddd), 3.70-3.78 (1H, m), 3.81 (2H, br d), 4.74 (1H, d), 5.05 (1H, dd), 7.23 (1H, dd), 7.30 (1H, d), 7.64 (1H, d), 11.06 (1H, s); *m/z*: ES⁺, [M+H]⁺ = 358.

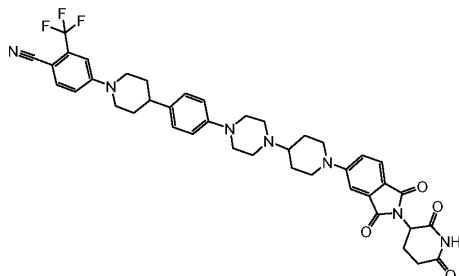
Intermediate 98b: 2-(2,6-Dioxopiperidin-3-yl)-5-(4-oxopiperidin-1-yl)isoindoline-1,3-dione



- 2-(2,6-Dioxopiperidin-3-yl)-5-(4-hydroxypiperidin-1-yl)isoindoline-1,3-dione (25 mg, 0.07 mmol) was dissolved in DCM. Dess-Martin periodinane (59 mg, 0.14 mmol) was added. The mixture was stirred at RT for 2h then concentrated. Purification by FSC (gradient: hexanes to EtOAc) gave the title compound (18 mg, 72 %); ¹H NMR (500 MHz, CDCl₃) 2.61-2.64 (4H, m), 2.70-3.03 (4H, m), 3.82-3.85 (4H, m), 4.88-5.02 (1H, m),

7.10 (1H, dd), 7.30-7.34 (1H, m), 7.73-7.76 (1H, m), 8.15 (1H, s); m/z : ES^+ , $[M+H]^+ = 356$.

Example 98: 4-((4-((4-((1-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)piperidin-4-yl)piperazin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile

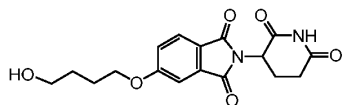


5

Intermediate 97b was reacted with Intermediate 98b using the general synthetic method illustrated by Example 2 to give the title compound (as a formate salt) after purification by flash C-18 chromatography (Eluent A); ^1H NMR: (500 MHz, $CDCl_3$) 1.72-1.92 (4H, m), 1.97-2.02 (2H, m), 2.14-2.24 (4H, m), 2.71-2.97 (5H, m), 3.01-3.12 (7H, m), 3.41 (4H, br s), 4.06 (4H, br t), 4.97 (1H, dd), 6.92 (2H, d), 7.01 (1H, br d), 7.10 (1H, br d), 7.13-7.19 (3H, m), 7.32 (1H, s), 7.64 (1H, d), 7.73 (1H, d), 8.00 (1H, br s), 8.10 (1H, s); m/z : ES^+ $[M+H]^+ = 754.4$.

10

Intermediate 99a: 2-((2,6-dioxopiperidin-3-yl)-5-(4-hydroxybutoxy)isoindoline-1,3-dione

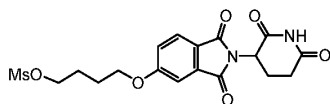


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DMF (1 mL) was added to a mixture of 4-bromobutan-1-ol (112 mg, 0.73 mmol), K_2CO_3 (111 mg, 0.80 mmol) and 2-((2,6-dioxopiperidin-3-yl)-5-hydroxyisoindoline-1,3-dione (200 mg, 0.73 mmol). The resulting suspension was stirred at 50°C overnight then concentrated. Water (10 mL) was then added and the mixture was extracted with EtOAc (3×10 mL). The combined organic solutions were dried (Na_2SO_4) and concentrated. Purification by FSC (gradient: hexanes to EtOAc) and further purification using a 30g C18 column (Eluent A) gave the title compound (35 mg, 14 %); ^1H NMR (500 MHz) 1.53-1.61 (2H, m), 1.78 (2H, quin), 2.01-2.11 (1H, m), 2.55-2.65 (2H, m), 2.83-2.93 (1H, m), 3.45 (2H, q), 4.18 (2H, t), 4.46 (1H, t), 5.07-5.15 (1H, m), 7.33 (1H, dd), 7.41 (1H, d), 7.82 (1H, d), 11.10 (1H, s); m/z : ES^+ , $[M+H]^+ = 347$.

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Intermediate 99b: 4-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)butyl methanesulfonate

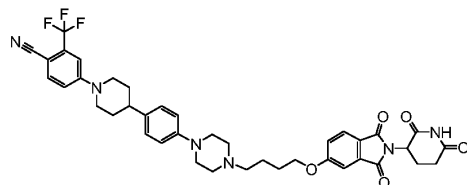


25

Et_3N (0.027 mL, 0.19 mmol) was added to a mixture of methanesulfonic anhydride (19.92 mg, 0.11 mmol) and 2-((2,6-dioxopiperidin-3-yl)-5-(4-hydroxybutoxy)isoindoline-1,3-dione (33 mg, 0.10 mmol) in anhydrous DCM (1 mL) at 0°C. The mixture was then stirred at RT for 0.5h, diluted with DCM (10 mL) washed with water (1 mL), dried (Na_2SO_4) and concentrated to give the title compound; ^1H NMR (500 MHz, $CDCl_3$) 1.50-

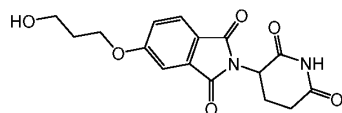
1.55 (3H, m), 2.13-2.19 (1H, m), 2.72-2.96 (4H, m), 3.05 (3H, s), 4.13-4.20 (2H, m), 4.29-4.39 (2H, m), 4.97 (1H, dd), 7.16-7.23 (1H, m), 7.35 (1H, d), 7.80 (1H, d), 7.96 (1H, br s); m/z : ES^+ , $[M+H]^+ = 425$.

Example 99: 4-(4-{4-[4-{2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl}oxy]-butyl}piperazin-1-yl}phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



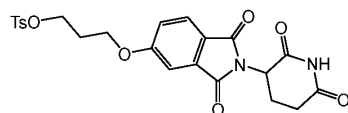
DMF (0.5 mL) was added to a mixture of NaI (12.71 mg, 0.08 mmol), DIPEA (0.044 mL, 0.25 mmol), 4-(4-(4-(piperazin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (35 mg, 0.08 mmol) and 4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)oxybutyl methanesulfonate (36 mg, 0.08 mmol). The resulting solution was stirred at 60°C for 1h then concentrated to dryness. DCM (10 mL) was added and the resulting mixture was washed with water, sat. $NaHCO_3$ (2 mL), dried (Na_2SO_4) and concentrated. Purification by FSC (eluent: hexanes to EtOAc then 5% MeOH in EtOAc) gave the title compound (12 mg, 19%); ^1H NMR: (500 MHz, $CDCl_3$) 1.50-1.55 (2H, m), 1.76 (3H, qd), 1.90-2.01 (4H, m), 2.14-2.22 (1H, m), 2.46-3.29 (15H, m), 4.03 (2H, br d), 4.12-4.17 (2H, m), 4.97 (1H, dd), 6.90 (2H, d), 6.97-7.02 (1H, m), 7.11-7.15 (2H, m), 7.16 (1H, d), 7.20 (1H, dd), 7.34 (1H, d), 7.62 (1H, d), 7.79 (1H, d), 7.97 (1H, s); m/z : ES^+ $[M+H]^+ = 743.3$.

Intermediate 100a: 2-(2-(2,6-Dioxopiperidin-3-yl)-5-(3-hydroxypropoxy)isoindoline-1,3-dione



DMF (0.5 mL) was added to a mixture of 3-bromopropan-1-ol (84 mg, 0.60 mmol), K_2CO_3 (151 mg, 1.09 mmol) and 2-(2-(2,6-dioxopiperidin-3-yl)-5-hydroxyisoindoline-1,3-dione (Intermediate 97c) (150 mg, 0.55 mmol). The resulting suspension was stirred at 50°C for 5h and then concentrated under reduced pressure. Water (10 mL) was added, and the phases separated. The aqueous portion was extracted with EtOAc (3×10 mL). The combined organic solutions were dried (Na_2SO_4) and concentrated. Purification by FSC (gradient: hexanes to EtOAc) gave the title compound (50.0 mg, 28 %); ^1H NMR (500 MHz, $CDCl_3$) 2.08-2.22 (3H, m), 2.71-2.94 (3H, m), 3.89 (2H, t), 4.26 (2H, t), 4.97 (1H, dd), 7.22 (1H, dd), 7.38 (1H, d), 7.80 (1H, d), 7.99 (1H, br s); m/z : ES^+ , $[M+H]^+ = 333$.

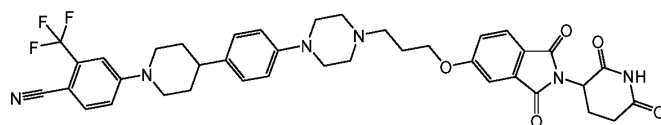
Intermediate 100b: 3-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)oxy)propyl 4-methylbenzenesulfonate



DCM (1 mL) was added to a mixture of *p*-toluenesulfonyl chloride (33.6 mg, 0.18 mmol), 2-(2,6-dioxo-

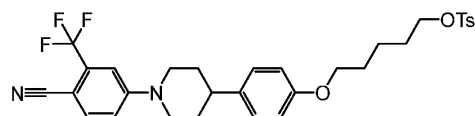
- piperidin-3-yl)-5-(3-hydroxypropoxy)isoindoline-1,3-dione (45 mg, 0.14 mmol), DIPEA (0.047 mL, 0.27 mmol) and DMAP (16.54 mg, 0.14 mmol). The mixture was stirred at RT overnight. After diluting with DCM (5 mL), the resulting solution was washed with water, dried (Na_2SO_4) and concentrated. Purification by FSC (gradient: hexanes to EtOAc) gave the title compound (27 mg, 41 %) as a sticky film; ^1H NMR (500 MHz, CDCl_3) 2.12-2.26 (3H, m), 2.40 (3H, s), 2.72-2.95 (3H, m), 4.10 (2H, t), 4.26 (2H, t), 4.97 (1H, dd), 7.09 (1H, dd), 7.19-7.26 (1H, m), 7.28-7.32 (2H, m), 7.75-7.81 (3H, m), 8.05 (1H, br s); m/z : ES^+ , $[\text{M}+\text{H}]^+ = 487$.

Example 100: 4-(4-{4-[4-(3-{2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl}oxy}propyl)piperazin-1-yl]phenyl}piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



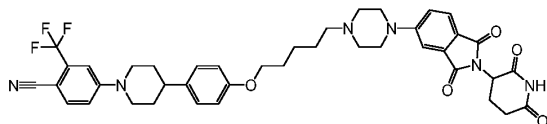
- DMF (0.5 mL) was added to a mixture of NaI (14 mg, 0.10 mmol), DIPEA (0.051 mL, 0.29 mmol), 4-(4-(piperazin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (Intermediate 97b) (40 mg, 0.10 mmol), 3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)oxy)propyl 4-methylbenzenesulfonate (47 mg, 0.10 mmol). The resulting solution was stirred at 60°C for 1h. The mixture was then concentrated to dryness then DCM (10 mL) was added. This solution was washed with water then sat. NaHCO_3 (2mL), dried (Na_2SO_4) and concentrated. Purification by FSC (eluent: hexanes to EtOAc then 5% MeOH in EtOAc) gave the title compound (39 mg, 54.0 %); ^1H NMR: (500 MHz) 1.55-1.65 (2H, m), 1.79-1.87 (2H, m), 1.89-1.97 (2H, m), 2.01-2.07 (1H, m), 2.51-2.64 (7H, m), 2.68-2.75 (1H, m), 2.84-2.91 (1H, m), 2.98-3.12 (7H, m), 4.16 (2H, br d), 4.23 (2H, br t), 5.06-5.17 (1H, m), 6.85 (2H, br d), 7.08 (2H, br d), 7.23-7.28 (1H, m), 7.31 (1H, br s), 7.33-7.37 (1H, m), 7.43 (1H, br d), 7.75-7.86 (2H, m), 11.10 (1H, s), 2 protons underneath solvent peak; m/z : ES^+ $[\text{M}+\text{H}]^+ = 729.3$.

Intermediate 101a: 5-(4-(1-(4-Cyano-3-(trifluoromethyl)phenyl)piperidin-4-yl)phenoxy)pentyl 4-methylbenzenesulfonate



- 4-(4-(4-Hydroxyphenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (0.150 g, 0.43 mmol), PPh_3 (0.284 g, 1.08 mmol) and 5-hydroxypentyl 4-methylbenzenesulfonate (0.168 g, 0.65 mmol) were dissolved in anhydrous DCM (4.3 mL) under N_2 . The mixture was cooled to 0°C and di-*tert*-butyl (E)-diazene-1,2-dicarboxylate (0.199 g, 0.87 mmol) was added. This mixture was stirred at RT overnight, then washed with sat. NaHCO_3 (2 mL), dried (Na_2SO_4) and concentrated. Purification by FSC (gradient: hexanes to DCM) gave the title compound (0.200 g, 79 %) as a colourless oil; ^1H NMR (500 MHz, CDCl_3) 1.48-1.55 (2H, m), 1.69-1.85 (6H, m), 1.99 (2H, br d), 2.45 (3H, s), 2.75 (1H, tt), 3.07 (2H, td), 3.90 (2H, t), 4.00-4.09 (4H, m), 6.83 (2H, d), 7.02 (1H, dd), 7.13 (2H, d), 7.19 (1H, d), 7.34 (2H, d), 7.57-7.69 (1H, m), 7.80 (2H, d); m/z : ES^+ , $[\text{M}+\text{H}]^+ = 587$.

Example 101: 4-(4-{4-[(5-{4-[2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]-piperazin-1-yl}pentyl)oxy]phenyl}piperidin-1-yl)-2-(trifluoromethyl)benzonitrile

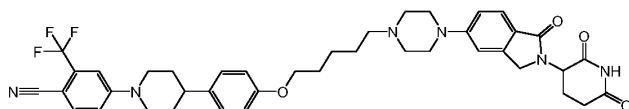


Intermediate 63e was reacted with Intermediate 101a using the general synthetic method illustrated by

- 5 Example 12 to give the title compound after purification by FSC (gradient: 0-100% EtOAc in hexanes); ¹H NMR: (500 MHz) 1.38-1.46 (2H, m), 1.46-1.54 (2H, m), 1.55-1.66 (2H, m), 1.67-1.75 (2H, m), 1.83 (2H, br d), 1.98-2.04 (1H, m), 2.27-2.39 (3H, m), 2.51-2.66 (3H, m), 2.71-2.78 (1H, m), 2.81-2.92 (1H, m), 3.03 (2H, br t), 3.41 (4H, br s), 3.92 (2H, t), 4.16 (2H, br d), 4.97-5.20 (1H, m), 6.84 (2H, d), 7.14 (2H, d), 7.21-7.28 (2H, m), 7.29-7.37 (2H, m), 7.66 (1H, d), 7.80 (1H, d), 11.05 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 757.3.

10

Example 102: 4-(4-{4-[(5-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl}pentyl)oxy]phenyl}piperidin-1-yl)-2-(trifluoromethyl)benzonitrile

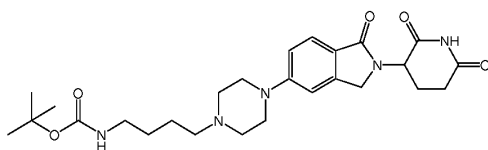


Intermediate 2c was reacted with Intermediate 101a using the general synthetic method illustrated by Example

- 15 12 to give the title compound after purification by C-18 chromatography (Eluent A, Basic Work-up A); ¹H NMR: (500 MHz) 1.39-1.46 (2H, m), 1.47-1.54 (2H, m), 1.55-1.66 (2H, m), 1.67-1.76 (2H, m), 1.79-1.86 (2H, m), 1.91-2.01 (1H, m), 2.29-2.39 (4H, m), 2.52-2.65 (2H, m), 2.72-2.79 (1H, m), 2.84-2.94 (1H, m), 3.03 (2H, br t), 3.22-3.28 (6H, m), 3.92 (2H, t), 4.11-4.22 (3H, m), 4.27-4.37 (1H, m), 5.03 (1H, dd), 6.84 (2H, br d), 7.00-7.08 (2H, m), 7.14 (2H, br d), 7.25 (1H, br d), 7.31 (1H, s), 7.51 (1H, d), 7.79 (1H, s), 10.92 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 743.4.

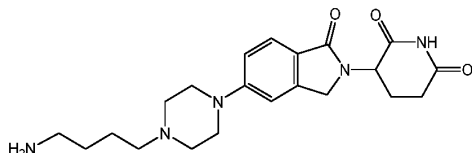
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Intermediate 103a: *tert*-Butyl (4-(4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazin-1-yl)butyl)carbamate

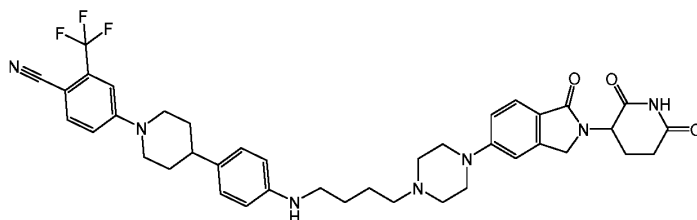


- 25 DMF (2 mL) was added to a mixture of *tert*-butyl (4-bromobutyl)carbamate (256 mg, 1.01 mmol), 3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride salt (370 mg, 1.01 mmol) and KI (168 mg, 1.01 mmol). The mixture was stirred at 90°C for 24h, then cooled to RT and the solvents removed under reduced pressure. Purification by FSC (eluting with hexanes to DCM then 10% MeOH in DCM) gave the title compound (340 mg, 67 %); ¹H NMR (500 MHz) 1.23-1.31 (2H, m), 1.32-1.46 (12H, m), 1.92-1.98 (1H, m), 2.36 (2H, qd), 2.53-2.64 (2H, m), 2.83-3.01 (4H, m), 3.08-3.18 (1H, m), 3.31 (4H, br s), 4.12-4.24 (1H, m), 4.29-4.43 (1H, m), 5.04 (1H, dd), 6.84 (1H, br s), 7.10 (2H, br s), 7.43-7.67 (1H, m), 10.93 (1H, s); *m/z*: ES⁺, [M+H]⁺ = 500.

30

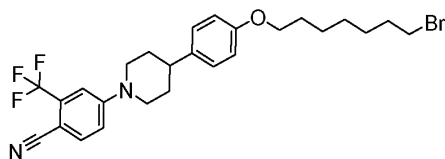
Intermediate 103b: 3-(5-(4-(4-Aminobutyl)piperazin-1-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione

HCl 4M in 1,4-dioxane (5.1 mL, 20.42 mmol) and DCM (10 mL) were added to *tert*-butyl 4-(4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazin-1-yl)butylcarbamate (340 mg, 0.68 mmol) to give a suspension. The resulting suspension was stirred at RT for 1h then concentrated to dryness. Et₂O (10 mL) was added to the residue to give a brown suspension. The solid was collected by filtration to give the title compound as a hydrochloride salt (270 mg, 91 %); ¹H NMR (500 MHz) 1.59-1.69 (2H, m), 1.77-1.85 (2H, m), 1.93-2.03 (1H, m), 2.30-2.41 (1H, m), 2.54-2.66 (2H, m), 2.77-2.96 (3H, m), 3.06-3.23 (4H, m), 3.26-3.38 (2H, m), 3.96-4.04 (2H, m), 4.07-4.25 (2H, m), 4.32-4.40 (1H, m), 5.00-5.12 (1H, m), 7.08-7.25 (2H, m), 7.58 (1H, d), 7.97 (3H, br s), 10.93 (1H, s); *m/z*: ES⁺, [M+H]⁺ = 400.

Example 103: 4-(4-{4-[(4-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isindol-5-yl]piperazin-1-yl}butyl)amino]phenyl}piperidin-1-yl)-2-(trifluoromethyl)benzonitrile

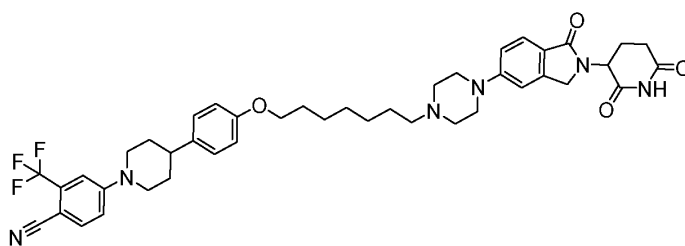
4-(4-(4-Bromophenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (73 mg, 0.18 mmol), sodium *tert*-butoxide (78 mg, 0.81 mmol), 3-(5-(4-(4-aminobutyl)piperazin-1-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione bis-hydrochloride salt (70 mg, 0.15 mmol), Brettphos Pd G3 (13 mg, 0.01 mmol) and anhydrous DMF (1.482 mL) were added to a flask. The mixture was degassed, the flask filled with N₂ and the mixture was then stirred at 100°C for 1.5h. After cooling to RT the reaction was quenched with AcOH (49 mg, 0.81 mmol) in MeCN (0.1 mL) to give a cloudy solution. DMSO (1 mL) was added and the mixture was filtered. Purification by C-18 50 g column (0.1% Formic acid in water to 0.1% formic acid in MeCN, over 15 min) gave the title compound as a formate salt (20 mg, 17 %); ¹H NMR: (500 MHz) 1.49-1.65 (7H, m), 1.79 (2H, br d), 1.92-2.00 (1H, m), 2.28-2.42 (4H, m), 2.54-2.68 (4H, m), 2.83-2.94 (2H, m), 2.95-3.30 (8H, m), 4.13 (2H, br d), 4.17-4.24 (1H, m), 4.28-4.41 (1H, m), 5.03 (1H, br dd), 6.49 (2H, br d), 6.93 (2H, br d), 7.00-7.08 (2H, m), 7.24 (1H, br d), 7.30 (1H, s), 7.51 (1H, d), 7.79 (1H, d), 8.02-8.18 (1H, m), 10.92 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 728.4.

Intermediate 104a: 4-(4-(4-((7-Bromoheptyl)oxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



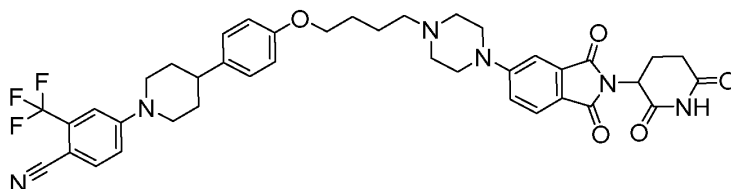
- 4-(4-(4-Hydroxyphenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (0.170 g, 0.49 mmol), PPh₃ (0.283 g, 1.08 mmol) and 7-bromoheptan-1-ol (0.144 g, 0.74 mmol) were dissolved in anhydrous DCM (4.9 mL) under N₂ and cooled to 0°C. Di-*tert*-butyl (*E*)-diazene-1,2-dicarboxylate (0.170 g, 0.74 mmol) was added dropwise.
- 5 The mixture was then stirred at RT for 1h. Additional di-*tert*-butyl (*E*)-diazene-1,2-dicarboxylate (40 mg), PPh₃ (40 mg) and 7-bromoheptan-1-ol (0.144 g, 0.74 mmol) were then added and the mixture stirred at RT overnight. The mixture was then washed with sat. NaHCO₃ (2 mL) and dried (Na₂SO₄). Purification by FSC (gradient: hexanes to DCM) gave the title compound (0.170 g, 66 %) as white solid; ¹H NMR (500 MHz, CDCl₃) 1.37-1.44 (2H, m), 1.45-1.52 (4H, m), 1.74-1.83 (4H, m), 1.88 (2H, dt), 1.96-2.02 (2H, m), 2.75 (1H, tt), 3.07 (2H, td), 3.39-3.46 (2H, m), 3.95 (2H, t), 3.99-4.07 (2H, m), 6.82-6.89 (2H, m), 7.02 (1H, dd), 7.11-7.15 (2H, m), 7.18 (1H, d), 7.63 (1H, d); *m/z*: ES⁺, [M+H]⁺ = 523.
- 10

Example 104: 4-(4-{4-[(7-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazin-1-yl}heptyl)oxy]phenyl}piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



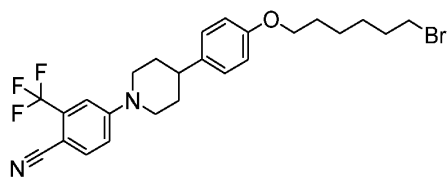
- 15 Intermediate 2c was reacted with Intermediate 104a using the general synthetic method illustrated by Example 12 to give the title compound as a formate salt after purification by C-18 chromatography (Eluent A); ¹H NMR: (500 MHz) 1.28-1.45 (6H, m), 1.51-1.65 (4H, m), 1.69 (2H, dt), 1.82 (2H, br d), 1.92-1.99 (1H, m), 2.29-2.42 (2H, m), 2.54-2.62 (2H, m), 2.75 (2H, ddd), 2.85-2.95 (2H, m), 2.99-3.08 (3H, m), 3.29-3.35 (4H, m), 3.91 (2H, t), 4.13-4.24 (3H, m), 4.31 (1H, s), 5.04 (1H, dd), 6.83 (2H, d), 7.05-7.11 (2H, m), 7.13 (2H, d), 7.25 (1H, dd), 7.31 (1H, d), 7.54 (1H, d), 7.80 (1H, d), 8.12 (1H, s), 10.93 (1H, s), 4 protons under solvent peak; *m/z*: ES⁺ [M+H]⁺ = 771.5.
- 20

Example 105: 4-{4-[4-(4-{4-[2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazin-1-yl}butoxy)phenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile



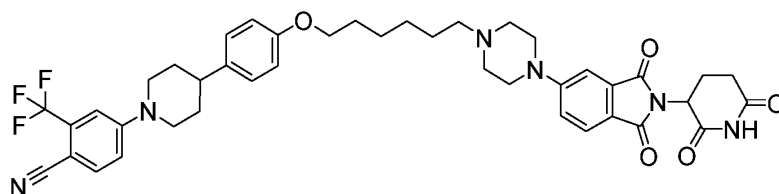
- Intermediate 50a was reacted with Intermediate 63e using the general synthetic method illustrated by Example 5 to give the title compound as a formate salt after purification by C-18 chromatography (Eluent A); ¹H NMR: (500 MHz) 1.55-1.66 (4H, m), 1.68-1.78 (2H, m), 1.79-1.87 (2H, m), 1.95-2.04 (1H, m), 2.38 (2H, br t), 2.53-2.65 (2H, m), 2.68-2.80 (1H, m), 2.80-2.96 (1H, m), 2.98-3.08 (2H, m), 3.38-3.53 (4H, m), 3.95 (2H, t), 4.16 (2H, br d), 4.94-5.34 (1H, m), 6.85 (2H, d), 7.14 (2H, d), 7.21-7.28 (2H, m), 7.31 (2H, dd), 7.66 (1H, d), 7.80 (1H, d), 8.13 (1H, s), 11.06 (1H, s), 3 protons under solvent peak; *m/z*: ES⁺ [M+H]⁺ = 743.3.

Intermediate 106a: 4-(4-(4-((6-Bromohexyl)oxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



- 10 4-(4-(4-Hydroxyphenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (0.170 g, 0.49 mmol), PPh₃ (0.257 g, 0.98 mmol) and 6-bromohexan-1-ol (0.133 g, 0.74 mmol) were dissolved in anhydrous DCM (4.9 mL) under N₂ and cooled to 0°C. Di-*tert*-butyl (*E*)-diazene-1,2-dicarboxylate (0.170 g, 0.74 mmol) was then added and the mixture stirred at RT for 1h. Further di-*tert*-butyl (*E*)-diazene-1,2-dicarboxylate (40 mg), PPh₃ (40 mg) and 6-bromohexan-1-ol (1 eq) were then added. This mixture was stirred at RT for 6h then washed with sat.
- 15 NaHCO₃ (2 mL) and dried (Na₂SO₄). Purification by FSC (gradient: hexanes to DCM) gave the title compound (0.150 g, 60 %) as white solid; ¹H NMR (500 MHz, CDCl₃) 1.48-1.57 (4H, m), 1.77-1.94 (6H, m), 2.00 (2H, br d), 2.71-2.82 (1H, m), 3.03-3.14 (2H, m), 3.39-3.46 (2H, m), 3.96 (2H, t), 4.02 (2H, br d), 6.86 (2H, d), 7.10 (1H, dd), 7.14 (2H, d), 7.22-7.25 (1H, m), 7.65 (1H, d); *m/z*: ES⁺, [M+H]⁺ = 509.

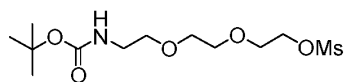
20 **Example 106: 4-(4-{4-[2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]-piperazin-1-yl}hexyl)oxy]phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile**



- Intermediate 63e was reacted with Intermediate 106a using the general synthetic method illustrated by Example 5 to give the title compound (as a formate salt) after purification by C-18 chromatography (Eluent A); ¹H NMR: (500 MHz) 1.30-1.38 (2H, m), 1.38-1.45 (2H, m), 1.45-1.52 (2H, m), 1.56-1.64 (2H, m), 1.65-1.74 (2H, m), 1.79-1.86 (2H, m), 1.98-2.03 (1H, m), 2.30-2.37 (2H, m), 2.52-2.64 (4H, m), 2.71-2.79 (1H, m), 2.83-2.92 (1H, m), 2.99-3.06 (2H, m), 3.37-3.47 (4H, m), 3.91 (2H, t), 4.15 (2H, br d), 5.06 (1H, dd), 6.78-6.90 (2H, m), 7.13 (2H, d), 7.21-7.27 (2H, m), 7.31 (2H, dd), 7.66 (1H, d), 7.76-7.85 (1H, m), 8.12 (1H, s), 11.05 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 771.5.

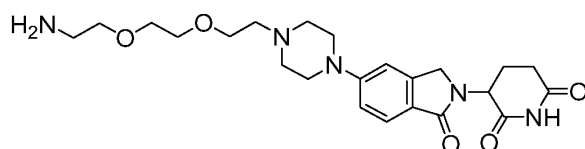
30

Intermediate 107a: 2-[2-[2-(tert-butoxycarbonylamino)ethoxy]ethoxy]ethyl methanesulfonate



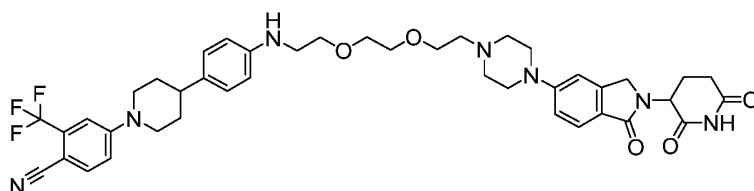
- Et₃N (2.24 mL, 16.04 mmol) was added slowly to *tert*-butyl (2-(2-(2-hydroxyethoxy)ethoxy)ethyl)carbamate (2.00 g, 8.02 mmol) and methanesulfonyl chloride (0.750 mL, 9.63 mmol) in DCM (20 mL) at 0°C. The resulting mixture was stirred at RT for 1h. The mixture was then diluted with DCM (100 mL) and washed with water (10 mL) then sat. brine (10 mL). The organic solution was then dried (Na₂SO₄) and concentrated to give the title compound (2.10 g, 80 %) as a pale yellow oil; ¹H NMR (CDCl₃) 1.36 (9H, s), 2.67 (4H, d), 4.36 (3H, s), 5.00 (6H, s), 5.29 (2H, s), 7.32 (1H, s); *m/z* ES⁺, [M+H]⁺ = 328.

Intermediate 107b: 3-(5-(4-(2-(2-(2-Aminoethoxy)ethoxy)ethyl)piperazin-1-yl)-1-oxoisindolin-2-yl)-piperidine-2,6-dione



- Cs₂CO₃ (1.79 g, 5.48 mmol) was added to 2-[2-(2-(*tert*-butoxycarbonylamino)ethoxy)ethoxy]ethyl methanesulfonate (1.44 g, 4.39 mmol), 3-(1-oxo-5-(piperazin-1-yl)isindolin-2-yl)piperidine-2,6-dione (1.20 g, 3.65 mmol) and KI (0.728 g, 4.39 mmol) in DMF (12 mL). The resulting mixture was stirred at 65°C for 2h. The solvent was then removed under reduced pressure. DCM (15 mL) was added to the residue and the mixture was filtered. 4M HCl in 1,4-dioxane (20 mL) was then added dropwise to the filtrate and the mixture was stirred at RT for 1h. Purification by flash C18-flash chromatography (eluent: 100% water) gave the title compound (0.699 g, 85 %) as a pale yellow solid; *m/z* ES⁺, [M+H]⁺ = 460.

Example 107: 4-{4-[4-(2-[2-(2-(4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isindol-5-yl]-piperazin-1-yl)ethoxy)ethoxy]ethyl}amino)phenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile

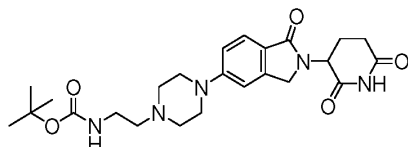


- 4-(4-(4-Bromophenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (65 mg, 0.16 mmol), sodium *tert*-butoxide (70 mg, 0.72 mmol), 3-(5-(4-(2-(2-(2-aminoethoxy)ethoxy)ethyl)piperazin-1-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione bis-hydrochloride salt (70 mg, 0.13 mmol), Brettphos Pd G3 (12 mg, 0.01 mmol) and anhydrous DMF (953 μL) were added to a flask. The mixture was degassed, the flask filled with N₂ then the mixture was stirred at 100°C for 1.5h. After cooling to RT the mixture was quenched using 2M AcOH in THF (362 μL, 0.72 mmol) to give a cloudy solution. The THF was removed under reduced pressure. DMSO (1 mL) was added and the mixture was filtered. Purification by C18 chromatography (0.1% formic acid in water to 0.1% formic acid in MeCN, over 15 min) gave the title compound as a formate salt (20 mg, 17%); ¹H NMR: (500 MHz) 1.48-1.61 (2H, m), 1.73-1.80 (2H, m), 1.91-2.00 (1H, m), 2.32-2.41 (2H, m), 2.53-2.68 (4H, m),

2.84-2.95 (2H, m), 2.96-3.05 (3H, m), 3.13-3.18 (3H, m), 3.52-3.67 (8H, m), 3.74-3.81 (2H, m), 4.12 (2H, br d), 4.19-4.25 (1H, m), 4.31 (1H, br s), 4.97-5.14 (1H, m), 6.52 (2H, br d), 6.93 (2H, br d), 7.07 (1H, br d), 7.10 (1H, br s), 7.23 (1H, br d), 7.29 (1H, br s), 7.56 (1H, br d), 7.79 (1H, br d), 8.12 (1H, s), 10.94 (1H, s), exchangeable protons missing; m/z : ES^+ $[M+H]^+ = 788.3$.

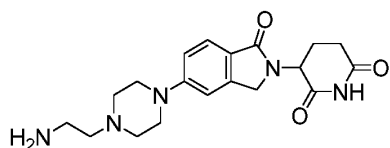
5

Intermediate 108a: *tert*-Butyl (2-(4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazin-1-yl)ethyl)carbamate



- 10 DIPEA (4.79 mL, 27.41 mmol) was added to 3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione (3.00 g, 9.14 mmol) and *tert*-butyl (2-bromoethyl)carbamate (2.46 g, 10.96 mmol) in DMF (30 mL) and the mixture was stirred at RT for 40h. The mixture was then diluted with EtOAc (100 mL), and washed with water (20 mL) then sat. brine (20 mL). The organic solution was then dried (Na_2SO_4) and concentrated to give the title compound which was used in the next step without further purification; m/z : ES^+ $[M+H]^+ = 472$.

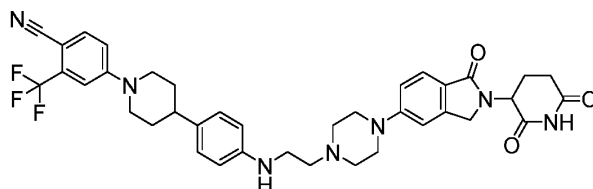
- 15 **Intermediate 108b: 3-(5-(4-(2-Aminoethyl)piperazin-1-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione**



- 20 *tert*-Butyl (2-(4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazin-1-yl)ethyl)carbamate (1.60 g, 3.39 mmol) was added to 4M HCl in 1,4-dioxane (1 mL). The resulting mixture was stirred at RT for 2h. The solvent was removed under reduced pressure to give the title compound (1.25 g, 99 %) as a white solid; m/z : ES^+ $[M+H]^+ = 372$.

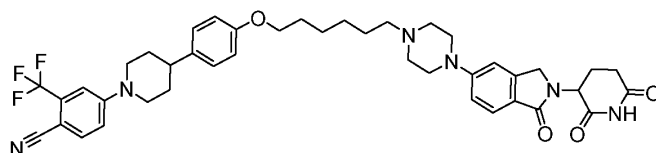
25

Example 108: 4-(4-{4-[(2-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl}ethyl)amino]phenyl}piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



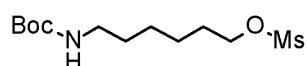
- 4-(4-(4-Bromophenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (77 mg, 0.19 mmol), sodium *tert*-butoxide (91 mg, 0.95 mmol), 3-(5-(4-(2-aminoethyl)piperazin-1-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione bis-hydrochloride salt (70 mg, 0.16 mmol) and Brettphos Pd G3 (14.28 mg, 0.02 mmol) were suspended in anhydrous DMF (1.103 mL). The mixture was degassed, filled with N₂ then stirred at 100°C for 1.5h. After cooling to RT the reaction was quenched with AcOH (2M in THF, 473 µL, 0.95 mmol) to give a cloudy solution. The THF was removed under reduced pressure. DMSO (1 mL) was added and the mixture was filtered. Purification by reverse phase (C18) chromatography (0.1% formic acid in water to 0.1% formic acid in MeCN, over 15 min) gave the title compound as a formate salt (30 mg, 23 %); ¹H NMR: (500 MHz) 1.54-1.65 (2H, m), 1.77-1.84 (2H, m), 1.83-1.91 (1H, m), 1.93-2.00 (1H, m), 2.34-2.42 (1H, m), 2.54-2.64 (3H, m), 2.65-2.72 (2H, m), 2.85-2.95 (2H, m), 2.99-3.07 (3H, m), 3.42 (7H, br d), 4.15 (2H, br d), 4.20-4.27 (1H, m), 4.32-4.39 (1H, m), 5.05 (1H, dd), 6.59 (2H, d), 6.99-7.03 (2H, m), 7.13-7.19 (2H, m), 7.23-7.27 (1H, m), 7.30-7.31 (1H, m), 7.58 (1H, d), 7.80 (1H, d), 8.12 (1H, s), 10.93 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 700.3.

Example 109: 4-(4-{4-[(6-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isindol-5-yl]piperazin-1-yl}hexyl)oxy]phenyl}piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



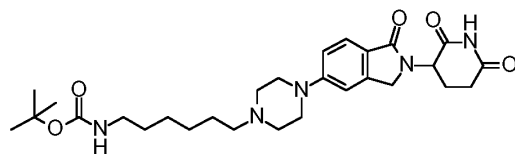
- Intermediate 2c was reacted with Intermediate 106a using the general synthetic method illustrated by Example 12 to give the title compound after purification by C-18 chromatography (Eluent A); ¹H NMR: (500 MHz) 1.31-1.40 (2H, m), 1.41-1.49 (2H, m), 1.56-1.65 (2H, m), 1.68-1.75 (3H, m), 1.79-1.87 (2H, m), 1.93-2.00 (1H, m), 2.31-2.42 (1H, m), 2.56-2.64 (2H, m), 2.71-2.80 (1H, m), 2.85-2.95 (1H, m), 3.00-3.07 (2H, m), 3.07-3.20 (6H, m), 3.54-3.64 (2H, m), 3.88-4.06 (4H, m), 4.13-4.20 (2H, m), 4.20-4.27 (1H, m), 4.31-4.44 (1H, m), 4.98-5.12 (1H, m), 6.84 (2H, br d), 7.12-7.18 (3H, m), 7.26 (1H, br d), 7.31 (1H, br s), 7.57-7.60 (1H, m), 7.80 (1H, br d), 10.93 (1H, s); one exchangeable not observed; *m/z*: ES⁺ [M+H]⁺ = 757.4.

Intermediate 110a: 6-((*tert*-Butoxycarbonyl)amino)hexyl methanesulfonate



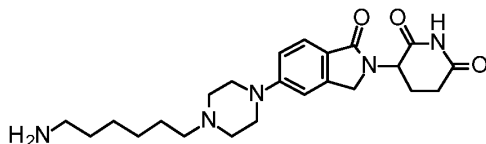
- Et₃N (1.28 mL, 9.20 mmol) was added slowly to *tert*-butyl (6-hydroxyhexyl)carbamate (1.00 g, 4.60 mmol) and methanesulfonyl chloride (0.430 mL, 5.52 mmol) in DCM (15 mL) at 0°C. The resulting mixture was stirred at RT for 1h. The mixture was then diluted with DCM (50 mL) and washed with water (10 mL) then sat. brine (10 mL). The organic solution was then dried (Na₂SO₄) and concentrated to give the title compound (1.350 g, 99 %) as a colourless oil; ¹H NMR (300 MHz, CDCl₃) 1.46 (15H, s), 1.76 (2H, dt), 3.03 (3H, s), 3.13 (2H, dd), 4.24 (2H, t), 4.54 (1H, s).

Intermediate 110b: *tert*-Butyl (6-(4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazin-1-yl)hexyl)carbamate



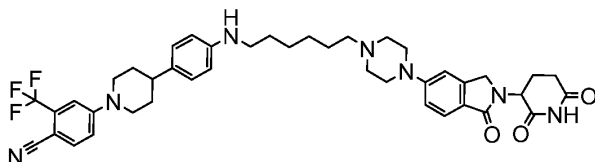
- 5 Cs₂CO₃ (4.47 g, 13.70 mmol) was added to 6-((*tert*-butoxycarbonyl)amino)hexyl methanesulfonate (4.32 g, 14.62 mmol), 3-(1-oxo-5-(piperazin-1-yl)isindolin-2-yl)piperidine-2,6-dione (3.00 g, 9.14 mmol) and KI (2.43 g, 14.62 mmol) in DMF (15 mL). The resulting mixture was stirred at 65°C for 3h. Purification by FSC (gradient: 0-100% EtOAc in petroleum ether) gave the title compound (0.800 g, 17 %) as a yellow solid; *m/z* ES⁺, [M+H]⁺ = 528.

Intermediate 110c: 3-(5-(4-(6-Aminoethyl)piperazin-1-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione

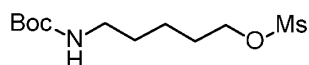


- 10 4M HCl in 1,4-dioxane (15 mL, 1.52 mmol) was added dropwise to *tert*-butyl (6-(4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazin-1-yl)hexyl)carbamate (800 mg, 1.52 mmol) in DCM (10 mL). The resulting mixture was stirred at RT for 1h. Purification by C18-flash chromatography (eluent: 100% water) gave the title compound (425 mg, 66 %) as a pale yellow solid; *m/z* ES⁺, [M+H]⁺ = 428.

- 15 **Example 110: 4-(4-{4-[(6-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isindol-5-yl]piperazin-1-yl}hexyl)amino]phenyl}piperidin-1-yl)-2-(trifluoromethyl)benzonitrile**

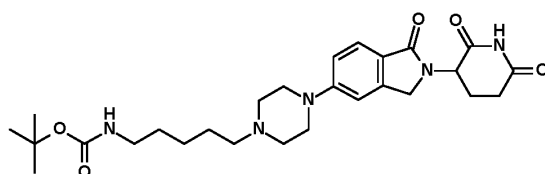


- 4-(4-(4-Bromophenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (68.7 mg, 0.17 mmol), sodium *tert*-butoxide (73.9 mg, 0.77 mmol), 3-(5-(4-(6-aminoethyl)piperazin-1-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione bis-hydrochloride salt (70 mg, 0.14 mmol), Brettphos Pd G3 (12.68 mg, 0.01 mmol) were suspended in anhydrous DMF (1391 μL). The mixture was degassed, filled with N₂ then stirred at 100°C for 1.5h. The mixture was then cooled to RT, quenched with 10% AcOH in MeCN (0.2 mL) to give a cloudy solution. DMSO (1 mL) was added and the mixture was filtered. The filtrate was directly loaded on C-18 50 g column (eluent: 0.1% formic acid in water to 0.1% formic acid in MeCN, over 15 min) to give the title compound (41 mg, 37 %) as a formate salt. ¹H NMR: (500 MHz) 1.28-1.43 (4H, m), 1.48-1.63 (5H, m), 1.67 (2H, br s), 1.71-1.86 (3H, m), 1.87-2.02 (1H, m), 2.33-2.42 (1H, m), 2.54-2.69 (3H, m), 2.84-3.20 (12H, m), 4.14 (2H, br d), 4.18-4.28 (1H, m), 4.34 (1H, br d), 5.05 (1H, dd), 6.48 (2H, br d), 6.94 (2H, d), 7.00-7.20 (2H, m), 7.22-7.26 (1H, m), 7.30 (1H, d), 7.58 (1H, d), 7.79 (1H, d), 8.12 (1H, s), 10.93 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 756.5.

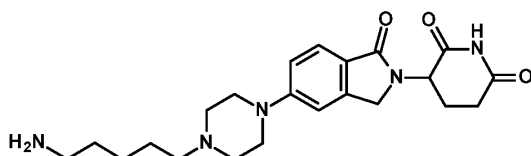
Intermediate 111a: 5-((*tert*-Butoxycarbonyl)amino)pentyl methanesulfonate

- Et₃N (1.37 mL, 9.84 mmol) was added to *tert*-butyl (5-hydroxypentyl)carbamate (1.00 g, 4.92 mmol) and methanesulfonyl chloride (0.46 mL, 5.90 mmol) in DCM (12 mL) at 0°C. The resulting mixture was stirred at RT for 1h. The mixture was then diluted with DCM (50 mL) and washed with water (10 mL) then sat. brine (10 mL). The organic solution was dried (Na₂SO₄) and concentrated to give the title compound (1.35 g, 98%) as a colourless oil; ¹H NMR (300 MHz, CDCl₃) 1.40-1.60 (13H, m), 1.80 (2H, p), 3.03 (3H, s), 3.09-3.21 (2H, m), 4.25 (2H, t), 4.57 (1H, s).

10 **Intermediate 111b: *tert*-Butyl (5-(4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazin-1-yl)pentyl)carbamate**

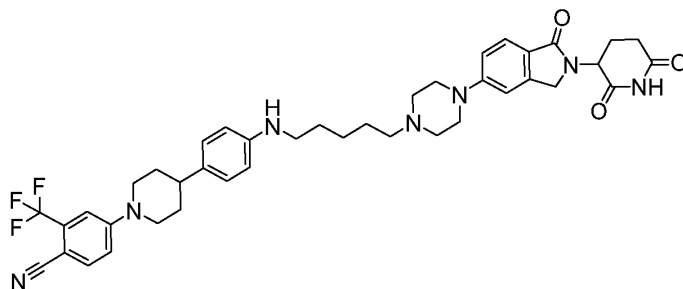


- Cs₂CO₃ (1.49 g, 4.57 mmol) was added to 5-((*tert*-butoxycarbonyl)amino)pentyl methanesulfonate (1.71 g, 6.09 mmol) and 3-(1-oxo-5-(piperazin-1-yl)isindolin-2-yl)piperidine-2,6-dione (1.00 g, 3.05 mmol) in DMF (12 mL). The resulting mixture was stirred at 65°C for 12h. Purification by C-18 (eluent: water) gave the title compound (800 mg, 66%) as a brown oil; *m/z*: ES⁺ [M+H]⁺ = 514.

Intermediate 111c: 3-(5-(4-(5-Aminopentyl)piperazin-1-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione

- 20 4M HCl in 1,4-dioxane (20 mL, 2.53 mmol) was added dropwise to *tert*-butyl (5-(4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazin-1-yl)pentyl)carbamate (1.30 g, 2.53 mmol) in DCM (15 mL). The resulting mixture was stirred at RT for 1h. Purification by flash C18-flash chromatography (eluent: 100% water) gave the title compound (1.00 g, 96 %) as a pale yellow solid; ¹H NMR (CD₃OD) 1.54 (2H, p), 1.77 (2H, h), 1.97-1.86 (2H, m), 2.23-2.10 (1H, m), 2.50 (1H, qd), 2.85-2.70 (1H, m), 2.96-2.87 (1H, m), 2.99 (2H, q), 3.31-3.22 (4H, m), 3.37 (2H, s), 3.74 (2H, d), 7.71 (1H, d), 4.08 (2H, d), 4.53-4.37 (2H, m), 5.13 (1H, dd), 7.23-7.16 (2H, m); *m/z*: ES⁺ [M+H]⁺ = 414.

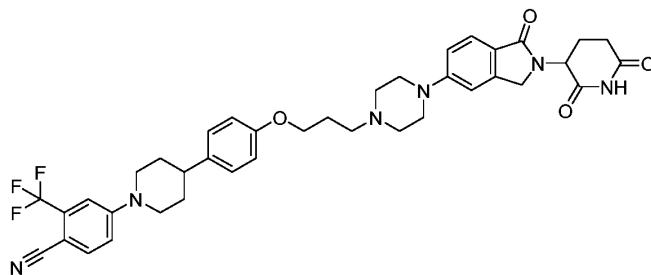
Example 111: 4-(4-[4-[(5-[4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isindol-5-yl]piperazin-1-yl]pentyl)amino]phenyl]piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



Intermediate 4a was reacted with Intermediate 111c using the general synthetic method illustrated by Example 110 to give the title compound (as a bis-formate salt) after purification by C-18 chromatography (Eluent A).

¹H NMR: (500 MHz) 1.33-1.42 (2H, m), 1.45-1.61 (7H, m), 1.74-1.85 (2H, m), 1.91-2.00 (1H, m), 2.28-2.39 (4H, m), 2.53-2.68 (3H, m), 2.84-3.07 (6H, m), 3.29-3.48 (3H, m), 4.09-4.17 (2H, m), 4.17-4.24 (1H, m), 4.28-4.40 (1H, m), 5.03 (1H, br dd), 6.48 (2H, br d), 6.92 (2H, br d), 7.21-7.27 (1H, m), 7.30 (1H, br s), 7.51 (1H, br d), 7.79 (1H, br d), 8.14 (2H, s), 10.92 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 742.5.

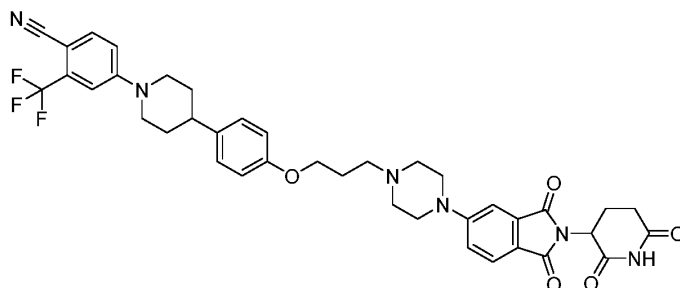
Example 112: 4-{4-[4-(3-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl}propoxy)phenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile



Intermediate 2c was reacted with Intermediate 13a using the general synthetic method illustrated by Example 5 to give the title compound after purification by HPLC (Column A, Eluent A, Basic Work-up A). ¹H NMR: (500 MHz) 1.61 (2H, qd), 1.81-1.87 (2H, m), 1.87-1.92 (2H, m), 1.93-2.00 (1H, m), 2.31-2.40 (2H, m), 2.51-2.64 (7H, m), 2.71-2.80 (1H, m), 2.84-2.93 (1H, m), 3.03 (2H, br t), 3.98 (2H, t), 4.12-4.23 (3H, m), 4.28-4.34 (1H, m), 5.03 (1H, dd), 6.85 (2H, d), 7.00-7.10 (2H, m), 7.14 (2H, d), 7.22-7.29 (1H, m), 7.31 (1H, s), 7.51 (1H, d), 7.80 (1H, d), 10.92 (1H, s), 3 protons under solvent peak; *m/z*: ES⁺ [M+H]⁺ = 715.3.

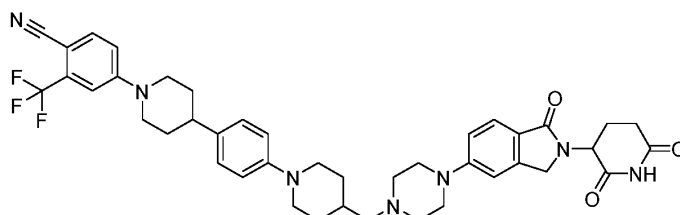
20

Example 113: 4-{4-[4-(3-{4-[2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl}propoxy)phenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile



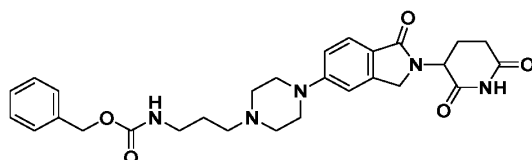
Intermediate 13a was reacted with Intermediate 63e using the general synthetic method illustrated by Example 5 to give the title compound after purification by FSC (eluent: 0-10% MeOH in EtOAc). ¹H NMR: (500 MHz) 1.56-1.67 (2H, m), 1.80-1.92 (4H, m), 1.97-2.05 (1H, m), 2.54-2.64 (4H, m), 2.71-2.80 (2H, m), 2.82-2.92 (2H, m), 3.00-3.07 (2H, m), 3.43 (5H, br s), 3.96-4.03 (2H, m), 4.16 (2H, br d), 5.05 (1H, dd), 6.85 (2H, d), 7.14 (2H, d), 7.22-7.28 (2H, m), 7.31 (2H, br d), 7.66 (1H, d), 7.80 (1H, d), 11.05 (1H, br s); *m/z*: ES⁺ [M+H]⁺ = 729.4.

Example 114: 4-(4-{4-[4-({4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl}methyl)piperidin-1-yl]phenyl}piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



Intermediate 2c was reacted with Intermediate 4c using the general synthetic method illustrated by Example 2 to give the title compound after purification by flash alumina chromatography (eluent: 0-100% EtOAc in heptane then 20% EtOH in EtOAc); ¹H NMR: (CDCl₃) 1.37 (2H, tt), 1.61-1.7 (1H, m), 1.76 (2H, qd), 1.89 (2H, d), 1.96 (2H, s), 2.20 (1H, ddq), 2.26-2.3 (2H, m), 2.3-2.38 (1H, m), 2.55-2.62 (4H, m), 2.64-2.77 (3H, m), 2.77-2.87 (1H, m), 2.87-2.96 (1H, m), 2.99-3.12 (2H, m), 3.24-3.37 (4H, m), 3.66 (2H, d), 4.01 (2H, d), 4.25 (1H, d), 4.41 (1H, d), 5.19 (1H, dd), 6.84-6.93 (3H, m), 6.99 (2H, dt), 7.10 (2H, d), 7.15 (1H, d), 7.61 (1H, d), 7.73 (1H, d), 7.87 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 754.3.

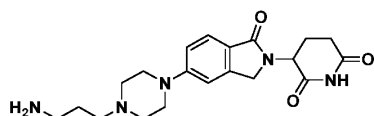
Intermediate 115a: Benzyl (3-(4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazin-1-yl)propyl)carbamate



3-(1-Oxo-5-(piperazin-1-yl)isindolin-2-yl)piperidine-2,6-dione hydrochloride salt (0.700 g, 1.92 mmol) was dissolved in a mixture of DCM (5 mL) and MeOH (5 mL). Benzyl (3-oxopropyl)carbamate (1.19 g, 5.76

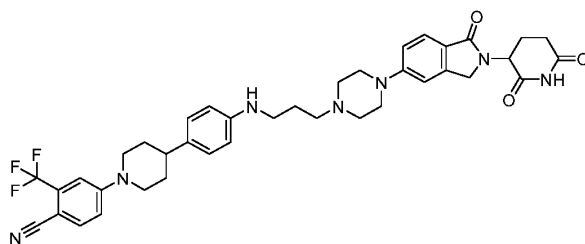
- mmol) was then added and the mixture was stirred at RT for 10 mins. Then NaBH(OAc)₃ (1.63 g, 7.67 mmol) was added and the mixture was stirred at RT for 1h. Additional benzyl (3-oxopropyl)carbamate (1.19 g, 5.76 mmol) was then added. The mixture was stirred at RT for 10 min and additional NaBH(OAc)₃ (1.63 g, 7.67 mmol) was added and stirring continued at RT for 1h. After concentrating under reduced pressure, EtOAc (20 mL) was added to the residue. The resulting solution was washed with sat. NaHCO₃ solution (10 mL), brine (10 mL) and dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: hexanes to DCM then 10% MeOH in DCM) gave the title compound (0.800 g, 80 %) colourless dry film; ¹H NMR (500 MHz, CDCl₃) 1.76 (2H, br s), 2.14-2.26 (1H, m), 2.33 (1H, br dd), 2.49-2.57 (2H, m), 2.58-2.72 (4H, m), 2.78-2.87 (1H, m), 2.88-2.96 (1H, m), 3.32 (6H, br s), 4.26 (1H, d), 4.42 (1H, d), 5.11 (2H, s), 5.18-5.25 (1H, m), 5.68 (1H, br s), 6.87 (1H, s), 6.98 (1H, br d), 7.35 (5H, br s), 7.74 (1H, d), 8.02-8.25 (1H, m); *m/z* ES⁺, [M+H]⁺ = 520.

Intermediate 115b: 3-(5-(4-(3-Aminopropyl)piperazin-1-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione



- Benzyl (3-(4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazin-1-yl)propyl)carbamate (0.800 g, 1.54 mmol) was dissolved in MeOH (30 mL). Pd-on-C, (10% wet, 0.410 g, 0.38 mmol) was added and the suspension was degassed, filled with H₂ (balloon used), and stirred at RT for 3h. The mixture was then filtered through celite and washed through with a mixture of MeCN/MeOH (1:1, 100 mL). The filtrate was concentrated to dryness to give the title compound (0.660 g, 94 %); ¹H NMR (500 MHz) 1.93-2.03 (1H, m), 2.06-2.19 (2H, m), 2.34-2.45 (1H, m), 2.51 (1H, br s), 2.58-2.69 (1H, m), 2.88-3.03 (3H, m), 3.07-3.14 (1H, m), 3.20-3.30 (2H, m), 3.32-3.43 (2H, m), 3.52-3.62 (2H, m), 3.94-4.10 (2H, m), 4.20-4.30 (1H, m), 4.33-4.42 (1H, m), 5.07 (1H, dd), 7.08-7.27 (2H, m), 7.60 (1H, d), 7.95-8.28 (3H, m), 10.95 (1H, s), 11.21-11.41 (1H, m); *m/z* ES⁺, [M+H]⁺ = 386.

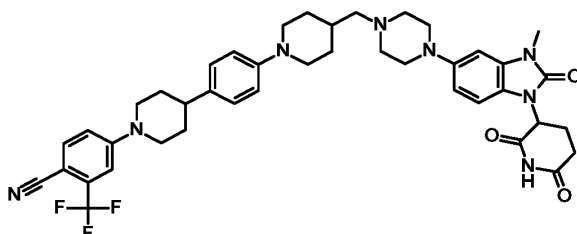
Example 115: 4-(4-{4-[(3-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isindol-5-yl]piperazin-1-yl}propyl)amino]phenyl}piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



- Intermediate 4a was reacted with Intermediate 115b using the general synthetic method illustrated by Example 110 to give the title compound after purification by C-18 chromatography (Eluent A); The title compound was converted to a hydrochloride salt by mixing with 0.1mL of 1N HCl water solution and then concentrating the solution to dryness. ¹H NMR: (500 MHz) 1.55-1.69 (2H, m), 1.75-1.89 (2H, m), 1.91-1.99 (1H, m), 2.33-2.45 (2H, m), 2.54-2.65 (2H, m), 2.67-2.80 (1H, m), 2.83-2.95 (1H, m), 2.99-3.11 (2H, m), 3.11-3.28 (5H, m), 3.75-4.11 (8H, m), 4.11-4.19 (3H, m), 4.19-4.27 (2H, m), 4.32-4.41 (1H, m), 4.98-5.12 (1H, m), 7.02-7.22 (4H, m),

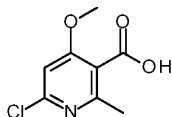
7.22-7.30 (1H, m), 7.29-7.36 (1H, m), 7.49-7.63 (1H, m), 7.70-7.86 (1H, m), 10.93 (1H, s); 2 exchangeable protons not observed; m/z : $ES^+ [M+H]^+ = 714.5$.

5 **Example 116: 4-[4-[4-[4-[1-[2,6-Dioxo-3-piperidyl]-3-methyl-2-oxo-benzimidazol-5-yl]piperazin-1-yl]methvl]-1-piperidyl]phenyl]-1-piperidyl]-2-(trifluoromethyl)benzonitrile**



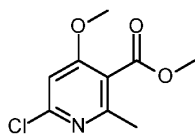
Intermediate 4b was reacted with Intermediate 29g using the general synthetic method illustrated by Example 1 to give the title compound after purification by HPLC (Column A, Eluent A). ^1H NMR: (500 MHz) 1.55-1.69 (2H, m), 1.75-1.89 (2H, m), 1.91-1.99 (1H, m), 2.33-2.45 (2H, m), 2.54-2.65 (2H, m), 2.67-2.80 (1H, m), 2.83-2.95 (1H, m), 2.99-3.11 (2H, m), 3.11-3.28 (5H, m), 3.75-4.11 (8H, m), 4.11-4.19 (3H, m), 4.19-4.27 (2H, m), 4.32-4.41 (1H, m), 4.98-5.12 (1H, m), 7.02-7.22 (4H, m), 7.22-7.30 (1H, m), 7.29-7.36 (1H, m), 7.49-7.63 (1H, m), 7.70-7.86 (1H, m), 10.93 (1H, s); 2 exchangeable protons not observed; m/z : $ES^+ [M+H]^+ = 769.3$.

15 **Intermediate 117a: 6-Chloro-4-methoxy-2-methylnicotinic acid**



To a stirred solution of ethyl 4,6-dichloro-2-methylnicotinate (2.00 g, 8.54 mmol) in DCM (30 mL) was added sodium methoxide (2.22 mL, 11.96 mmol) at 0°C. The mixture was then stirred at RT for 16h. The mixture was then poured into crushed ice, and the pH was adjusted to 4-5 using 2N AcOH. The mixture was then extracted with DCM (50 mL $\times$ 2). The combined organic solutions were washed with water (30 mL), dried (Na_2SO_4) and concentrated to give the title compound (2.00 g) which was used in the next step without further purification; m/z : $ES^+ [M+H]^+ = 202.2$.

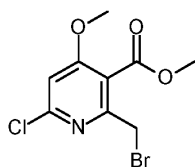
Intermediate 117b: Methyl 6-chloro-4-methoxy-2-methylnicotinate



25 To a stirred solution of 6-chloro-4-methoxy-2-methylnicotinic acid (2.50 g, 12.40 mmol) in DMF (30 mL) was added K_2CO_3 (2.06 g, 14.88 mmol) and MeI (1.16 mL, 18.60 mmol) at RT. The mixture was then stirred at RT for 16h. The mixture was then diluted with water (50 mL) and extracted with MTBE (50 mL $\times$ 3). The

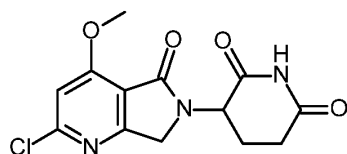
combined organic solutions were washed with brine (50 mL $\times$ 2), dried (Na₂SO₄) and concentrated under reduced pressure (bath temperature: 45°C) to give the title compound (2.50 g, 7.04 mmol, 57 % yield) as yellow solid which was used in the next step without further purification; *m/z*: ES⁺ [M+H]⁺ = 216.1.

5 **Intermediate 117c: Methyl 2-(bromomethyl)-6-chloro-4-methoxynicotinate**



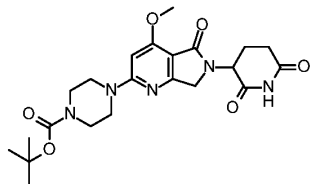
- 10 *tert*-Butyl acetate (30 mL) was added to methyl 6-chloro-4-methoxy-2-methylnicotinate (1.50 g, 6.96 mmol) in under N₂ at RT. NBS (1.610 g, 9.04 mmol) and AIBN (0.228 g, 1.391 mmol) were then added at RT. The mixture was then stirred at 110°C for 16h. The mixture was then diluted with water (30 mL) and extracted with EtOAc (40 mL $\times$ 2). The combined organic solutions were washed with brine (30 mL), dried (Na₂SO₄) and concentrated under reduced pressure (bath temperature: 45°C) give the title compound (2.00 g, 35 % yield) as brown liquid which was used in the next step without further purification; *m/z*: ES⁺ [M+H]⁺ = 294.

15 **Intermediate 117d: 3-(2-Chloro-4-methoxy-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione**



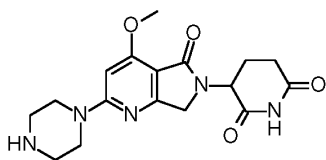
- 20 3-Aminopiperidine-2,6-dione hydrochloride salt (0.335 g, 2.037 mmol) and DIPEA (1.053 g, 8.15 mmol) were added to a solution of methyl 2-(bromomethyl)-6-chloro-4-methoxynicotinate (2.00 g, 2.037 mmol) in MeCN (30 mL) under N₂ at RT. The mixture was then heated to 85°C for 18h. The mixture was then cooled slowly to RT and the resulting solids were collected by filtration, washed with MeCN (5 mL) and dried under vacuum to give the title compound (0.44 g, 66%) as brown solid; ¹H NMR: 1.93-2.02 (1H, m), 2.32-2.41 (1H, m), 2.59 (1H, d), 2.83-2.97 (1H, m), 4.01 (3H, s), 4.22-4.29 (1H, m), 4.38-4.49 (1H, m), 5.09 (1H, dd), 7.30 (1H, s), 10.99 (1H, s). *m/z*: ES⁺ [M+H]⁺ = 310.1.

25 **Intermediate 117e: *tert*-Butyl 4-(6-(2,6-dioxopiperidin-3-yl)-4-methoxy-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)piperazine-1-carboxylate**



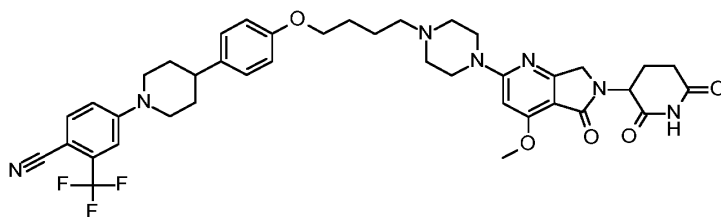
- Pd-PEPPSI-IHept (Cl) (47.1 mg, 0.048 mmol) was added to *tert*-butyl piperazine-1-carboxylate (541 mg, 2.91 mmol), Cs₂CO₃ (947 mg, 2.91 mmol) and 3-(2-chloro-4-methoxy-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione (300 mg, 0.969 mmol) in 1,4-dioxane (10 mL) at RT under N₂. The resulting suspension was stirred for 2h at 120°C. The mixture was then diluted with DCM (20 mL) and washed with 5% AcOH in water (20 mL), water (20 mL), sat. NaHCO₃ (20 mL) and then sat. brine (20 mL). The organic solution was then dried (Na₂SO₄) and concentrated. Trituration with EtOAc (4 mL) and washing with MTBE (16 mL) gave a solid which was collected by filtration and dried under vacuum to give the title compound (340 mg, 70 % yield) as brown powder; ¹H NMR: 1.43 (9H, s), 1.87-1.98 (1H, m), 2.28-2.37 (1H, m), 2.56-2.62 (1H, m), 2.84-2.95 (1H, m), 3.37-3.47 (4H, m), 3.62-3.70 (4H, m), 3.90 (3H, s), 4.01 (1H, d), 4.12 (d, 1H), 5.00 (1H, dd), 6.29 (1H, s), 10.92 (1H, br s); *m/z*: ES⁺ [M+H]⁺ = 460.2.

Intermediate 117f: 3-(4-Methoxy-5-oxo-2-(piperazin-1-yl)-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione



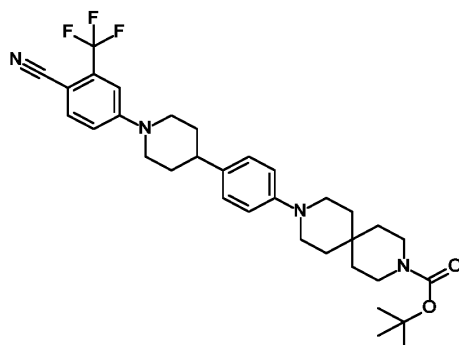
- To a stirred solution of *tert*-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-4-methoxy-5-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-2-yl)piperazine-1-carboxylate (340 mg, 0.740 mmol) in DCM (10 mL) was added 4M HCl (3.70 mL, 14.80 mmol) in 1,4-dioxane at 0°C. The mixture was then stirred at RT for 1h under N₂. Concentration of the mixture then gave the title compound as a hydrochloride salt (300 mg, 88 %) as a brown solid; ¹H NMR: 1.88-1.99 (1H, m), 2.29-2.38 (1H, m), 2.59 (1H, br s), 2.84-2.96 (1H, m), 3.17-3.20 (4H, m), 3.92-4.00 (7H, s), 4.01-4.08 (1H, m), 4.18 (1H, s), 5.02 (1H, dd), 6.41 (1H, s), 9.35 (2H, br s), 10.92 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 360.2.

Example 117: 4-(4-(4-(4-(6-(2,6-dioxopiperidin-3-yl)-4-methoxy-5-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-2-yl)piperazin-1-yl)butoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



- Intermediate 117f was reacted with Intermediate 50a using the general synthetic method illustrated by Example 5 to give the title compound after purification by HPLC (Column; Zorbax- C18, 5μm; 50 × 21.2 mm, Eluent C, Basic Work-Up A); ¹H NMR: 1.56-1.67 (4H, m), 1.69-1.79 (2H, m), 1.80-1.88 (2H, m), 1.88-1.96 (1H, m), 2.34-2.40 (3H, m), 2.40-2.45 (4H, m), 2.59 (1H, s), 2.77 (1H, t), 2.84-2.95 (1H, m), 3.04 (2H, t), 3.60-3.63 (4H, m), 3.89 (3H, s), 3.93-4.03 (3H, m), 4.10-4.23 (3H, m), 5.00 (1H, br dd), 6.27 (1H, s), 6.86 (2H, d), 7.16 (2H, d), 7.23-7.36 (2H, m), 7.82 (1H, d), 10.91 (1H, br s); *m/z*: ES⁺ [M+H]⁺ = 760.2.

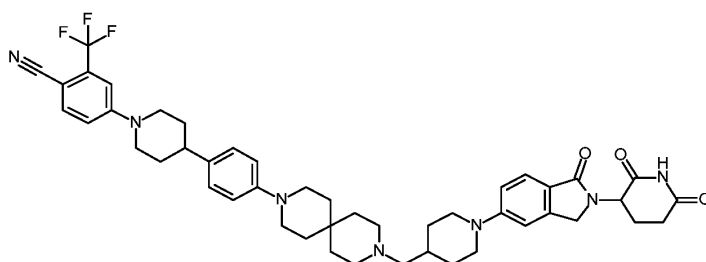
Intermediate 118a: *tert*-Butyl 9-(4-(1-(4-cyano-3-(trifluoromethyl)phenyl)piperidin-4-yl)phenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate



- 5 4-(4-(4-Bromophenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (Intermediate 4a) (0.500 g, 1.22 mmol), *tert*-butyl 3,9-diazaspiro[5.5]undecane-3-carboxylate (0.342 g, 1.34 mmol), RuPhos Pd G3 (0.102 g, 0.12 mmol), RuPhos (0.057 g, 0.12 mmol) and sodium 2-methylpropan-2-olate (0.352 g, 3.67 mmol) were weighed into a microwave vial. Anhydrous 1,4-dioxane (8 mL) was then added. The mixture was degassed by bubbling N₂ through the mixture for 5 mins and was then heated and stirred at 100°C for 2h in a microwave. The
- 10 mixture was then cooled to RT and water (20 mL) was added. A precipitate formed which was collected by filtration. The cake was washed with Et₂O (2 × 15 mL) to give the title compound (0.578 g, 81 %) as a grey solid; ¹H NMR: 1.33-1.44 (13H, m), 1.5-1.69 (6H, m), 1.84 (2H, d), 2.68-2.78 (1H, m), 3-3.12 (6H, m), 3.29-3.38 (4H, m), 4.17 (2H, d), 6.86 (2H, d), 7.08 (2H, d), 7.26 (1H, dd), 7.32 (1H, d), 7.81 (1H, d); *m/z*: ES⁺ [M+H]⁺ 583.3.

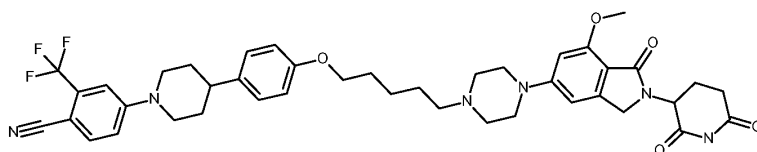
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Example 118: 4-(4-(4-(9-((1-(2-(2,6-Dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecan-3-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile

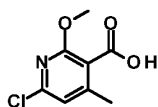


- Intermediate 118a was reacted with Intermediate 27f using the general synthetic method illustrated by
- 20 Example 1 to give the title compound after purification (Column A, Eluent A); ¹H NMR (CDCl₃) 1.42 (2H, q), 1.62-1.88 (10H, m), 1.89-2.09 (5H, m), 2.12-2.23 (1H, m), 2.24-2.39 (1H, m), 2.65-2.78 (3H, m), 2.79-3.22 (13H, m), 3.81 (2H, d), 4.01 (2H, d), 4.24 (1H, d), 4.39 (2H, d), 5.16 (1H, dd), 6.78-6.92 (3H, m), 6.97 (2H, ddd), 7.07-7.2 (3H, m), 7.60 (1H, d), 7.70 (1H, d), 8.42 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 822.5.

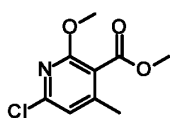
- 25 **Example 119: 4-[4-[4-[5-[4-[2-(2,6-dioxo-3-piperidyl)-7-methoxy-1-oxo-isindolin-5-yl]]piperazin-1-**

yl]pentoxy]phenyl]-1-piperidyl]-2-(trifluoromethyl)benzonitrile

- Prepared from 4-(4-(4-bromophenyl)piperidin-1-yl)-2-(trifluoro-methyl)benzonitrile (Intermediate 4a) using the general synthetic method illustrated by Example 12 but using pentane-1,5-diol to give the title compound after purification (Column A, Eluent A); ¹H NMR (CDCl₃) 1.75 (2H, qd), 1.97 (2H, d), 2.13-2.34 (4H, m), 2.34-2.48 (2H, m), 2.64-2.93 (9H, m), 3.06 (2H, td), 3.29-3.39 (4H, m), 3.94 (3H, s), 4.02 (2H, d), 4.13-4.26 (3H, m), 4.36 (1H, d), 5.13 (1H, dd), 6.36 (1H, d), 6.46 (1H, s), 6.79-6.9 (2H, m), 6.99 (1H, dd), 7.09-7.19 (3H, m), 7.61 (1H, d), 7.89 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 773.5.

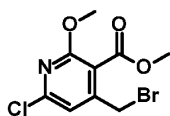
Intermediate 120a: 6-Chloro-2-methoxy-4-methylnicotinic acid

- To a stirred solution of sodium methoxide (10.3 mL, 55.8 mmol) in THF (25 mL) was added 2,6-dichloro-4-methylnicotinic acid (5.00 g, 24.27 mmol) in THF (25 mL) at 0°C. The mixture was then heated at 70°C for 16h. After cooling to RT the mixture was acidified with a 1.5N aq. HCl to pH 3-4, then extracted with EtOAc (60 mL × 2). The combined organic solutions were washed with water and brine, dried (Na₂SO₄) and concentrated to give the title compound (4.00 g, 76 %) which was used in the next step without further purification; ¹H NMR: 2.27 (3H, s), 3.87 (3H, s), 7.10 (1H, s), 13.43 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 202.1

Intermediate 120b: Methyl 6-chloro-2-methoxy-4-methylnicotinate

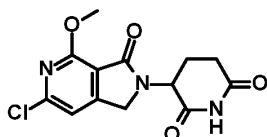
- To a stirred solution of 6-chloro-2-methoxy-4-methylnicotinic acid (4.40 g, 20.19 mmol) in DMF (50 mL) was added K₂CO₃ (3.35 g, 24.23 mmol) and MeI (1.89 mL, 30.3 mmol) at RT. The mixture was then stirred at RT for 16h. The mixture was then diluted with water (50 mL) and extracted with MTBE (50 mL × 3). The combined organic solutions were washed with brine (50 mL × 2), dried (Na₂SO₄) and concentrated under reduced pressure (bath temperature: 45°C) to give the title compound (4.00 g, 76 %) as pale yellow solid; ¹H NMR: 2.26 (3H, s), 3.84 (3H, s), 3.87 (3H, s), 7.13 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 216.1.

Intermediate 120c: Methyl 4-(bromomethyl)-6-chloro-2-methoxynicotinate



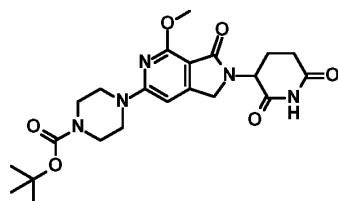
- tert*-Butyl acetate (150 mL) was added to methyl 6-chloro-2-methoxy-4-methylnicotinate (8.00 g, 37.1 mmol) under N₂. NBS (9.24 g, 51.9 mmol) and benzoyl peroxide (1.80 g, 7.42 mmol) were then added at RT. The mixture was stirred at 110°C for 14h. Further NBS (2.64 g, 14.84 mmol) was then added and stirring continued at 110°C for 12h. The mixture was then diluted with 10% NaHCO₃ solution (50 mL) and extracted with EtOAc (60 mL × 2). The combined organic solutions were washed with brine (80 mL), dried (Na₂SO₄) and concentrated under reduced pressure to give the title compound (11.00 g, 27%) as brown liquid, which was used directly in the next step without further purification; *m/z*: ES⁺ [M+H]⁺ = 294.

10 **Intermediate 120d: 3-(6-Chloro-4-methoxy-3-oxo-1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)piperidine-2,6-dione**



- 3-Aminopiperidine-2,6-dione hydrochloride salt (1.65 g, 10.01 mmol) and DIPEA (5.17 g, 40.0 mmol) were added to methyl 4-(bromomethyl)-6-chloro-2-methoxynicotinate (11.00 g, 10.01 mmol) in MeCN (80 mL) at RT under N₂. The mixture was then stirred at 85°C for 16h then cooled slowly to RT. The mixture was then diluted with DCM (200 mL) and washed with 5% AcOH in water (200 mL), water (200 mL), sat. NaHCO₃ (200 mL) and then sat. brine (200 mL). The organic solution was dried (Na₂SO₄) and concentrated. Trituration with EtOAc (10 mL) and washing with MTBE (30 mL) gave a solid which was collected by filtration and dried under vacuum to give the title compound (1.60 g, 44%) as brown solid; ¹H NMR: 1.89-2.02 (1H, m), 2.30-2.35 (1H, m), 2.50-2.59 (1H, m), 2.84-2.98 (1H, m), 3.99 (3H, s), 4.26-4.39 (1H, m), 4.40-4.53 (1H, m), 5.05 (1H, dd), 7.40 (1H, s), 10.99 (1H, br s); *m/z*: ES⁺ [M+H]⁺ = 310.2.

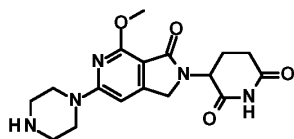
Intermediate 120e: *tert*-Butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-methoxy-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-yl)piperazine-1-carboxylate



- Pd-PEPPSI-IHept (Cl) (47.1 mg, 0.048 mmol) was added to *tert*-butyl piperazine-1-carboxylate (541 mg, 2.91 mmol), Cs₂CO₃ (947 mg, 2.91 mmol) and 3-(6-chloro-4-methoxy-3-oxo-1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)piperidine-2,6-dione (300 mg, 0.969 mmol) in 1,4-dioxane (10 mL) at RT under N₂. The resulting suspension was stirred for 2h at 120°C. After cooling the reaction mixture was diluted with DCM (20

- mL) and washed with 5% AcOH in water (20 mL), water (20 mL), sat. NaHCO₃ (20 mL) and then sat. brine (20 mL). The organic portion was dried (Na₂SO₄) and concentrated. Trituration using EtOAc (4 mL) and washing with MTBE (16 mL) gave a solid which was collected by filtration and dried under vacuum to give the title compound (260 mg, 50%) as brown solid; ¹H NMR: 1.43 (9H, s), 1.88-2.00 (1H, m), 2.29-2.39 (1H, m), 2.58-2.68 (1H, m), 2.86-2.96 (1H, m), 3.34-3.44 (4H, m), 3.53-3.63 (4H, m), 3.90 (3H, s), 4.09-4.18 (1H, m), 4.24-4.34 (1H, m), 4.97 (1H, br dd), 6.50 (1H, s), 10.92 (1H, br s); *m/z*: ES⁺ [M+H]⁺ = 460.2.

Intermediate 120f: 3-(4-Methoxy-3-oxo-6-(piperazin-1-yl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridin-2-yl)piperidine-2,6-dione

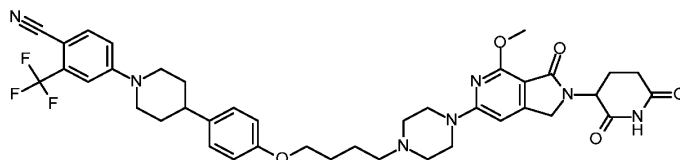


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To a stirred solution of *tert*-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-methoxy-3-oxo-2,3-dihydro-1H-pyrrolo-[3,4-c]pyridin-6-yl)piperazine-1-carboxylate (260 mg, 0.566 mmol) in DCM (10 mL) was added 4M HCl (2.83 mL, 11.32 mmol) in 1,4-dioxane at 0°C. The mixture was stirred at RT for 12h under N₂. The mixture was then concentrated under reduced pressure to give the title compound as a hydrochloride salt (240 mg, 63 % yield), as brown solid; *m/z*: ES⁺ [M+H]⁺ = 360.2.

15

Example 120: 4-(4-(4-(4-(2-(2,6-Dioxopiperidin-3-yl)-4-methoxy-3-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)piperazin-1-yl)butoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile

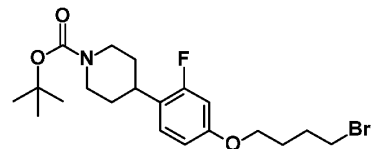


20

Intermediate 50a was reacted with Intermediate 120f using the general synthetic method illustrated by Example 5 to give the title compound after purification (Column: Zorbax-C18, 5μm; 50 × 21.2 mm, Eluent C, Basic Work-Up A); ¹H NMR: 1.55-1.69 (4H, m), 1.69-1.78 (2H, m), 1.81-1.95 (3H, m), 2.27-2.38 (3H, m), 2.46 (3H, br s), 2.57-2.68 (1H, m), 2.77 (1H, br t), 2.83-2.97 (1H, m), 3.04 (2H, br t), 3.50-3.59 (4H, m), 3.84-3.93 (3H, m), 3.97 (2H, br t), 4.09-4.20 (3H, m), 4.22-4.31 (1H, m), 4.96 (1H, dd), 6.48 (1H, s), 6.86 (2H, d), 7.16 (2H, d), 7.27 (1H, d), 7.33 (1H, br s), 7.82 (1H, d), 10.91 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 760.2.

25

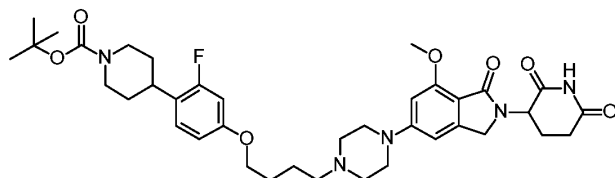
Intermediate 121a: *tert*-Butyl 4-(4-(4-bromobutoxy)-2-fluorophenyl)piperidine-1-carboxylate



K₂CO₃ (421 mg, 3.05 mmol) and 1,4-dibromobutane (910 µL, 7.62 mmol) were added consecutively to a solution of *tert*-butyl 4-(2-fluoro-4-hydroxyphenyl)piperidine-1-carboxylate (Intermediate 38B) (450 mg, 1.52 mmol) in DMF (5 mL). The resulting mixture was stirred overnight at 70°C. After cooling to RT the mixture was diluted with EtOAc (20 mL) and water (20 mL) then brine (20 mL). The organic portion was collected and washed with further portions of brine (3 × 20 mL), dried (MgSO₄) and concentrated. Purification by FSC (gradient: 0-25% EtOAc in heptane) gave the title compound (0.305 g, 47 %) as an colourless oil; ¹H NMR (CDCl₃) 1.48 (9H, s), 1.55-1.67 (2H, m), 1.73-1.82 (2H, m), 1.88-1.98 (2H, m), 2-2.1 (2H, m), 2.81 (2H, td), 2.91 (1H, tt), 3.48 (2H, t), 3.96 (2H, t), 4.17-4.3 (2H, m), 6.58 (1H, dd), 6.63 (1H, dd), 7.07 (1H, t); *m/z*: ES⁺ [MH-Boc] 330.0.

10

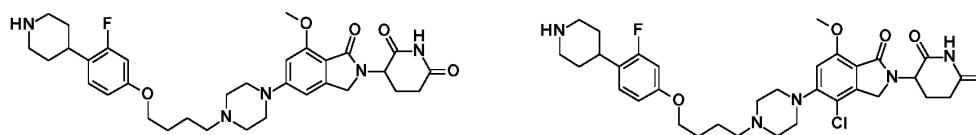
Intermediate 121b: *tert*-Butyl 4-(4-(4-(2-(2,6-dioxopiperidin-3-yl)-7-methoxy-1-oxoisindolin-5-yl)piperazin-1-yl)butoxy)-2-fluorophenyl)piperidine-1-carboxylate



DIPEA (729 µL, 4.18 mmol) was added to a mixture of 3-(7-methoxy-1-oxo-5-(piperazin-1-yl)isindolin-2-yl)piperidine-2,6-dione hydrochloride salt (303 mg, 0.77 mmol) (Intermediate 1f), *tert*-butyl 4-(4-(4-bromobutoxy)-2-fluorophenyl)piperidine-1-carboxylate (300 mg, 0.70 mmol) and KI (347 mg, 2.09 mmol) in DMSO (5 mL) and the resulting mixture was heated to 70°C for 4h. The mixture was cooled to RT and diluted with water (20 mL) and EtOAc (20 mL). The organic portion was collected and the aqueous portion was washed with further EtOAc (20 mL). The combined organics were washed with water (2 × 20 mL), brine (2 × 20 mL), dried (MgSO₄) and concentrated. Purification by FSC (gradient: 0-10% MeOH in DCM) gave the title compound (0.200 g, 41 %) as a pale yellow liquid; ¹H NMR (CDCl₃) 1.48 (9H, s), 1.53-1.67 (6H, m), 1.72-1.81 (3H, m), 1.86 (2H, s), 2.13-2.24 (1H, m), 2.31 (1H, dd), 2.73-2.98 (6H, m), 3.06-3.78 (6H, m), 3.94 (3H, s), 3.95-4.02 (2H, m), 4.16-4.29 (3H, m), 4.36 (1H, d), 5.12 (1H, dd), 6.36 (1H, s), 6.48 (1H, s), 6.58 (1H, dd), 6.63 (1H, dd), 7.07 (1H, t), 7.98 (1H, s); *m/z*: ES⁺ [M+H]⁺ 708.6.

25

Intermediates 121c and 121d: 3-(5-(4-(4-(3-Fluoro-4-(piperidin-4-yl)phenoxy)butyl)piperazin-1-yl)-7-methoxy-1-oxoisindolin-2-yl)piperidine-2,6-dione and 3-(4-chloro-5-(4-(4-(3-fluoro-4-(piperidin-4-yl)phenoxy)butyl)piperazin-1-yl)-7-methoxy-1-oxoisindolin-2-yl)piperidine-2,6-dione



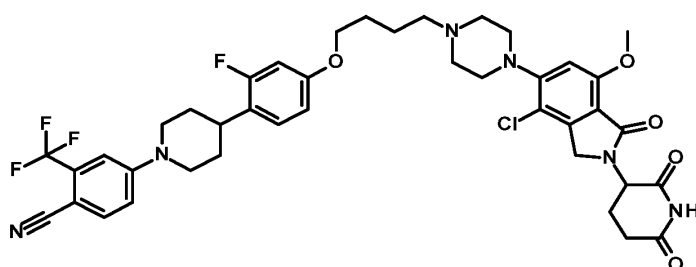
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4M HCl in 1,4-dioxane (706 µL, 2.83 mmol) was added in one portion to *tert*-butyl 4-(4-(4-(2-(2,6-dioxopiperidin-3-yl)-7-methoxy-1-oxoisindolin-5-yl)piperazin-1-yl)butoxy)-2-fluorophenyl)piperidine-1-carboxylate (200 mg, 0.28 mmol) in DCM (1 mL) at RT. The resulting mixture was stirred at RT for 0.5h. The

mixture was then concentrated under reduced pressure to give a mixture of the title compounds 121c and bi-product 121d in 1:2 ratio as a pale brown solid which was used in the next step without further manipulation.

Example 121: 4-(4-(4-(4-(4-Chloro-2-(2,6-dioxopiperidin-3-yl)-7-methoxy-1-oxoisindolin-5-yl)piperazin-1-yl)butoxy)-2-fluorophenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile

5

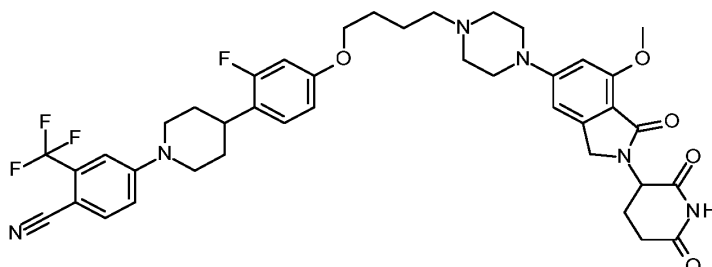


A (1:2) mixture of Intermediates 121c and 121d was reacted with 4-fluoro-2-(trifluoromethyl)benzonitrile using the general synthetic method illustrated by Example 16 to give the title compound (as a formate salt) after purification (Column A, Eluent A); ^1H NMR (CDCl_3) 1.79 (6H, ddd), 1.95 (2H, d), 2.14-2.24 (1H, m), 2.27-2.41 (1H, m), 2.76-2.94 (4H, m), 2.96-3.14 (7H, m), 3.31-3.33 (4H, m), 3.89-4.07 (7H, m), 4.21 (1H, d), 4.36 (1H, d), 5.13 (1H, dd), 6.13 (1H, s), 6.54-6.67 (3H, m), 6.98 (1H, dd), 7.07 (1H, t), 7.15 (1H, d), 7.61 (1H, d), 8.33 (1H, s); m/z : ES^+ $[\text{M}+\text{H}]^+ = 811.6$.

10

Example 122: 4-(4-(4-(4-(2-(2,6-Dioxopiperidin-3-yl)-7-methoxy-1-oxoisindolin-5-yl)piperazin-1-yl)butoxy)-2-fluorophenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile

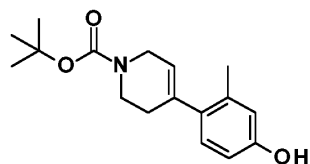
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A (1:2) mixture of Intermediates 121c and 121d was reacted with 4-fluoro-2-(trifluoromethyl)benzonitrile using the general synthetic method illustrated by Example 16 to give the title compound as a formate salt after purification (Column A, Eluent A); ^1H NMR (CDCl_3) 1.71-1.89 (6H, m), 1.95 (2H, d), 2.1-2.22 (1H, m), 2.30 (1H, qd), 2.64-2.73 (2H, m), 2.76-2.94 (6H, m), 2.98-3.16 (3H, m), 3.41-3.51 (4H, m), 3.94 (3H, s), 3.95-4.08 (4H, m), 4.20 (1H, d), 4.36 (1H, d), 5.13 (1H, dd), 6.36 (1H, d), 6.47 (1H, s), 6.57-6.69 (2H, m), 6.99 (1H, dd), 7.07 (1H, t), 7.15 (1H, d), 7.62 (1H, d), 7.96 (1H, s), 8.19 (0.5H, s); m/z : ES^+ $[\text{M}+\text{H}]^+ = 777.4$.

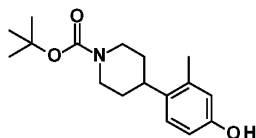
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Intermediate 123a: *tert*-Butyl 4-(4-hydroxy-2-methylphenyl)-3,6-dihydropyridine-1(2H)-carboxylate



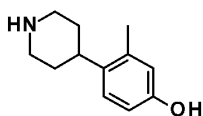
- Na₂CO₃ (3.11 g, 29.4 mmol) was added to a stirred solution of 4-bromo-3-methylphenol (1.83 g, 9.78 mmol) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (3.63 g, 11.74 mmol) in toluene (20 mL), EtOH (10 mL) and water (5 mL) and the flask was purged with N₂ for 20 mins. PdCl₂(dppf)-DCM (0.799 g, 0.978 mmol) was then added under N₂ at RT and then the mixture was stirred at 110°C for 16h. After cooling the mixture was filtered through celite and washed through with EtOAc. The filtrate was concentrated under reduced pressure to give gummy mass which was dissolved in EtOAc (100 mL). This solution was washed with water (30 mL) and brine (30 mL), dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 5-17% EtOAc in hexane) gave the title compound (2.27 g, 72%) as pale yellow solid; ¹H NMR: 1.43 (9H, s), 2.15 (3H, s), 3.33 (2H, s), 3.50 (2H, br t), 3.93 (2H, br s), 5.47 (1H, br s), 6.51-6.56 (1H, m), 6.58 (1H, d), 6.87 (1H, d), 9.21 (1H, s); *m/z*: ES⁺[M-Boc]⁺ 190.4.

Intermediate 123b: *tert*-Butyl 4-(4-hydroxy-2-methylphenyl)piperidine-1-carboxylate



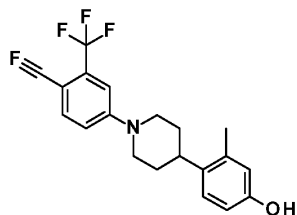
- A solution of *tert*-butyl 4-(4-hydroxy-2-methylphenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (2.25 g, 7.78 mmol) in EtOAc (40 mL) had N₂ gas bubbled through it for a period of 10 mins. Pd-on-C (10 % dry basis, 0.80 g, 7.52 mmol) was then added under N₂. The mixture was then stirred under H₂ at RT for 24h. The mixture was then filtered through celite and washed through with EtOAc. The filtrate was concentrated under reduced pressure to give the title compound (2.22 g, 95%) as an off white solid; ¹H NMR: 1.42 (9H, s), 1.57-1.66 (4H, m), 2.21 (3H, s), 2.74 (1H, br t), 3.57 (4H, br s), 6.54 (2H, s), 6.93-6.96 (1H, m), 8.94-9.16 (1H, m); *m/z*: ES⁺[M-Boc]⁺ 192.2.

Intermediate 123c: 3-Methyl-4-(piperidin-4-yl)phenol



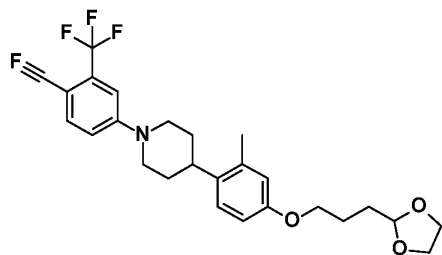
- 4M HCl in 1,4-dioxane (10 mL, 40.0 mmol) was added to a mixture of *tert*-butyl 4-(4-hydroxy-2-methylphenyl)piperidine-1-carboxylate (500 mg, 1.72 mmol) in DCM (5 mL) at RT under N₂. The mixture was then stirred at RT for 24h. Removal of solvent under reduced pressure then gave the title compound as a hydrochloride salt (390 mg, 96%) as an off-white solid; *m/z*: ES⁺[M+H]⁺ 192.2.

- Intermediate 123d: 4-(4-(4-Hydroxy-2-methylphenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile**



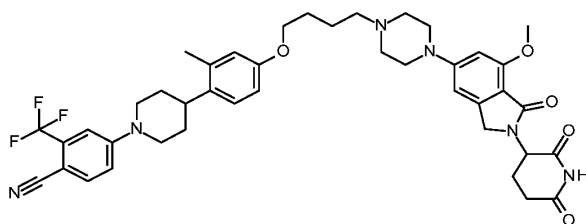
- DIPEA (3.95 mL, 22.61 mmol) was added to a mixture of 3-methyl-4-(piperidin-4-yl)phenol hydrochloride salt (1.03 g, 4.52 mmol) and 4-fluoro-2-(trifluoromethyl)benzonitrile (1.00 g, 5.29 mmol) in DMSO (10 mL) at RT under air for 18h. The mixture was then poured into water (20 mL) and extracted with EtOAc (3 × 50 mL). The combined organic solutions were dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-50% EtOAc in petroleum ether) gave the title compound (0.880 g, 54 %) as a yellow solid; ¹H NMR: 1.59 (2H, qd), 1.75 (2H, d), 2.26 (3H, s), 2.91 (1H, ddd), 3-3.14 (2H, m), 4.17 (2H, d), 6.44-6.64 (2H, m), 6.94 (1H, d), 7.22-7.37 (2H, m), 7.81 (1H, d), 9.01 (1H, s); *m/z*: ES⁺ [M+H]⁺ 361.1.

10 **Intermediate 123e: 4-(4-(4-(3-(1,3-Dioxolan-2-yl)propoxy)-2-methylphenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile**



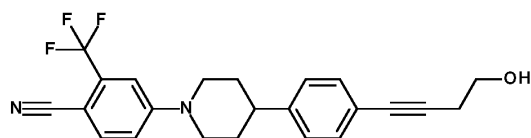
- 2-(3-Bromopropyl)-1,3-dioxolane (0.364 mL, 2.69 mmol) was added in one portion to 4-(4-(4-hydroxy-2-methylphenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (0.88 g, 2.44 mmol) and K₂CO₃ (1.012 g, 7.33 mmol) in MeCN (10 mL) at RT under N₂. The resulting suspension was stirred at 80°C for 24h. The mixture was then filtered after cooling to RT. The filtrate was diluted with water (50 mL) and a resulting yellow precipitate was collected by filtration to give the title compound (1.10 g, 95%); ¹H NMR: 1.55-1.66 (2H, m), 1.67-1.73 (2H, m), 1.73-1.8 (4H, m), 2.31 (3H, s), 2.86-3.01 (1H, m), 3.08 (2H, t), 3.74-3.81 (2H, m), 3.87-3.91 (2H, m), 3.94 (2H, t), 4.18 (2H, d), 4.84 (1H, t), 6.69 (1H, dd), 6.73 (1H, d), 7.06 (1H, d), 7.27 (1H, dd), 7.32 (1H, d), 7.81 (1H, d); *m/z*: ES⁺ [M+H]⁺ 475.4.

Example 123: 4-(4-(4-(4-(2-(2,6-Dioxopiperidin-3-yl)-7-methoxy-1-oxoisindolin-5-yl)piperazin-1-yl)butoxy)-2-methylphenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



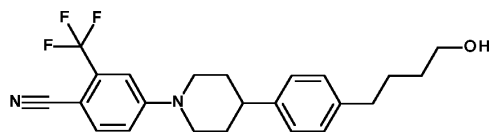
Intermediate 123e was reacted with Intermediate 1e using the general synthetic method illustrated by Example 1 to give the title compound after purification (Column A, Eluent A, Basic Work-Up A); ^1H NMR: 0.84-0.93 (4H, m), 0.97-1.05 (4H, dt), 1.12-1.25 (1H, m), 1.35 (3H, d), 1.59 (5H, d), 1.65 (2H, t), 1.84 (1H, d), 2.09-2.28 (2H, m), 2.35 (2H, t), 3.11 (3H, s), 3.22 (2H, t), 3.33-3.58 (4H, m), 4.23 (1H, dd), 5.75 (1H, s), 5.87 (1H, s), 5.92-6.06 (2H, m), 6.33 (1H, d), 6.53 (1H, dd), 6.59 (1H, s), 7.08 (1H, d), 10.15 (1H, s); m/z : $\text{ES}^+ [\text{M}+\text{H}]^+ = 773.3$.

Intermediate 124a: 4-(4-(4-(4-Hydroxybut-1-yn-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile

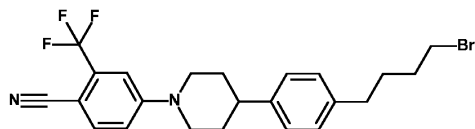


But-3-yn-1-ol (154 mg, 2.20 mmol) and diethylamine (357 mg, 4.89 mmol) were added to a mixture of 4-(4-(4-bromophenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (Intermediate 4a) (500 mg, 1.222 mmol) and DMF (5 mL) at RT under N_2 . Bis(triphenylphosphine)palladium(II) chloride (42.9 mg, 0.061 mmol), PPh_3 (22.43 mg, 0.086 mmol) and CuI (11.63 mg, 0.061 mmol) were then added under N_2 . The mixture was then stirred at 80°C for 16h. After cooling, the mixture was filtered through celite and washed through with DCM (20 mL $\times$ 3). The filtrate was then concentrated under reduced pressure then diluted with DCM (50 mL). This solution was washed with water (20 mL $\times$ 2) and brine (20 mL), dried (Na_2SO_4) and concentrated. Purification by FSC (gradient: 5-40% EtOAc in hexane) gave the title compound (220 mg, 29%) as a yellow solid; m/z : $\text{ES}^+ [\text{M}+\text{H}]^+ 399.0$.

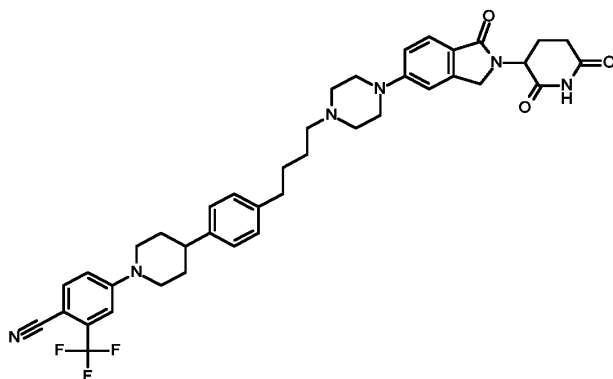
Intermediate 124b: 4-(4-(4-(4-Hydroxybutyl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



A solution of 4-(4-(4-(4-hydroxybut-1-yn-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (200 mg, 0.502 mmol) in EtOH (10 mL) had N_2 gas bubbled through it for a period of 10 mins. 10% Pd-on-C (150 mg, 1.410 mmol) was then added under N_2 . The mixture was then stirred under H_2 at RT for 5h. The mixture was then filtered through celite and washed through with EtOH. Concentration of the filtrate gave the title compound as a gummy mass (160 mg, 46%); m/z : $\text{ES}^+ [\text{M}+\text{H}]^+ 403.4$.

Intermediate 124b: 4-(4-(4-(4-Bromobutyl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile

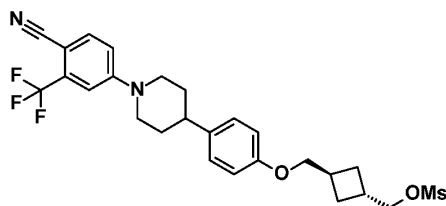
- 5 PPh₃ (201 mg, 0.765 mmol) and CBr₄ (254 mg, 0.765 mmol) were added to a solution of 4-(4-(4-(4-hydroxybutyl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (154 mg, 0.383 mmol) in DCM (5 mL) at 0°C then the mixture was stirred at RT for 3h. The reaction was then quenched with water (10 mL). The mixture was extracted with DCM (15 mL × 2) and the combined organic solutions were washed with brine (10 mL), dried (Na₂SO₄) and concentrated. Purification by FSC (Snap- ultra silica-gel, 100-200 mesh size, gradient: 5-15% EtOAc in hexane) gave the title compound (71 mg, 32 % yield) as brown gummy liquid; *m/z*: ES⁺
- 10 [M+H]⁺ 467.

Example 124: 4-(4-(4-(4-(2-(2,6-Dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazin-1-yl)butyl)phenyl)-piperidin-1-yl)-2-(trifluoromethyl)benzonitrile

- 15 Intermediate 124c was reacted with Intermediate 2c using the general synthetic method illustrated by Example 5 to give the title compound after purification (Column B, Eluent A, Basic Work-up A); ¹H NMR: 1.48-1.68 (6H, m), 1.87 (2H, br d), 1.94-1.99 (1H, m), 2.33-2.40 (3H, m), 2.57 (5H, br s), 2.80-2.95 (2H, m), 3.06 (2H, br t), 3.27 (6H, br s), 4.16-4.23 (3H, m), 4.29-4.36 (1H, m), 5.05 (1H, dd), 7.04-7.07 (2H, m), 7.13-7.19 (4H, m), 7.28 (1H, dd), 7.33 (1H, s), 7.52 (1H, d), 7.82 (1H, d), 10.94-10.96 (1H, m); *m/z*: ES⁺ [M+H]⁺ = 713.0.

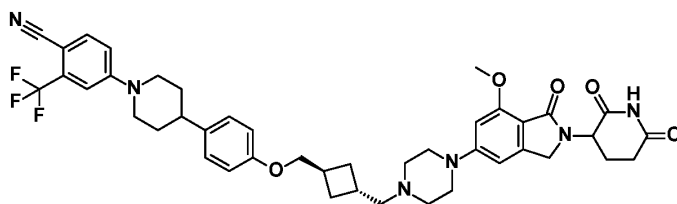
20

Intermediate 125a: ((1*r*,3*r*)-3-((4-(1-(4-Cyano-3-(trifluoromethyl)phenyl)piperidin-4-yl)phenoxy)methyl)-cyclobutyl)methyl methanesulfonate



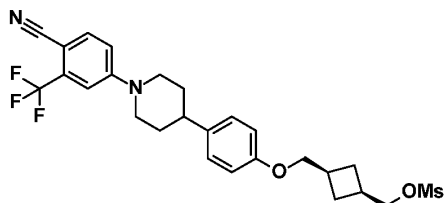
- To a stirred solution of 4-(4-(4-(((1r,3r)-3-(hydroxymethyl)cyclobutyl)methoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (Intermediate 36b) (90 mg, 0.202 mmol) in DCM (2 mL) was added Et₃N (41.0 mg, 0.405 mmol) and methanesulfonyl chloride (46.4 mg, 0.405 mmol) at 0°C. The mixture was then stirred for 1h at RT. The reaction was then quenched with water (25 mL). The mixture was then extracted with DCM (30 mL × 2) and the combined organic solutions were washed with brine (20 mL), dried (Na₂SO₄) and concentrated to give the title compound (100 mg, 92 % yield) which was used directly in the next step without further purification; *m/z*: ES⁺ [M+H]⁺ = 523.0.

- Example 125: 4-[4-(4-(((1r,3r)-3-(4-[2-(2,6-Dioxopiperidin-3-yl)-7-methoxy-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazin-1-yl)methyl)cyclobutyl)methoxy}phenyl)piperidin-1-yl]-2-(trifluoromethyl)benzonitrile**



- Intermediate 125a was reacted with Intermediate 1f using the general synthetic method illustrated by Example 12 to give the title compound after purification (Column B, Eluent A, Basic Work-Up A); ¹H NMR: 1.56-1.69 (2H, m), 1.77-1.98 (7H, m), 2.33 (2H, d), 2.41-2.47 (4H, m), 2.61-2.70 (2H, m), 2.77 (1H, t), 2.84-2.95 (1H, m), 3.05 (2H, t), 3.27-3.29 (4H, m), 3.83 (3H, s), 3.98 (2H, d), 4.07-4.30 (4H, m), 4.96 (1H, dd), 6.48 (1H, s), 6.60 (1H, s), 6.87 (2H, d), 7.16 (2H, d), 7.28 (1H, dd), 7.33 (1H, d), 7.82 (1H, d), 10.90 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 785.4.

- Intermediate 126a: ((1s,3s)-3-((4-(1-(4-Cyano-3-(trifluoromethyl)phenyl)piperidin-4-yl)phenoxy)-methyl)cyclobutyl)methyl methanesulfonate**

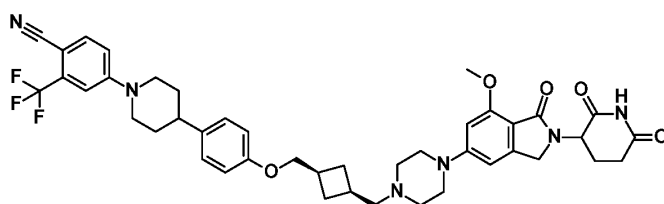


- To a stirred solution of 4-(4-(4-(((1s,3s)-3-(hydroxymethyl)cyclobutyl)methoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (Intermediate 36c) (100 mg, 0.225 mmol) in DCM (2 mL) was added Et₃N

(0.063 mL, 0.450 mmol) and methanesulfonyl chloride (0.035 mL, 0.450 mmol) at 0°C, followed by stirring for 1h at RT. The reaction was then quenched with water (25 mL) and extracted with DCM (30 mL × 2). The combined organic solutions were washed with brine (20 mL), dried (Na₂SO₄) and concentrated to give the title compound (100 mg, 83 %) which was used directly in the next step without further purification; *m/z*: ES⁺

5 [M+H]⁺ = 523.0.

Example 126: 4-[4-(4-[(1*s*,3*s*)-3-({4-[2-(2,6-Dioxopiperidin-3-yl)-7-methoxy-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazin-1-yl)methyl]cyclobutyl)methoxy}phenyl)piperidin-1-yl]-2-(trifluoromethyl)benzonitrile



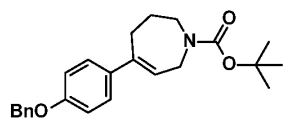
10

Intermediate 126a was reacted with Intermediate 1f using the general synthetic method illustrated by Example 12 to give the title compound after purification (Column B, Eluent A, Basic Work-Up A); ¹H NMR: 1.48-1.70 (5H, m), 1.81-1.96 (3H, m), 2.14-2.26 (2H, m), 2.37-2.42 (2H, m), 2.58-2.72 (2H, m), 2.74-2.95 (2H, m), 3.00-3.13 (2H, m), 3.27-3.31 (3H, m), 3.82-3.87 (5H, m), 4.04-4.25 (4H, m), 4.96 (1H, dd), 6.48 (1H, s), 6.60 (1H, s), 6.84 (2H, d), 7.15 (2H, d), 7.27 (1H, dd), 7.33 (1H, d), 7.82 (1H, d), 10.90 (1H, br s); *m/z*: ES⁺

15

[M+H]⁺ = 785.0.

Intermediate 127a: *tert*-Butyl 5-(4-(benzyloxy)phenyl)-2,3,4,7-tetrahydro-1*H*-azepine-1-carboxylate

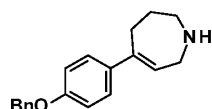


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To a stirred solution of 1-(benzyloxy)-4-bromobenzene (4.00 g, 15.20 mmol) in THF (40 mL) was added *n*-BuLi (1.6M in hexane, 14.25 mL, 22.80 mmol) at -78°C then the mixture was stirred for 1h at -78°C. *tert*-Butyl 4-oxoazepane-1-carboxylate (3.89 g, 18.24 mmol) was then added at -78°C. The mixture was stirred for 2h at -78°C then stirred for 1h at RT. The reaction was quenched with sat. NH₄Cl solution and extracted with EtOAc (2 × 20 mL). The combined organic solutions were dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 20-30% EtOAc in hexane) gave the title compound (3.50 g, 55%) as pale yellow liquid; ¹H NMR: 1.42 (9H, d), 1.63-1.92 (4H, m), 2.01-2.14 (1H, m), 3.10-3.29 (2H, m), 3.39-3.62 (3H, m), 4.89 (1H, s), 5.08 (2H, s), 6.94 (2H, dd), 7.10-7.35 (3H, m), 7.36-7.42 (2H, m), 7.42-7.49 (2H, m).

25

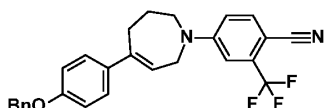
Intermediate 127b: 5-(4-(Benzyloxy)phenyl)-2,3,4,7-tetrahydro-1*H*-azepine



30

- To a solution of *tert*-butyl 5-(4-(benzyloxy)phenyl)-2,3,4,7-tetrahydro-1*H*-azepine-1-carboxylate (3.00 g, 7.91 mmol) in DCM (30 mL) was added TFA (2.70 g, 23.72 mmol) at 0°C and the reaction was stirred for 2h while warming slowly to RT. Concentration under reduced pressure and washing with MTBE gave the title compound as a TFA salt (2.98 g, 100 % yield); ¹H NMR: 1.19-1.38 (1H, m), 1.58-1.98 (2H, m), 2.69-2.91 (2H, m), 2.96-3.39 (5H, m), 5.10-5.17 (3H, m), 6.05 (1H, s), 6.98 (2H, d), 7.20-8.26 (7H, m), 8.47-9.08 (2H, m).

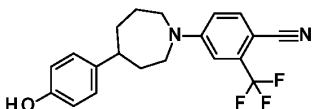
Intermediate 127c: 4-(5-(4-(Benzyloxy)phenyl)-2,3,4,7-tetrahydro-1*H*-azepin-1-yl)-2-(trifluoromethyl)-benzonitrile



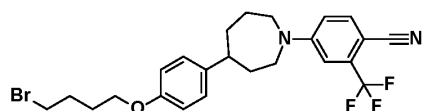
- To a stirred solution of 5-(4-(benzyloxy)phenyl)-2,3,4,7-tetrahydro-1*H*-azepine (3.0 g, 7.97 mmol) in DMSO (30 mL) was added DIPEA (5.15 g, 39.9 mmol) and 4-fluoro-2-(trifluoro-methyl)benzonitrile (1.809 g, 9.56 mmol) at RT. The mixture was then stirred at 100°C for 16h. After cooling, the mixture was poured ice-cold water and extracted with EtOAc (100 mL × 2). The combined organic solutions were washed with brine (100 mL), dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 25-35 % EtOAc in hexane) gave the title compound (2.30 g, 64 %) as an off-white solid; ¹H NMR: 1.90-2.08 (1H, m), 2.54-2.66 (2H, m), 2.78-2.89 (1H, m), 3.68-3.92 (3H, m), 4.22 (1H, d), 5.09 (2H, s), 5.85-6.27 (1H, m), 6.94 (2H, d), 7.06-7.18 (2H, m), 7.21-7.53 (7H, m), 7.63-8.02 (1H, m); *m/z*: ES⁺ [M+H]⁺ = 449.0.

Intermediate 127d and 127e: 4-(4-(4-Hydroxyphenyl)azepan-1-yl)-2-(trifluoromethyl)benzonitrile

- (Enantiomer 1 and Enantiomer 2)

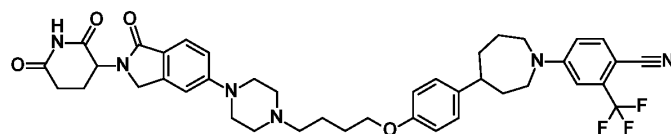


- A solution of 4-(5-(4-(benzyloxy)phenyl)-2,3,4,7-tetrahydro-1*H*-azepin-1-yl)-2-(trifluoromethyl)benzonitrile (2.3 g, 5.13 mmol) in MeOH (25 mL) was bubbled with N₂ for 5 mins. To this mixture 10% Pd-on-C (1.092 g, 10.26 mmol) was added under N₂. The mixture was then stirred under H₂ using a H₂ bladder at RT for 3h. The mixture was then filtered through celite and washed through with MeOH (150 mL). The filtrate was concentrated to obtain a pale yellow sticky liquid. Trituration with MTBE gave the title compound as a racemic mixture (1.80 g, 92 %) which was separated by chiral SFC (Column: LUX A3, (LUXA3_MeOH_3-40_CHIRALHPLC-SFCME), Eluent CO₂/MeOH) to give enantiomer 1 (eluting first) (500 mg) and enantiomer 2 (500 mg);
- Enantiomer 1 (127d):** ¹H NMR: 1.43-1.64 (1H, m), 1.68-1.85 (3H, m), 1.89-2.03 (2H, m), 2.52-2.70 (2H, m), 3.48-3.61 (2H, m), 3.63-3.83 (2H, m), 6.64 (2H, d), 6.95 (2H, d), 7.03-7.12 (2H, m), 7.07 (2H, s), 7.78 (1H, d), 8.98-9.34 (1H, m); *m/z*: ES⁺ [M+H]⁺ = 361.0.
- Enantiomer 2 (127e):** ¹H NMR: 1.46-1.61 (1H, m), 1.63-1.80 (3H, m), 1.88-2.04 (2H, m), 2.54-2.75 (2H, m), 3.40-3.62 (2H, m), 3.65-3.85 (2H, m), 6.64 (2H, d), 6.96 (2H, d), 7.02-7.17 (2H, m), 7.78 (1H, d), 9.12 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 361.0.

Intermediate 127f: 4-(4-(4-(4-Bromobutoxy)phenyl)azepan-1-yl)-2-(trifluoromethyl)benzonitrile**Enantiomer 1**

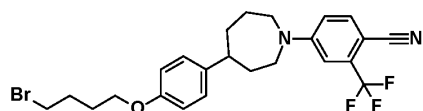
- 5 To a stirred solution of 4-(4-(4-hydroxyphenyl)azepan-1-yl)-2-(trifluoromethyl)benzonitrile (**enantiomer 1, 127d**) (300 mg, 0.832 mmol) in MeCN (3 mL) was added K₂CO₃ (230 mg, 1.67 mmol) and 1,4-dibromobutane (270 mg, 1.249 mmol) at RT and the mixture was stirred for 6h at 70°C. The mixture was then quenched with water (20 mL) and extracted with EtOAc (30 mL × 2). The combined organic solutions were washed with brine (20 mL), dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-20% EtOAc in
- 10 hexane) gave the title compound (255 mg, 60 %) as pale yellow gummy material; ¹H NMR: 1.53-1.65 (1H, m), 1.73-1.85 (5H, m), 1.90-2.03 (4H, m), 2.57-2.69 (1H, m), 3.46-3.63 (4H, m), 3.64-3.83 (2H, m), 3.95 (2H, t), 6.81 (2H, d), 6.99-7.20 (4H, m), 7.79 (1H, d); *m/z*: ES⁺ [M+H]⁺ = 496.9.

15 **Example 127: 4-{4-[4-(4-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazin-1-yl}butoxy)phenyl]azepan-1-yl}-2-(trifluoromethyl)benzonitrile (ISOMER 1)** (Absolute stereochemistry not confirmed)



- 20 Intermediate 127e was reacted with Intermediate 2c using the general synthetic method illustrated by Example 5 to give the title compound after purification (Column B, Eluent A, Basic Work-Up A); ¹H NMR: 1.53-1.65 (3H, m), 1.70-1.81 (5H, m), 1.92-2.05 (3H, m), 2.38 (2H, d), 2.54-2.79 (5H, m), 2.83-2.94 (1H, m), 3.27 (4H, d), 3.46-3.61 (2H, m), 3.65-3.82 (2H, m), 3.95 (2H, t), 4.15-4.27 (1H, m), 4.29-4.40 (1H, m), 5.05 (1H, d), 6.82 (2H, d), 6.99-7.18 (6H, m), 7.52 (1H, d), 7.78 (1H, d), 10.95 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 743.2.

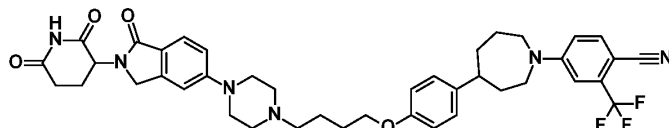
- 25 **Intermediate 128a: 4-(4-(4-(4-Bromobutoxy)phenyl)azepan-1-yl)-2-(trifluoromethyl)benzonitrile (enantiomer 2)**



- 30 K₂CO₃ (345 mg, 2.50 mmol) and 1,4-dibromobutane (270 mg, 1.249 mmol) were added to a stirred solution of 4-(4-(4-hydroxyphenyl)azepan-1-yl)-2-(trifluoromethyl)benzonitrile (**enantiomer 2, 127e**) (300 mg, 0.832 mmol) in MeCN (3 mL) at RT then the mixture was stirred for 6h at 70°C. The mixture was then quenched with water (20 mL) and extracted with EtOAc (30 mL × 2). The combined organic solutions were washed with brine (20 mL), dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-20% EtOAc in hexane) gave

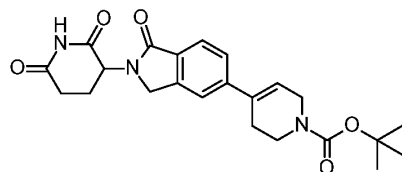
the title compound (250 mg, 58 % yield) as pale yellow gummy material; ^1H NMR: 1.59 (1H, q), 1.68-1.84 (5H, m), 1.92-2.02 (4H, m), 2.61 (1H, t), 3.50-3.63 (4H, m), 3.64-3.82 (2H, m), 3.95 (3H, t), 6.81 (2H, d), 6.97-7.24 (4H, m), 7.63-7.84 (1H, m); m/z : $\text{ES}^+ [\text{M}+\text{H}]^+ = 496.8$.

- 5 **Example 128: 4-{4-[4-(4-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl]butoxy}phenyl)azepan-1-yl]-2-(trifluoromethyl)benzonitrile**
(ISOMER 2) (Absolute stereochemistry not confirmed)



- 10 Intermediate 128a was reacted with Intermediate 2c using the general synthetic method illustrated by Example 5 to give the title compound after purification (Column B, Eluent A, Basic Work-Up A); ^1H NMR: 1.53-1.65 (3H, m), 1.70-1.81 (5H, m), 1.92-2.05 (3H, m), 2.38 (2H, d), 2.54-2.79 (5H, m), 2.83-2.94 (1H, m), 3.27 (4H, d), 3.46-3.61 (2H, m), 3.65-3.82 (2H, m), 3.95 (2H, t), 4.15-4.27 (1H, m), 4.29-4.40 (1H, m), 5.05 (1H, d), 6.82 (2H, d), 6.99-7.18 (6H, m), 7.52 (1H, d), 7.78 (1H, d), 10.95 (1H, s); m/z : $\text{ES}^+ [\text{M}+\text{H}]^+ = 743.2$.

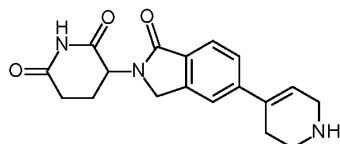
- 15 **Intermediate 129a: *tert*-Butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate**



- 20 *tert*-Butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (574 mg, 1.86 mmol) and Cs_2CO_3 (1008 mg, 3.09 mmol) were added to a solution of 3-(5-bromo-1-oxoisindolin-2-yl)piperidine-2,6-dione (500 mg, 1.55 mmol) in 1,4-dioxane (10 mL) that was purged with N_2 for 15 mins. $\text{PdCl}_2(\text{dppf})\text{-CH}_2\text{Cl}_2$ adduct (126 mg, 0.155 mmol) was then added and the mixture was stirred at 120°C for 5h. After cooling, the crude mixture was diluted with DCM and filtered through celite. The filtrate was washed with water. The organic layer was separated and dried (Na_2SO_4) and concentrated to give the title compound as brown gummy liquid (600 mg, 38%); m/z : $\text{ES}^+ [\text{M}+\text{H}]^+ = 426.1$.

25

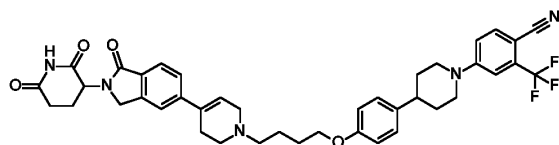
Intermediate 129b: 3-(1-Oxo-5-(1,2,3,6-tetrahydropyridin-4-yl)isoindolin-2-yl)piperidine-2,6-dione



4M HCl in 1,4-dioxane (2.0 mL, 8.00 mmol) was added to a solution of *tert*-butyl-4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (200 mg, 0.47 mmol) in DCM (5 mL) at

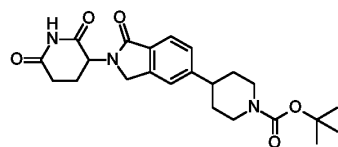
0°C. After stirring for 2h the solvent was removed under reduced pressure to give the title compound as a hydrochloride salt (140 mg, 80%) which was used directly in the next step; m/z : $ES^+ [M+H]^+ = 326.2$.

5 **Example 129: 4-(4-(4-(4-(2-(2,6-Dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)-3,6-dihydropyridin-1(2H)-yl)butoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile**



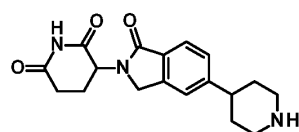
Intermediate 50a was reacted with Intermediate 129b using the general synthetic method illustrated by Example 5 to give the title compound after purification (Column B, Eluent C, Basic Work-Up A); ^1H NMR: 1.43-1.69 (5H, m), 1.69-1.90 (4H, m), 1.97-2.06 (1H, m), 2.30-2.41 (1H, m), 2.59-2.67 (3H, m), 2.70-2.84 (1H, m), 2.84-3.15 (5H, m), 3.97 (2H, t), 4.17 (2H, d), 4.27-4.47 (2H, m), 5.04-5.20 (1H, m), 6.32 (1H, s), 6.87 (2H, d), 7.15 (2H, d), 7.24-7.36 (2H, m), 7.59 (1H, d), 7.63-7.71 (2H, m), 7.82 (1H, d), 10.83-11.22 (1H, m); m/z : $ES^+ [M+H]^+ = 726.4$.

15 **Intermediate 130a: *tert*-Butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperidine-1-carboxylate**



10% Pd-on-C (75 mg, 0.705 mmol) was added to a solution of *tert*-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (Intermediate 129a) (150 mg, 0.353 mmol) in MeOH (5 mL) and the mixture was stirred under H_2 for 16h. Removal of solvent under reduced pressure gave the title compound (140 mg, 93%) which was used directly in the next step without further purification; m/z : $ES^+ [M-Boc]^+ = 328.0$.

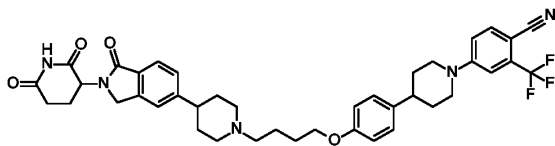
Intermediate 130b: 3-(1-Oxo-5-(piperidin-4-yl)isindolin-2-yl)piperidine-2,6-dione hydrochloride



25 To a solution of *tert*-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperidine-1-carboxylate (150 mg, 0.351 mmol) in DCM (5 mL) add 4M HCl in 1,4-dioxane (2 mL, 8.00 mmol) and the mixture was stirred for 1h. Concentration under reduced pressure gave the title compound (120 mg, 85%) which was used directly in the next step.

30 **Example 130: 4-(4-(4-(4-(2-(2,6-Dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperidin-1-**

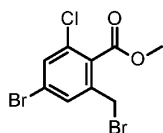
yl)butoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



Intermediate 50a was reacted with Intermediate 130b using the general synthetic method illustrated by Example 5 to give the title compound after purification C-18 chromatography (Eluent C, Basic Work-Up A);

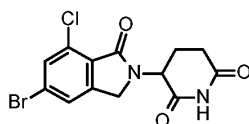
- 5 ¹H NMR: 1.58-1.87 (1H, m), 1.94-2.04 (3H, m), 2.32-2.42 (3H, m), 2.58-2.92 (4H, m), 2.97-3.11 (4H, m), 3.93-4.01 (2H, m), 4.12-4.21 (2H, m), 4.24-4.47 (2H, m), 5.00-5.14 (1H, m), 6.80-6.93 (2H, m), 7.12-7.18 (2H, m), 7.24-7.30 (1H, m), 7.32 (1H, s), 7.35-7.42 (1H, m), 7.49 (1H, s), 7.58-7.70 (1H, m), 7.82 (1H, d), 10.82 (1H, bs); *m/z*: ES⁺ [M+H]⁺ = 728.2.

10 **Intermediate 131a: Methyl 4-bromo-2-(bromomethyl)-6-chlorobenzoate**



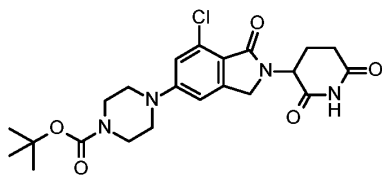
NBS (3.24 g, 18.22 mmol) was added to a stirred solution of methyl 4-bromo-2-chloro-6-methylbenzoate (3.00 g, 11.38 mmol) and AIBN (0.374 g, 2.28 mmol) in CHCl_3 (72 mL) and the reaction stirred at 80°C under reflux. After 3h, additional NBS (1.62 g, 9.11 mmol) and AIBN (0.187 mg, 1.14 mmol) were added and heating continued at reflux for a further 0.5h. The mixture was then cooled to RT. Water (150 mL) was added. The mixture was extracted with DCM (2×150 mL). The combined organic solutions were dried (Na_2SO_4) and concentrated to give the title compound which was used without further purification; ^1H NMR (500 MHz, CDCl_3) 3.99 (3H, s), 4.44 (2H, s), 7.49 (1H, d), 7.54 (1H, d).

20 Intermediate 131b: 3-(5-Bromo-7-chloro-1-oxoisindolin-2-yl)piperidine-2,6-dione



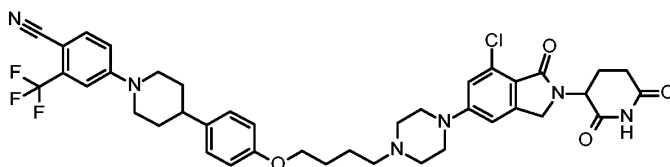
DIPEA (6.08 mL, 34.14 mmol) was added in one portion to a stirred solution of methyl 4-bromo-2-(bromomethyl)-6-chlorobenzoate (3.90 g, 11.38 mmol) and 3-aminopiperidine-2,6-dione hydrochloride (2.060 g, 12.52 mmol) in MeCN (120 mL) at RT under air. The resulting mixture was stirred at 80°C for 20h then cooled to RT with stirring. The resulting solid was collected by filtration, washed with MeCN (2 × 10 mL) and dried to give the title compound (1.49 g, 37 %) as a grey/purple solid; ¹H NMR (500 MHz) 2.02 (1H, ddd), 2.39 (1H, ddd), 2.60 (1H, d), 2.91 (1H, ddd), 4.34 (1H, d), 4.45 (1H, d), 5.09 (1H, dd), 7.83 (1H, d), 7.88 (1H, d), 11.01 (1H, s); *m/z*: ES⁺ [M+H]⁺ 356.8.

30 Intermediate 131 c: tert-Butyl-4-(7-chloro-2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazine-1-
carboxylate



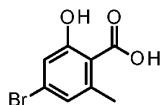
- tert*-Butyl piperazine-1-carboxylate (40.1 mg, 0.22 mmol), 3-(5-bromo-7-chloro-1-oxoisindolin-2-yl)piperidine-2,6-dione (70 mg, 0.20 mmol) and oven-dried Cs₂CO₃ (191 mg, 0.59 mmol) were placed in an oven-dried microwave vial and the tube flushed with N₂. DMF (1.75 mL) was added and the mixture was
- 5 purged with N₂. diMeiHept-Cl-Pd(cinnamyl)Cl (10.45 mg, 9.79 μmol) was added and the mixture again purged with N₂. The tube was sealed and the mixture heated at 100°C for 4 h then cooled to RT. The mixture was diluted with DCM (50 mL), poured into 5% AcOH in water (50 mL) and shaken. Sat. brine (5 mL) was added to separate the layers. The aqueous layer was extracted with DCM (30 mL) and the extracts combined with the organic layer. The combined organic fractions were washed with water (2 × 50 mL) and filtered
- 10 through a phase-separating paper. The crude product was purified by preparative HPLC (Column A, Eluent A). Fractions containing the desired compound were concentrated to a volume such that the MeCN had been removed. The resulting aqueous suspension was basified to pH 7 and extracted with DCM (3 × 15 mL). The combined DCM extracts were dried (Na₂SO₄) and concentrated to give the title compound (0.028 g, 27 %) as a white solid; ¹H NMR (500 MHz) 1.43 (9H, s), 1.93-2.01 (1H, m), 2.31-2.42 (1H, m), 2.59 (1H, d), 2.90 (1H, ddd), 3.33-3.37 (4H, m), 3.42-3.51 (4H, m), 4.20 (1H, d), 4.32 (1H, d), 5.02 (1H, dd), 7.01 (1H, d), 7.04 (1H, s), 10.96 (1H, s); *m/z*: ES⁺ [M+H]⁺ 463.0.
- 15

Example 131: 4-{4-[4-(4-{4-[7-Chloro-2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazin-1-yl}butoxy)phenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile



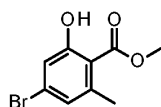
- 4-(4-(4-(3-(1,3-Dioxolan-2-yl)propoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (Example 1h) (28.8 mg, 0.06 mmol) and *tert*-butyl-4-(7-chloro-2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazine-1-carboxylate (29 mg, 0.06 mmol) were heated at 60°C in formic acid (2 mL) for 1h. The mixture was then
- 25 concentrated and then diluted in NMP (2 mL) at RT under air. NaBH(OAc)₃ (33.2 mg, 0.16 mmol) was added in one portion after 5 mins and the resulting suspension was stirred at RT for 18h. Purification by preparative HPLC (Column A, Eluent A) gave the title compound as a formate salt (0.034 g, 67 %) as a beige solid; ¹H NMR: 1.64-1.89 (6H, m), 1.97 (2H, d), 2.09-2.22 (1H, m), 2.31 (1H, qd), 2.66-3 (9H, m), 3.07 (2H, d), 3.26-3.57 (4H, m), 3.93-4.14 (4H, m), 4.20 (1H, d), 4.33 (1H, d), 5.12 (1H, dd), 6.75 (1H, s), 6.78-6.88 (3H, m), 6.95-7.04 (1H, m), 7.06-7.18 (3H, m), 7.60 (1H, d), 8.28 (1H, s), 8.54-8.94 (1H, m); *m/z*: ES⁺ [M+H]⁺ 763.2.
- 30

Intermediate 132a: 4-Bromo-2-hydroxy-6-methylbenzoic acid



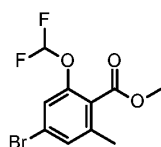
- 5 Powdered NaOH (2.06 g, 51.49 mmol) was added to a solution of 4-bromo-2-fluoro-6-methylbenzoic acid (3.00 g, 12.87 mmol) in 1,3-dimethylimidazolidin-2-one (33.4 mL, 308.96 mmol). The mixture was heated to 120°C for 3h. The mixture was then cooled to RT and was poured into water (400 mL). The mixture was acidified to pH3 with 2M HCl with stirring. A resulting solid was collected by filtration, washed with water and dried under vacuum to give the title compound (2.13 g, 72 %) as a white solid; ¹H NMR (500 MHz) 2.29 (3H, s), 6.92-6.94 (2H, m), 11.19 (1H, br.s), 13.00 (1H, br.s.); *m/z*: ES- [M-H]⁻ 229.

Intermediate 132b: Methyl 4-bromo-2-hydroxy-6-methylbenzoate



- 10 Sulfuric acid (1.04 mL, 19.48 mmol) was added to a solution of 4-bromo-2-hydroxy-6-methylbenzoic acid (1.50 g, 6.49 mmol) in MeOH (40 mL). The mixture was heated to 80°C and stirred for 5 days and then concentrated to 15 mL volume. This mixture was diluted with EtOAc (100 mL) and ice (100 g) was added, followed by sat. NaHCO₃ solution (60 mL). The mixture was shaken; the organic layer was separated and washed with sat. NaHCO₃ solution (60 mL) and sat. brine (30 mL), dried (Na₂SO₄) and concentrated.
- 15 Purification by FSC (20% EtOAc in heptane) gave the title compound (1.43 g, 90 %) as a beige crystalline solid; ¹H NMR (500 MHz) 2.19 (3H, s), 3.80 (3H, s), 6.92 (1H, dd), 6.94 (1H, dd), 10.36 (1H, s); *m/z*: ES- [M-H]⁻ 243.

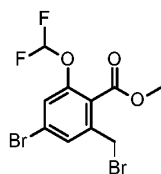
20 **Intermediate 132c: methyl 4-bromo-2-(difluoromethoxy)-6-methylbenzoate**



- 8.2M KOH solution (7.07 mL, 57.94 mmol) was added dropwise to a suspension of methyl 4-bromo-2-hydroxy-6-methylbenzoate (1.42 g, 5.79 mmol) in MeCN (7 mL) at -35°C under N₂. The 2-phase mixture was stirred at -35°C for 10 mins then diethyl (bromodifluoromethyl)phosphonate (2.06 mL, 11.59 mmol) was
- 25 added dropwise, keeping the temperature at -35°C. The cooling bath was removed and the resulting solution was allowed to warm with stirring. At -10°C, a rapid exotherm began; the cooling bath was reapplied at 5°C and a maximum temperature of 32°C was reached. The mixture was then stirred at RT for a further 90 mins. TLC showed almost complete conversion to a new product. The reaction was quenched with water (125 mL) and adjusted to pH=2 with 2M HCl. The mixture was extracted with EtOAc (2 × 125 mL); the combined
- 30 organic solutions were washed with sat. brine (75 mL), dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-10% EtOAc in heptane) gave the title compound (1.16 g, 68 %) as a white crystalline solid; ¹H

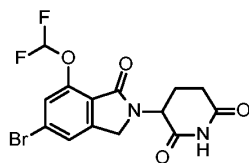
NMR (500 MHz) 2.27 (3H, s), 3.86 (3H, s), 7.30 (1H, t), 7.42 (1H, d), 7.49 (1H, dd).

Intermediate 132d: Methyl 4-bromo-2-(bromomethyl)-6-(difluoromethoxy)benzoate



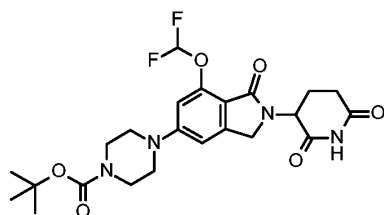
- 5 NBS (1.16 g, 6.51 mmol) was added to a stirred solution of methyl 4-bromo-2-(difluoromethoxy)-6-methylbenzoate (1.20 g, 4.07 mmol) and AIBN (134 mg, 0.81 mmol) in *t*-butyl acetate (45 mL) and the reaction stirred at 100°C for 35 mins. The mixture was then cooled to RT. Water (50 mL) was added. The mixture was extracted with EtOAc (2 × 50 mL). The combined organic solutions were washed with brine (50 mL), dried (Na₂SO₄) and concentrated to give the title compound (1.52 g, 100 %), as a beige gum, which was
- 10 used without further purification; ¹H NMR (500 MHz, CDCl₃) 3.97 (3H, s), 4.51 (2H, s), 6.49 (1H, t), 7.36 (1H, d), 7.48 (1H, d).

Intermediate 132e: 3-(5-Bromo-7-(difluoromethoxy)-1-oxoisindolin-2-yl)piperidine-2,6-dione



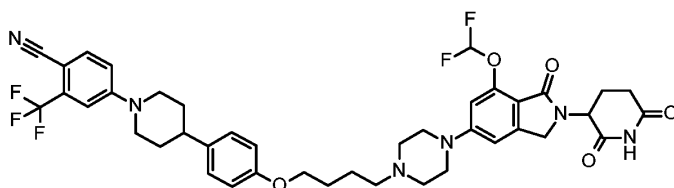
- 15 DIPEA (2.17 mL, 12.21 mmol) was added in one portion to a stirred solution/suspension of methyl 4-bromo-2-(bromomethyl)-6-(difluoromethoxy)benzoate (1.522 g, 4.07 mmol) and 3-aminopiperidine-2,6-dione hydrochloride (0.737 g, 4.48 mmol) in MeCN (45 mL) at RT under air. The resulting mixture was stirred at 80°C for 16h. The mixture was then cooled to RT and concentrated to 10 mL volume. Diethyl ether (30 mL) was added followed by stirring and sonication, causing precipitation of a dark solid. The solid was collected
- 20 by filtration and washed with MeCN. The filtrates were concentrated to give a brown gum. The gum was treated with DCM (30 mL) and was warmed and sonicated. A brown precipitate remained out of solution. This was collected by filtration and washed with DCM to give product as a brown solid. The filtrate was purified by FSC (gradient: 0-3% MeOH in DCM) gave the title compound (1.145 g, 72%) as a brown solid; ¹H NMR (500 MHz) 1.98 (1H, qd), 2.38 (1H, ddd), 2.60 (1H, dd), 2.90 (1H, ddd), 4.36 (1H, d), 4.48 (1H, d), 5.07 (1H, dd),
- 25 7.45 (1H, t), 7.53 (1H, s), 7.78 (1H, s), 11.01 (1H, s); *m/z*: ES⁺ [M+H]⁺ 389.

Intermediate 132f: *tert*-Butyl-4-(7-(difluoromethoxy)-2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazine-1-carboxylate



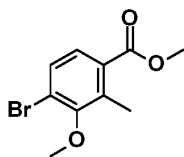
Pd-PEPPSI-IHept.Cl (11.25 mg, 0.01 mmol) was added to a N₂-purged mixture of 3-(5-bromo-7-(difluoromethoxy)-1-oxoisindolin-2-yl)piperidine-2,6-dione (90 mg, 0.23 mmol), *tert*-butyl piperazine-1-carboxylate (129 mg, 0.69 mmol) and in 1,4-dioxane (7.5 mL) and heated at 90°C for 5h. The mixture were then diluted with DCM (100 mL) and washed with 5% AcOH in water (100 mL), water (100 mL) and then sat. brine (50 mL). The organic solution was dried (Na₂SO₄) and concentrated. Purification by FSC (gradient: 0-3% MeOH in DCM) gave (after concentration and azeotroping with MeCN) the title compound (0.090 g, 32 %) as a grey solid; ¹H NMR (500 MHz) 1.43 (9H, s), 1.97 (1H, ddd), 2.37 (1H, ddd), 2.59 (1H, d), 2.89 (1H, ddd), 3.33-3.37 (4H, m), 3.43-3.50 (4H, m), 4.24 (1H, d), 4.35 (1H, d), 5.01 (1H, dd), 6.74 (1H, d), 6.96 (1H, d), 7.42 (1H, t), 10.96 (1H, s); *m/z*: ES⁺ [M+H]⁺ 495.1.

Example 132: 4-{4-[4-(4-{4-[7-(Difluoromethoxy)-2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isindol-5-yl]piperazin-1-yl}butoxy)phenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile



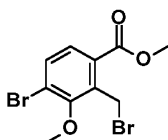
4-(4-(4-(3-(1,3-Dioxolan-2-yl)propoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (Example 1h) (50 mg, 0.11 mmol) and *tert*-butyl-4-(7-(difluoromethoxy)-2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazine-1-carboxylate (62.2 mg, 0.12 mmol) were heated at 60°C in formic acid (2 mL) for 0.5h. The mixture was then concentrated and the crude residue was stirred in NMP (2 mL) at RT under air. NaBH(OAc)₃ (57.5 mg, 0.27 mmol) was then added in one portion after 5 mins and the resulting suspension was stirred at RT for 2h. Purification by preparative HPLC (Waters XSelect CSH C18 ODB column, 5μm silica, 30 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 0.1% formic acid) and MeCN as eluents gave the title compound (0.073 g, 85 %) as a white solid; ¹H NMR: 1.55-1.69 (4H, m), 1.69-1.8 (2H, m), 1.85 (2H, d), 1.91-2.03 (1H, m), 2.36-2.46 (2H, m), 2.53-2.64 (2H, m), 2.77 (1H, t), 2.89 (1H, ddd), 3.05 (2H, td), 3.26-3.37 (8H, m), 3.97 (2H, t), 4.17 (2H, d), 4.23 (1H, d), 4.34 (1H, d), 5.00 (1H, dd), 6.72 (1H, d), 6.83-6.9 (2H, m), 6.93-6.98 (1H, m), 7.12-7.19 (2H, m), 7.27 (1H, dd), 7.32 (1H, d), 7.41 (1H, t), 7.81 (1H, d), 10.94 (1H, s); *m/z*: ES⁺ [M+H]⁺ 795.3.

Intermediate 133a: Methyl 4-bromo-3-methoxy-2-methylbenzoate



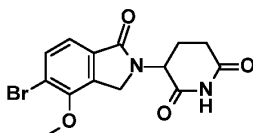
To a stirred solution of methyl 4-bromo-3-hydroxy-2-methylbenzoate (1.00 g, 4.08 mmol) in MeCN (10 mL) was added K_2CO_3 (1.69 g, 12.24 mmol) and MeI (0.38 mL, 6.12 mmol) at 0°C. The mixture was then stirred at RT for 16h. The reaction was then quenched with water (10 mL) and the mixture extracted with EtOAc (20 mL $\times$ 2). The combined organic solutions were washed with brine (10 mL), dried (Na_2SO_4) and concentrated. Purification by FSC (eluent: EtOAc-hexane 20%-35%) gave the title compound (600 mg, 57 %) as off-white solid; ^1H NMR ($CDCl_3$) 2.58 (3H, s), 3.83 (3H, s), 3.91 (3H, s), 7.46 (1H, d), 7.53 (1H, d).

Intermediate 133b: Methyl 4-bromo-2-(bromomethyl)-3-methoxybenzoate



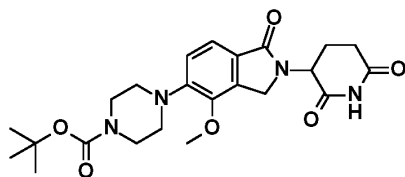
$CHCl_3$ (80 mL) was added to ethyl 4-bromo-3-methoxy-2-methylbenzoate (4.10 g, 15.82 mmol) under N_2 . NBS (3.94 g, 22.15 mmol) and AIBN (520 mg, 3.16 mmol) were then added at RT and the mixture was stirred at 75°C for 3h. The mixture was then diluted with water (100 mL) and extracted with DCM (100 mL $\times$ 2). The combined organic solutions were washed with brine (100 mL), dried (Na_2SO_4) and concentrated to give the title compound (5.00 g, 86 %) as brown liquid that was used directly without further purification; ^1H NMR: 3.88 (3H, s), 3.92 (3H, s), 5.01 (2H, s), 7.60 (1H, d), 7.80 (1H, d).

Intermediate 133c: 3-(5-Bromo-4-methoxy-1-oxoisindolin-2-yl)piperidine-2,6-dione



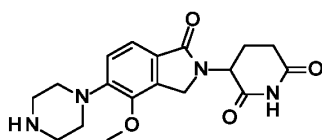
Methyl 4-bromo-2-(bromomethyl)-3-methoxybenzoate (5.70 g, 16.86 mmol) was dissolved in MeCN (60 mL). 3-Aminopiperidine-2,6-dione hydrochloride salt (2.78 g, 16.86 mmol) and DIPEA (11.78 mL, 67.5 mmol) were added at RT under N_2 . The mixture was then stirred at 85°C for 16h under N_2 . The mixture was then cooled slowly to RT, solids were collected by filtration, washed with MeCN (20 mL) and dried under vacuum to give the title compound (4.00 g, 62%) as an off white solid; ^1H NMR: 1.96-2.07 (1H, m), 2.40-2.49 (1H, m), 2.58-2.62 (1H, m), 2.85-3.00 (1H, m), 4.00 (3H, s), 4.52-4.61 (1H, m), 4.68-4.74 (1H, m), 5.12 (1H, dd), 7.36 (1H, d), 7.77 (1H, d), 11.02 (1H, s); m/z : ES^+ $[M+H]^+ = 355$.

Intermediate 133d: *tert*-Butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-methoxy-1-oxoisindolin-5-yl)piperazine-1-carboxylate



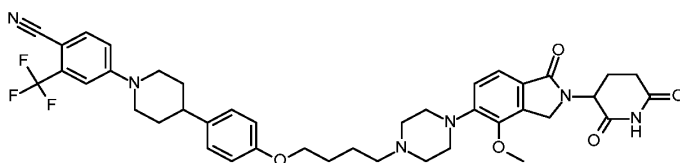
- Pd-PEPPSI-IHeptCl (83 mg, 0.085 mmol) was added to *tert*-butyl piperazine-1-carboxylate (949 mg, 5.10 mmol), Cs₂CO₃ (1661 mg, 5.10 mmol) and 3-(5-bromo-4-methoxy-1-oxoisoindolin-2-yl)piperidine-2,6-dione (600 mg, 1.699 mmol) in 1,4-dioxane (20 mL) at RT under N₂. The resulting suspension was stirred for 2h at 120°C. The mixture was then diluted with DCM (20 mL) and washed with 5% AcOH in water (20 mL), water (20 mL), sat. NaHCO₃ (20 mL) and then sat. brine (20 mL). The organic solution was dried (Na₂SO₄) and concentrated. Trituration with EtOAc (8 mL) and washing with MTBE (25 mL) gave a solid which was collected by filtration and dried under vacuum to give the title compound (700 mg, 77 %) as dark brown solid; ¹H NMR: 1.43 (9H, s), 1.88-2.06 (1H, m), 2.40-2.48 (1H, m), 2.58 (1H, br d), 2.76-3.00 (1H, m), 3.00-3.09 (4H, m), 3.41-3.58 (4H, m), 3.89 (3H, s), 4.26-4.34 (1H, m), 4.47 (1H, br d), 5.05 (1H, dd), 7.09 (1H, d), 7.40 (1H, d), 10.98 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 459.2.

Intermediate 133e: 3-(4-methoxy-1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione



- To a stirred solution of *tert*-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-methoxy-1-oxoisoindolin-5-yl)piperazine-1-carboxylate (700 mg, 1.527 mmol) in DCM (10 mL) was added 4M HCl (7.63 mL, 30.5 mmol) in 1,4-dioxane at 0°C. The mixture was stirred at RT for 2h under N₂. The mixture was then concentrated to give the title compound (600 mg, 78 %) as brown solid; ¹H NMR: 1.94-2.03 (1H, m), 2.43-2.47 (2H, m), 2.58-2.69 (1H, m), 2.85-2.97 (1H, m), 3.22-3.37 (8H, m), 3.90 (3H, s), 4.35-4.38 (1H, m), 4.51 (1H, d), 4.46-4.54 (1H, m), 5.08 (1H, dd), 7.14 (1H, d), 7.43 (1H, d), 9.42 (2H, br s), 10.98 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 359.

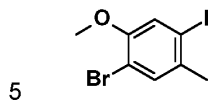
Example 133: 4-(4-(4-(4-(2-(2,6-Dioxopiperidin-3-yl)-4-methoxy-1-oxoisoindolin-5-yl)piperazin-1-yl)butoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



- Intermediate 133e was reacted with Intermediate 50a using the general synthetic method illustrated by Example 5 to give the title compound after purification by HPLC (Column: Zorbax-C18, 5μm; 50 × 21.2 mm, Eluent C, Basic Work-Up A); ¹H NMR: 1.55-1.69 (4H, m), 1.74 (2H, d), 1.84 (2H, d), 1.91-2.03 (1H, m), 2.39 (2H, d), 2.54-2.64 (5H, m), 2.71-2.82 (1H, m), 2.84-2.96 (1H, m), 2.98-3.15 (6H, m), 3.85 (3H, s), 3.97 (2H,

t), 4.18 (2H, d), 4.27 (1H, d), 4.39-4.51 (1H, m), 5.07 (1H, dd), 6.87 (2H, d), 7.07 (1H, d), 7.16 (2H, d), 7.27 (1H, d), 7.33 (1H, s), 7.39 (1H, d), 7.82 (1H, d), 10.96 (1H, br s); m/z : ES^+ $[M+H]^+ = 759$.

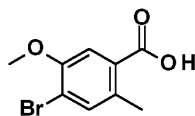
Intermediate 134a: 1-Bromo-4-iodo-2-methoxy-5-methylbenzene



THF (10 mL) was added to 4-bromo-5-methoxy-2-methylaniline (1.00 g, 4.63 mmol) then water (2.4 mL) and HCl (37%, 2.40 mL) were added at RT. The mixture was stirred at RT for 1h and was then cooled to 0°C. A solution of sodium nitrite (0.734 g, 10.64 mmol) in water (10 mL) was then added dropwise followed by the dropwise addition of KI (1.306 g, 7.87 mmol) solution in water (2 mL). The mixture was then warmed slowly to RT and stirred for 16h. The reaction was then quenched with sat. Na_2CO_3 solution and the pH was adjusted to 7-8. The mixture was then extracted with DCM (20 mL $\times$ 3). Combined organic solutions were washed with brine (20 mL), dried (Na_2SO_4) and concentrated. Purification by FSC using hexane (100 %) as the eluent gave the title compound (1.07 g, 62 %) as yellow solid; ^1H NMR: 2.29 (3H, s), 3.82 (3H, s), 7.45 (1H, s), 7.54 (1H, s); m/z : ES^+ $[M+H]^+ = 328.2$.

15

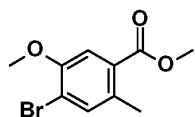
Intermediate 134b: 4-bromo-5-methoxy-2-methylbenzoic acid



THF (10 mL) was added to 1-bromo-4-iodo-2-methoxy-5-methylbenzene (1.05 g, 3.21 mmol), then $iPrMgCl$ (4.82 mL, 9.63 mmol) was added dropwise at $-78^\circ C$. The mixture was stirred at $-50^\circ C$ to $-20^\circ C$ for 40 min. Solid carbon dioxide (excess) was added and then the mixture was warmed slowly to RT and stirred for 1h. The reaction was then quenched with 1.5M HCl solution (10 mL) and extracted with EtOAc (2 $\times$ 30 mL). The combined organic solutions were washed with water (10 mL) and brine (10 mL), then dried (Na_2SO_4) and concentrated to give the title compound (0.80 g, 74%) as brown solid; m/z : ES^+ $[M+H]^+ = 245.9$.

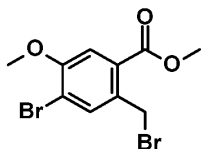
25

Intermediate 134c: Methyl 4-bromo-5-methoxy-2-methylbenzoate



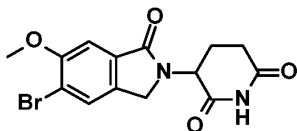
DMF (3 mL) was added to 4-bromo-5-methoxy-2-methylbenzoic acid (750 mg, 3.06 mmol). K_2CO_3 (846 mg, 6.12 mmol) and MeI (0.287 mL, 4.59 mmol, dropwise) were then added at RT and the mixture was then stirred at RT for 24h. The reaction was then quenched with ice cold water (20 mL) and extracted with EtOAc (30 mL $\times$ 2). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give the title compound (730 mg, 92%); ^1H NMR ($CDCl_3$) 2.58 (3H, s), 3.83 (3H, s), 3.91 (3H, s), 7.46 (1H, d), 7.53 (1H, d).

30

Intermediate 134d: Methyl 4-bromo-2-(bromomethyl)-5-methoxybenzoate

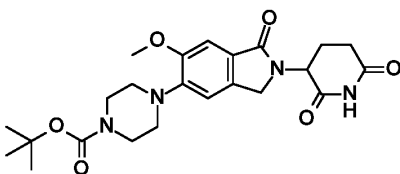
- 5 CHCl₃ (10 mL) was added to methyl 4-bromo-5-methoxy-2-methylbenzoate (720 mg, 2.78 mmol) under N₂ then NBS (692 mg, 3.89 mmol) and AIBN (91 mg, 0.556 mmol) were added at 0°C. The mixture was then stirred at 75°C for 32 h then quenched with sat. bicarbonate solution (5 mL). The pH was adjusted to 6-7 and the mixture was extracted with DCM (15 mL × 2). The combined organic extracts were washed with brine (15 mL), dried (Na₂SO₄) and concentrated to give the title compound as a brown liquid; ¹H NMR: 3.89 (3H, s), 3.93-4.00 (3H, m), 4.97 (2H, s), 7.48 (1H, s), 7.90 (1H, s).

10

Intermediate 134e: 3-(5-Bromo-4-methoxy-1-oxo-isoindolin-2-yl)piperidine-2,6-dione

- 15 MeCN (10 mL) was added to methyl 4-bromo-2-(bromomethyl)-5-methoxybenzoate (860 mg, 2.54 mmol) under N₂. 3-Aminopiperidine-2,6-dione hydrochloride (419 mg, 2.54 mmol) and DIPEA (1.78 mL, 10.18 mmol) were then added at RT and the mixture was stirred at 85°C for 16h. After cooling to RT, a precipitate was collected by filtration and washed with 5 mL MeCN then dried under reduced pressure to give the title compound (430 mg, 31 %) as grey solid; ¹H NMR: 1.95-2.09 (2H, m), 2.31-2.45 (2H, m), 3.95 (3H, s), 4.17-4.30 (2H, m), 4.36-4.42 (1H, m), 7.37 (1H, s), 7.90 (1H, s), 11.24-11.31 (1H, m); *m/z*: ES⁺ [M+H]⁺ = 355.0.

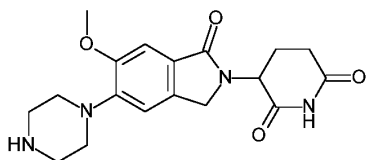
20

Intermediate 134f: *tert*-Butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-methoxy-1-oxoisoindolin-5-yl)piperazine-1-carboxylate

- 25 1,4-Dioxane (20 mL) was added to 3-(5-bromo-6-methoxy-1-oxoisoindolin-2-yl)piperidine-2,6-dione (430 mg, 1.22 mmol) under N₂. To this mixture, *tert*-butyl piperazine-1-carboxylate (680 mg, 3.65 mmol) and Cs₂CO₃ (1.19 g, 3.65 mmol) were added under N₂ at RT. To this mixture Pd-PEPPSI-IHepCl (71.1 mg, 0.073 mmol) was charged under N₂ then the mixture was stirred at 120°C for 2h. The mixture was then diluted with DCM (20 mL) and washed with 5% AcOH in water (25 mL), water (25 mL), sat. NaHCO₃ (25 mL) and then sat. brine (20 mL). The organic layer was dried (Na₂SO₄) and concentrated. Trituration with EtOAc (5 mL) and washing with MTBE (20 mL) gave a solid which was collected by filtration and dried under vacuum to

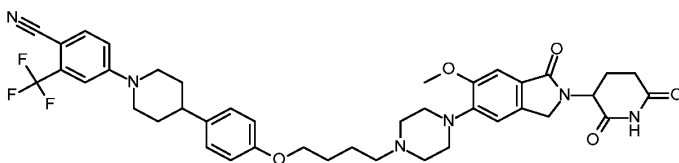
the title compound (253 mg, 36 % yield) as green solid; ^1H NMR: 1.43 (9H, s), 1.90-2.06 (1H, m), 2.35-2.44 (1H, m), 2.56-2.69 (2H, m), 2.85-2.96 (1H, m), 3.01 (3H, br d), 3.48 (4H, br s), 3.83-3.95 (3H, m), 4.12-4.44 (2H, m), 5.07 (1H, dd), 7.10 (1H, s), 7.20-7.25 (1H, m), 10.92-11.02 (1H, m); m/z : ES^+ $[\text{M}+\text{H}]^+ = 459.0$.

5 Intermediate 134g: 3-(6-Methoxy-1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride



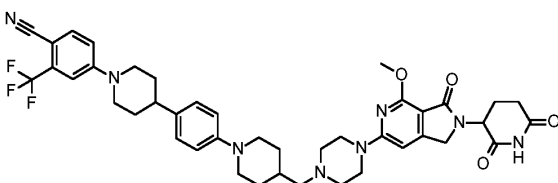
- DCM (2 mL) was added to *tert*-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-6-methoxy-1-oxoisoindolin-5-yl)piperazine-1-carboxylate (250 mg, 0.545 mmol), then 4M HCl in 1,4-dioxane (2.73 mL, 10.90 mmol) was added at 0°C and the mixture was then stirred at RT for 2h. The organic solvent was then removed under reduced pressure to give the title compound (250 mg, 99 %) as grey solid; ^1H NMR: 1.24 (1H, d), 1.95-2.03 (1H, m), 2.33-2.35 (2H, m), 2.67-2.71 (2H, m), 3.26 (8H, br s), 3.89 (3H, s), 4.18-4.38 (2H, m), 5.05-5.12 (1H, m), 7.17 (1H, s), 7.25 (1H, s), 10.94-11.00 (1H, m); m/z : ES^+ $[\text{M}+\text{H}]^+ = 359$.

15 Example 134: 4-(4-(4-(4-(2-(2,6-Dioxopiperidin-3-yl)-6-methoxy-1-oxoisoindolin-5-yl)piperazin-1-yl)butoxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



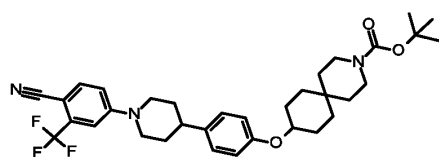
- Intermediate 50a was reacted with Intermediate 134g using the general synthetic method illustrated by Example 5 to give the title compound after purification (Column: X Select C18 150 × 21.1, Eluent C, Basic Work-Up A); ^1H NMR: 1.55-1.67 (4H, m), 1.68-1.78 (2H, m), 1.84 (2H, br d), 1.92-2.00 (1H, m), 2.29-2.43 (4H, m), 2.61-2.77 (2H, m), 2.81-2.92 (1H, m), 2.99-3.14 (6H, m), 3.86 (3H, s), 3.97 (2H, t), 4.14-4.24 (3H, m), 4.26-4.36 (1H, m), 5.07 (1H, dd), 6.86 (2H, d), 7.07 (1H, s), 7.13-7.20 (3H, m), 7.22-7.36 (2H, m), 7.82 (1H, d), 10.90-11.00 (1H, m); m/z : ES^+ $[\text{M}+\text{H}]^+ = 759.3$.

25 Example 135: 4-(4-(4-(4-(2-(2,6-Dioxopiperidin-3-yl)-4-methoxy-3-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)piperazin-1-yl)methyl)piperidin-1-yl)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



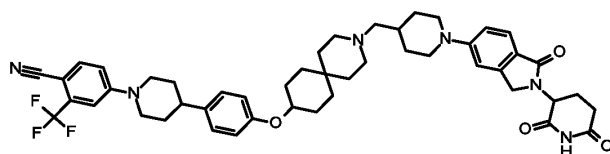
- Intermediate 4b was reacted with Intermediate 120e using the general synthetic method illustrated by Example 1 to give the title compound after purification (Column A, Eluent A); ¹H NMR: 1.14-1.34 (3H, m), 1.53-1.75 (4H, m), 1.75-1.95 (6H, m), 2.21 (2H, d), 2.43-2.47 (4H, m), 2.56-2.77 (2H, m), 2.82-2.95 (1H, m), 3.04 (2H, t), 3.61 (6H, s), 3.89 (3H, s), 4.08-4.22 (3H, m), 4.27 (1H, d), 4.95 (1H, dd), 6.48 (1H, s), 6.86 (2H, d), 7.08 (2H, d), 7.26 (1H, dd), 7.32 (1H, d), 7.80 (1H, d), 10.88 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 785.3.

Intermediate 136a: *tert*-Butyl 9-(4-(1-(4-cyano-3-(trifluoromethyl)phenyl)piperidin-4-yl)phenoxy)-3-azaspiro[5.5]undecane-3-carboxylate



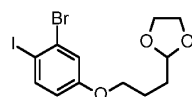
- 10 PPh₃ (757 mg, 2.89 mmol) was added to 4-(4-(4-hydroxyphenyl)piperidin-1-yl)-2-(trifluoromethyl)-benzonitrile (Example 1g) (500 mg, 1.44 mmol), *tert*-butyl 9-hydroxy-3-azaspiro[5.5]undecane-3-carboxylate (467 mg, 1.73 mmol) and DIAD (365 μL, 1.88 mmol) in THF (16 mL) at RT under N₂. The resulting mixture was stirred at RT for 16h. Concentration and purification by FSC (gradient 0-20% EtOAc in petroleum ether) gave the title compound (0.560 g, 65 %) as a yellow gum; ¹H NMR: 1.12-1.15 (5H, m), 1.23-1.36 (3H, m), 1.39 (9H, s), 1.47-1.55 (2H, m), 1.55-1.72 (3H, m), 1.76-1.87 (3H, m), 2.76 (1H, t), 2.98-3.09 (2H, m), 3.27-3.29 (6H, m), 4.24-4.33 (1H, m), 6.85 (2H, d), 7.14 (2H, d), 7.27 (1H, dd), 7.33 (1H, d), 7.82 (1H, d); *m/z* ES⁺ [M-Boc] = 498.3.

Example 136: 4-(4-(4-((3-((1-(2-(2,6-Dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperidin-4-yl)methyl)-3-azaspiro[5.5]undecan-9-yl)oxy)phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



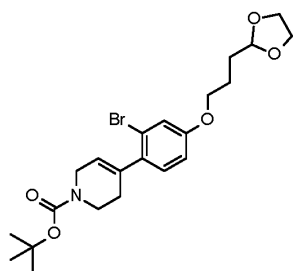
- Intermediate 27f was reacted with Intermediate 136a using the general synthetic method illustrated by Example 1 to give the title compound after purification by preparative TLC (DCM:MeOH, 15:1); ¹H NMR: 1.12-1.29 (4H, m), 1.35-1.65 (10H, m), 1.70-1.88 (7H, m), 1.92-1.99 (1H, m), 2.12-2.16 (2H, m), 2.24-2.40 (5H, m), 2.59 (1H, d), 2.71-2.93 (4H, m), 3.04 (2H, t), 3.86 (2H, d), 4.15-4.24 (3H, m), 4.24-4.36 (2H, m), 5.05 (1H, dd), 6.85 (2H, d), 7.00-7.07 (2H, m), 7.14 (2H, d), 7.27 (1H, dd), 7.33 (1H, d), 7.50 (1H, d), 7.82 (1H, d), 10.96 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 837.3.

Intermediate 137a: 2-[3-(3-Bromo-4-iodophenoxy)propyl]-1,3-dioxolane



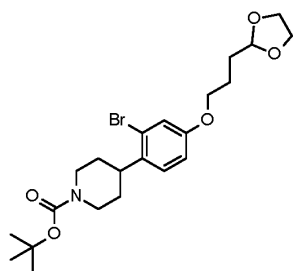
- 3-Bromo-4-iodophenol (5.0 g, 16.73 mmol) was added to 2-(3-bromopropyl)-1,3-dioxolane (4.7 g, 24.33 mmol) and K_2CO_3 (6.3 g, 45.62 mmol) in MeCN (100 mL). The mixture was stirred at 80 °C for 1 h, cooled to RT, filtered through silica and the solvent was evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% DCM in MeOH to give the title compound (5.0 g, 80 %) as a colourless oil; ^1H NMR: δ 1.65–1.73 (2H, m), 1.7–1.8 (2H, m), 1.76–1.95 (1H, m), 3.7–3.99 (5H, m), 4.8–4.87 (1H, m), 6.69–6.79 (1H, m), 7.26–7.33 (1H, m), 7.71–7.8 (1H, m); m/z : ES^+ $[M+H]^+ = 413.0$.

Intermediate 137b: *tert*-Butyl 4-{2-bromo-4-[3-(1,3-dioxolan-2-yl)propoxy]phenyl}-3,6-dihydropyridine-1(2H)-carboxylate



- $PdCl_2(dtbpf)$ (0.472 g, 0.65 mmol) was added to K_2CO_3 (2.20 g, 16.14 mmol), 2-[3-(3-bromo-4-iodophenoxy)propyl]-1,3-dioxolane (4.00 g, 9.68 mmol) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.99 g, 6.46 mmol) in 1,4-dioxane:water (4:1, 50 mL) at RT under nitrogen. The mixture was stirred at 80 °C for 1 h, cooled to RT, filtered through Celite® and the solvent was evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 60% EtOAc in Et_2O to give the title compound (2.3 g, 76 %) as a yellow oil; ^1H NMR: δ 1.43 (9H, s), 1.65–1.84 (4H, m), 2.31 (2H, s), 3.52 (2H, t), 3.71–3.84 (2H, m), 3.84–3.93 (2H, m), 3.94 (2H, s), 3.96–4.08 (2H, m), 4.85 (1H, t), 5.75 (1H, s), 6.88–6.98 (1H, m), 7.11–7.18 (2H, m); m/z : ES^+ $[M+H]^+ = 468.1$.

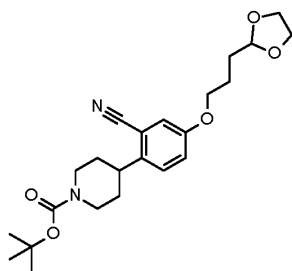
Intermediate 137c: *tert*-Butyl 4-{2-bromo-4-[3-(1,3-dioxolan-2-yl)propoxy]phenyl}piperidine-1-carboxylate



- Rhodium on carbon (5%, 2.1 g, 1.02 mmol) and *tert*-butyl 4-{2-bromo-4-[3-(1,3-dioxolan-2-yl)propoxy]phenyl}-3,6-dihydropyridine-1(2H)-carboxylate (2.1 g, 4.48 mmol) in EtOAc (10 mL) and MeOH

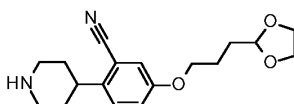
- (1 mL) was stirred under an atmosphere of hydrogen at RT for 3 h. The reaction mixture was filtered through Celite® and the solvent was evaporated to give the title compound (1.7 g, 81 %) which was used without further purification; ¹H NMR: δ 1.42 (9H, s), 1.53–1.65 (1H, m), 1.65–1.74 (4H, m), 1.71–1.86 (2H, m), 1.91 (1H, s), 2.60 (1H, s), 2.9–3.02 (1H, m), 3.35–3.47 (1H, m), 3.71–3.8 (2H, m), 3.84–3.9 (2H, m), 3.94–4.01 (2H, m), 4.09 (2H, d), 4.75–4.87 (1H, m), 6.91 (1H, dd), 7.14 (1H, d), 7.23 (1H, d).

Intermediate 137d: *tert*-Butyl 4-{2-cyano-4-[3-(1,3-dioxolan-2-yl)propoxy]phenyl}piperidine-1-carboxylate



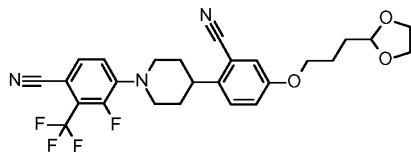
- 10 Copper(I) cyanide (0.38 g, 4.34 mmol) was added to *tert*-butyl 4-{2-bromo-4-[3-(1,3-dioxolan-2-yl)propoxy]phenyl}piperidine-1-carboxylate (1.7 g, 3.61 mmol) in NMP (14 mL) at RT. The mixture was stirred at 150 °C for 3 h. The reaction was cooled to RT and diluted with EtOAc (100 mL), washed with water (50 mL), saturated brine (50 mL), dried over Na₂SO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 30% EtOAc in Et₂O to give
- 15 the title compound (0.500 g, 33.2 %) as a yellow gum; ¹H NMR: δ 1.42 (9H, s), 1.55 (1H, d), 1.70 (6H, d), 1.77 (2H, d), 2.94 (1H, t), 3.73–3.83 (2H, m), 3.83–3.93 (2H, m), 3.99–4.11 (5H, m), 4.84 (1H, t), 7.22 (1H, dd), 7.34 (1H, d), 7.42 (1H, d); m/z: ES⁺ [M+H]⁺ = 417.2.

Intermediate 137e: 5-[3-(1,3-Dioxolan-2-yl)propoxy]-2-(piperidin-4-yl)benzonitrile



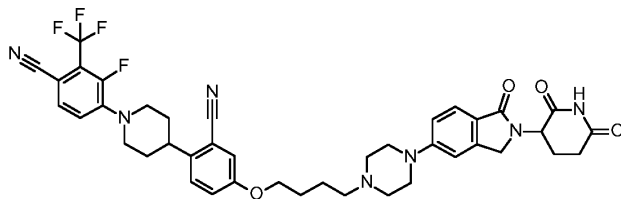
- 20 TMS-I (327 μl, 2.40 mmol) was added to *tert*-butyl 4-{2-cyano-4-[3-(1,3-dioxolan-2-yl)propoxy]phenyl}piperidine-1-carboxylate (500 mg, 1.20 mmol) in MeCN (1 mL). The mixture was stirred at RT for 1 min. The solvent was removed under reduced pressure to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% EtOAc in DCM to give the title
- 25 compound (0.350 g, 92 %) as a yellow solid; m/z: ES⁺ [M+H]⁺ = 317.2.

Intermediate 137f: 4-(4-{2-Cyano-4-[3-(1,3-dioxolan-2-yl)propoxy]phenyl}piperidin-1-yl)-3-fluoro-2-(trifluoromethyl)benzonitrile



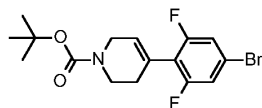
- Copper(I) cyanide (61.3 mg, 0.68 mmol) was added to 1-bromo-3,4-difluoro-2-(trifluoromethyl)benzene (170 mg, 0.65 mmol) in NMP (2 mL) at RT and stirred at 150 °C for 3 h. DIPEA (228 μ L, 1.30 mmol) and 5-[3-(1,3-dioxolan-2-yl)propoxy]-2-(piperidin-4-yl)benzonitrile (206 mg, 0.65 mmol) were added and the reaction was stirred at 100 °C for 1 h. The reaction mixture was cooled to RT and diluted with EtOAc (20 mL), washed with water (10 mL), saturated brine (10 mL), dried over Na₂SO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% EtOAc in Et₂O to give the title compound (0.150 g, 45.7 %) as a yellow solid; ¹H NMR: δ 1.67–1.74 (1H, m), 1.76–1.8 (3H, m), 1.84–1.89 (4H, m), 3.05–3.09 (3H, m), 3.71–3.8 (4H, m), 3.8–3.93 (2H, m), 4.04 (2H, t), 4.85 (1H, t), 7.24 (1H, dd), 7.37 (1H, d), 7.44–7.53 (2H, m), 7.83 (1H, d); m/z: ES⁺ [M+H]⁺ = 504.3.

Example 137: 4-{4-[2-Cyano-4-{3-(1,3-dioxolan-2-yl)propoxy}phenyl]piperidin-1-yl}-3-fluoro-2-(trifluoromethyl)benzonitrile



- 4-(4-{2-Cyano-4-[3-(1,3-dioxolan-2-yl)propoxy]phenyl}piperidin-1-yl)-3-fluoro-2-(trifluoromethyl)benzonitrile (152 mg, 0.30 mmol) was stirred in formic acid (1 mL) at 60 °C for 2 h. The reaction was cooled to RT and evaporated to dryness. *tert*-Butyl 4-[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazine-1-carboxylate (Intermediate 2b) (160 mg, 0.30 mmol) was stirred in formic acid (2 mL) at 40 °C for 1 h. The solvent was evaporated to dryness. The two residues were dissolved in NMP (1.5 mL) and the solution was stirred at RT for 16 h. The reaction mixture was purified by C18-flash chromatography, elution gradient 5 to 100% MeCN in water (1% NH₄HCO₃) to give the title compound (78 mg, 33 %) as a white solid; ¹H NMR: δ 1.56–1.66 (2H, m), 1.7–1.81 (2H, m), 1.85 (4H, s), 1.92–2 (1H, m), 2.29–2.44 (3H, m), 2.49 (3H, s), 2.53–2.56 (1H, s), 2.59 (1H, d), 2.84–2.97 (1H, m), 2.97–3.13 (3H, m), 3.21–3.3 (4H, m), 3.74 (2H, d), 4.06 (2H, t), 4.21 (1H, d), 4.33 (1H, d), 5.06 (1H, dd), 7.01–7.08 (2H, m), 7.25 (1H, dd), 7.38 (1H, d), 7.43–7.55 (3H, m), 7.82 (1H, d), 10.96 (1H, s); m/z: ES⁺ [M+H]⁺ = 772.3.

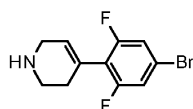
Intermediate 138a: *tert*-butyl 4-(4-bromo-2,6-difluorophenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate



tert-Butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate was reacted with 5-bromo-1,3-difluoro-2-iodobenzene using the general synthetic method illustrated by intermediate 9a to give the title compound; ¹H NMR (CDCl₃): δ 1.49 (9H, s), 2.37 (2H, d), 3.62 (2H, t), 4.03 – 4.12 (2H, m), 5.81 (1H, s), 7.05 – 7.12 (2H, m); m/z: ES⁺ [M-*t*Bu]⁺ = 318.0

5

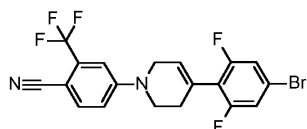
Intermediate 138b: 4-(4-Bromo-2,6-difluorophenyl)-1,2,3,6-tetrahydropyridine



tert-Butyl 4-(4-bromo-2,6-difluorophenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate was reacted using the general synthetic method illustrated by intermediate 26c to give the title compound in the form of an HCl salt which was used without further purification; ¹H NMR: δ 2.76 (2H, s), 3.45 (2H, d), 3.87 – 3.99 (2H, m), 5.87 (1H, s), 7.01 – 7.17 (2H, m), 10.11 (1H, s); m/z: ES⁺ [M+H]⁺ = 274.0.

10

Intermediate 138c: 4-[4-(4-Bromo-2,6-difluorophenyl)-3,6-dihydropyridin-1(2*H*)-yl]-2-(trifluoromethyl)benzonitrile

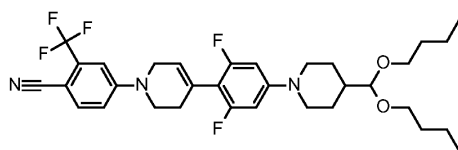


15

4-(4-Bromo-2,6-difluorophenyl)-1,2,3,6-tetrahydropyridine was reacted with 4-fluoro-2-(trifluoromethyl)benzonitrile using the general synthetic method illustrated by intermediate 4a to give the title compound; ¹H NMR: δ 2.57 – 2.64 (2H, m), 3.68 (2H, t), 4.04 (2H, q), 6.00 (1H, s), 6.96 (1H, dd), 7.08 – 7.16 (3H, m), 7.62 – 7.68 (1H, m); m/z: ES⁺ [M+H]⁺ = 443.0.

20

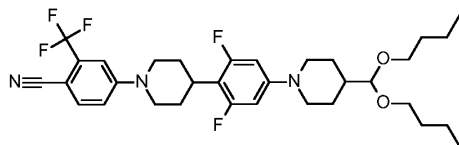
Intermediate 138d: 4-[4-{4-[4-(Dibutoxymethyl)piperidin-1-yl]-2,6-difluorophenyl}-3,6-dihydropyridin-1(2*H*)-yl]-2-(trifluoromethyl)benzonitrile



4-[4-(4-Bromo-2,6-difluorophenyl)-3,6-dihydropyridin-1(2*H*)-yl]-2-(trifluoromethyl)benzonitrile was reacted with 4-(dibutoxymethyl)piperidine (intermediate 27e) using the general synthetic method illustrated by intermediate 27c to give the title compound; ¹H NMR: δ 0.93 (6H, t), 1.35 – 1.47 (4H, m), 1.53 – 1.6 (6H, m), 1.72 – 1.89 (3H, m), 2.25 (2H, ddd), 2.65 – 2.77 (2H, m), 3.43 (2H, dt), 3.53 – 3.72 (5H, m), 3.80 (1H, dt), 3.91 (1H, s), 4.17 (1H, d), 5.03 (1H, d), 6.37 (2H, d), 6.67 (1H, dd), 7.03 (1H, dd), 7.19 (1H, d), 7.61 – 7.71 (1H, m); m/z: ES⁺ [M+H]⁺ = 606.3.

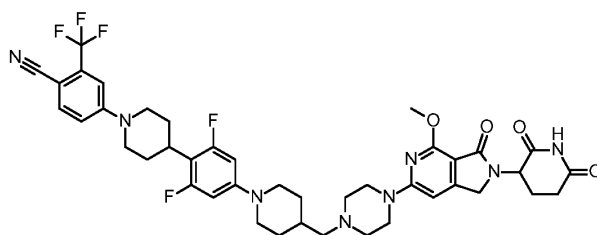
30

Intermediate 138e: 4-(4-{4-[4-(Dibutoxymethyl)piperidin-1-yl]-2,6-difluorophenyl}piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



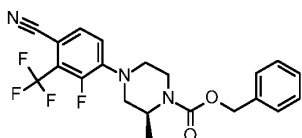
- 4-[4-{4-[4-(Dibutoxymethyl)piperidin-1-yl]-2,6-difluorophenyl}-3,6-dihydropyridin-1(2*H*)-yl]-2-(trifluoromethyl)benzonitrile was hydrogenated using the general synthetic method illustrated by intermediate 9b to give the title compound; ¹H NMR: δ 0.93 (6H, t), 1.36 – 1.44 (6H, m), 1.53 – 1.61 (4H, m), 1.72 – 1.92 (6H, m), 2.07 – 2.19 (2H, m), 2.68 (2H, td), 3.04 (2H, q), 3.43 (2H, dt), 3.64 (4H, ddd), 4.00 (2H, d), 4.17 (1H, d), 6.38 (2H, t), 6.98 (1H, td), 7.15 (1H, dd), 7.61 (1H, d); m/z: ES⁺ [M+H]⁺ = 608.4.

Example 138: 4-(4-{4-[4-(2-(2,6-Dioxopiperidin-3-yl)-4-methoxy-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-yl]piperazin-1-yl)methyl}piperidin-1-yl)-2,6-difluorophenyl}piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



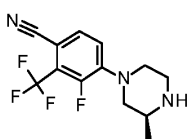
- 4-(4-{4-[4-(Dibutoxymethyl)piperidin-1-yl]-2,6-difluorophenyl}piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (65 mg, 0.11 mmol) and tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-4-methoxy-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-yl)piperazine-1-carboxylate (intermediate 120e) (54.1 mg, 0.12 mmol) were heated in formic acid (1 mL, 26.51 mmol) at 60 °C for 2 h. The reaction mixture was cooled to RT, evaporated and the residue was suspended in NMP (2 mL). The reaction mixture was stirred for 5 mins followed by addition of sodium triacetoxymethylborate (56.7 mg, 0.27 mmol). The suspension was stirred at RT for 2 h. Purification by preparative HPLC (Column A, Eluent A) gave the title compound in the form of a formate salt (25 mg, 28.5 %) as a yellow solid; ¹H NMR: δ 1.07 – 1.22 (2H, m), 1.7 – 1.82 (5H, m), 1.85 – 2 (3H, m), 2.16 – 2.23 (2H, m), 2.32 – 2.35 (1H, m), 2.42 – 2.47 (4H, m), 2.67 – 2.76 (2H, m), 2.83 – 2.95 (1H, m), 2.99 – 3.1 (2H, m), 3.57 – 3.65 (4H, m), 3.72 (2H, d), 3.89 (3H, s), 4.1 – 4.22 (3H, m), 4.28 (1H, d), 4.96 (1H, dd), 6.49 (1H, s), 6.54 – 6.59 (1H, m), 7.27 (1H, dd), 7.33 (1H, d), 7.79 – 7.89 (1H, m), 8.19 (1H, s), 10.91 (1H, s); m/z: ES⁺ [M+H]⁺ = 821.5.

Intermediate 139a: Benzyl (2*S*)-4-[4-cyano-2-fluoro-3-(trifluoromethyl)phenyl]-2-methylpiperazine-1-carboxylate



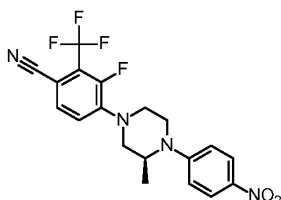
- 5 Benzyl (2*S*)-2-methylpiperazine-1-carboxylate was reacted with 4-fluoro-2-(trifluoromethyl)benzonitrile using the general synthetic method illustrated by intermediate 137f to give the title compound; ¹H NMR: δ 1.24 (3H, d), 2.92–3.04 (1H, m), 3.07–3.16 (1H, m), 3.28 (1H, d), 3.48 (1H, d), 3.54 (1H, d), 3.86–3.96 (1H, m), 4.26–4.35 (1H, m), 5.06–5.18 (2H, m), 7.3–7.35 (1H, m), 7.38 (5H, d), 7.42 (1H, d), 7.83 (1H, d); m/z: ES⁺ [M+H]⁺ = 422.2.

Intermediate 139b: 3-Fluoro-4-[(3*S*)-3-methylpiperazin-1-yl]-2-(trifluoromethyl)benzonitrile



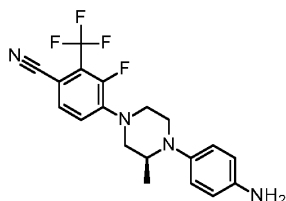
- 10 Benzyl (2*S*)-4-[4-cyano-2-fluoro-3-(trifluoromethyl)phenyl]-2-methylpiperazine-1-carboxylate was reacted with hydrogen gas using the general synthetic method illustrated by intermediate 123b to give the title compound; ¹H NMR: δ 1.03 (3H, d), 2.37–2.51 (2H, m), 2.67–2.84 (2H, m), 2.95 (1H, d), 3.86 (2H, t), 7.22 (1H, d), 7.28 (1H, s), 7.80 (1H, d), one proton exchanged; m/z: ES⁺ [M+H]⁺ = 288.2.

- 15 **Intermediate 139c: 3-Fluoro-4-[(3*S*)-3-methyl-4-(4-nitrophenyl)piperazin-1-yl]-2-(trifluoromethyl)benzonitrile**



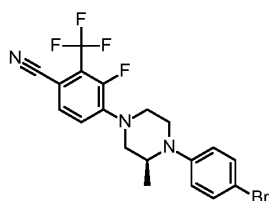
- 20 3-Fluoro-4-[(3*S*)-3-methylpiperazin-1-yl]-2-(trifluoromethyl)benzonitrile was reacted with 1-fluoro-4-nitrobenzene using the general synthetic method illustrated by intermediate 29a to give the title compound; ¹H NMR: δ 1.24 (3H, d), 3.17–3.28 (1H, m), 3.3–3.47 (2H, m), 3.62 (1H, dt), 3.74 (1H, d), 3.85–3.95 (1H, m), 4.38–4.45 (1H, m), 6.99–7.07 (2H, m), 7.45 (1H, t), 7.84 (1H, d), 8.05–8.14 (2H, m); m/z: ES⁺ [M+H]⁺ = 409.2.

- 25 **Intermediate 139d: 4-[(3*S*)-4-(4-Aminophenyl)-3-methylpiperazin-1-yl]-3-fluoro-2-(trifluoromethyl)benzonitrile**



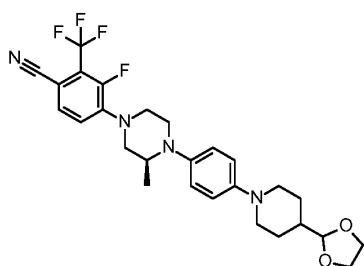
- 3-Fluoro-4-[(3*S*)-3-methyl-4-(4-nitrophenyl)piperazin-1-yl]-2-(trifluoromethyl)benzonitrile was reacted with iron and ammonium chloride using the general synthetic method illustrated by intermediate 29b to give the title compound; $^1\text{H NMR}$: δ 0.85–0.95 (3H, m), 2.54 (1H, s), 2.98–3.05 (2H, m), 3.08–3.17 (1H, m), 3.33–3.42 (2H, m), 3.45 (1H, d), 4.71–4.78 (2H, m), 6.49–6.6 (2H, m), 6.74–6.85 (2H, m), 6.95 (1H, s), 7.41–7.52 (1H, m), 7.82 (1H, d); m/z : ES^+ $[\text{M}+\text{H}]^+ = 379.2$.

Intermediate 139e: 4-[(3*S*)-4-(4-Bromophenyl)-3-methylpiperazin-1-yl]-3-fluoro-2-(trifluoromethyl)benzonitrile



- Copper bromide (682 mg, 4.76 mmol) was added to 4-[(3*S*)-4-(4-aminophenyl)-3-methylpiperazin-1-yl]-3-fluoro-2-(trifluoromethyl)benzonitrile (600 mg, 1.59 mmol) and *tert*-butylnitrite (491 mg, 4.76 mmol) in MeCN (15 mL) at RT and was stirred at RT for 3 h. The reaction mixture was diluted with DCM, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 30% EtOAc in Et₂O to give the title compound (130 mg, 18.5 %) as a yellow solid; $^1\text{H NMR}$: δ 1.06 (3H, d), 3.09–3.21 (2H, m), 3.25–3.32 (1H, m), 3.41–3.48 (1H, m), 3.5–3.58 (1H, m), 3.6–3.65 (1H, m), 4.09–4.15 (1H, m), 6.87–6.98 (2H, m), 7.34–7.4 (2H, m), 7.47 (1H, t), 7.84 (1H, d); m/z : ES^+ $[\text{M}+\text{H}]^+ = 442.1$.

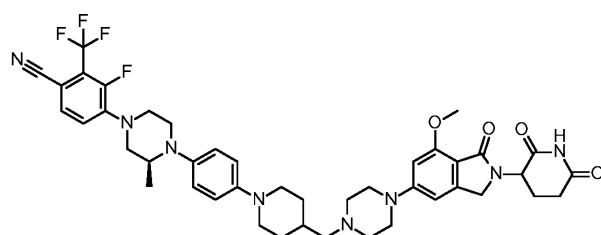
Intermediate 139f: 4-[(3*S*)-4-{4-[4-(1,3-Dioxolan-2-yl)piperidin-1-yl]phenyl}-3-methylpiperazin-1-yl]-3-fluoro-2-(trifluoromethyl)benzonitrile



$\text{Pd}(\text{t-Bu}_3\text{P})_2$ (0.11 g, 0.02 mmol) was added to 4-[(3*S*)-4-(4-bromophenyl)-3-methylpiperazin-1-yl]-3-fluoro-2-(trifluoromethyl)benzonitrile (0.1 g, 0.03 mmol), 4-(1,3-dioxolan-2-yl)piperidine (0.039 g, 0.25 mmol), Cs_2CO_3 (0.147 g, 0.45 mmol) and tri-*tert*-butylphosphonium tetrafluoroborate (0.006 g, 0.02 mmol) in 1,4-

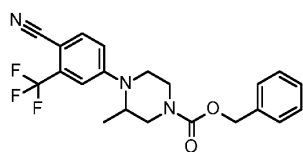
dioxane (3 mL) under nitrogen and was stirred at 100 °C for 2 h. The mixture was then cooled to RT and the solvent evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% EtOAc in Et₂O to give the title compound (0.80 g, 68 %) as a yellow solid; ¹H NMR δ 0.94 (3H, d), 1.15 (1H, d), 1.39 (2H, s), 1.4–1.46 (1H, m), 1.58 (2H, s), 1.73 (2H, d), 2.54 (1H, d), 3.06–3.12 (1H, m), 3.15 (1H, s), 3.28–3.39 (2H, m), 3.45–3.52 (1H, m), 3.56 (2H, d), 3.72–3.76 (2H, m), 3.74–3.92 (4H, m), 4.61 (1H, d), 6.87 (4H, s), 7.46 (1H, t), 7.83 (1H, d); m/z: ES⁺ [M+H]⁺ = 519.3.

Example 139: 4-[(3*S*)-4-{4-[4-{4-[2-(2,6-Dioxopiperidin-3-yl)-7-methoxy-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazin-1-yl}methyl]piperidin-1-yl]phenyl]-3-methylpiperazin-1-yl]-3-fluoro-2-(trifluoromethyl)benzonitrile

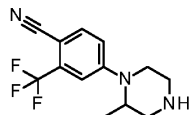


4-[(3*S*)-4-{4-[4-(1,3-Dioxolan-2-yl)piperidin-1-yl]phenyl]-3-methylpiperazin-1-yl]-3-fluoro-2-(trifluoromethyl)benzonitrile was reacted with tert-butyl 4-[2-(2,6-dioxopiperidin-3-yl)-7-methoxy-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazine-1-carboxylate (intermediate 1e) using the general synthetic method illustrated by example 137 and purified by flash silica chromatography, elution gradient 0 to 8 % MeOH in DCM to give the title compound; ¹H NMR: δ 0.95 (3H, d), 1.17 – 1.31 (3H, m), 1.57 – 1.73 (1H, m), 1.81 (2H, d), 1.88 – 1.95 (1H, m), 2.23 (2H, d), 2.27 – 2.38 (1H, m), 2.50 (7H, s), 2.52 – 2.62 (4H, m), 2.82 – 2.96 (1H, m), 3.03 – 3.21 (2H, m), 3.22 – 3.30 (1H, m), 3.31 – 3.43 (1H, m), 3.45 – 3.57 (3H, m), 3.70 – 3.78 (1H, m), 3.83 (3H, s), 4.17 (2H, dd), 4.96 (1H, dd), 6.46 – 6.51 (1H, m), 6.61 (1H, s), 6.88 (4H, s), 7.46 (1H, t), 7.83 (1H, d), 10.89 (1H, s); m/z: ES⁺ [M+H]⁺ = 817.3.

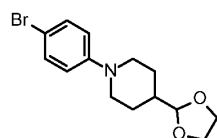
Intermediate 140a: Benzyl 4-[4-cyano-3-(trifluoromethyl)phenyl]-3-methylpiperazine-1-carboxylate



DIPEA (2.09 mL, 12.02 mmol) was added to benzyl 3-methylpiperazine-1-carboxylate (1.12 g, 4.81 mmol) and 4-fluoro-2-(trifluoromethyl)benzonitrile (1.0 g, 5.29 mmol) in NMP (12 mL) and was stirred at 100 °C for 24 h. The reaction mixture cooled to RT, diluted with EtOAc (50 mL), washed with water (50 mL), saturated brine (20 mL), dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% EtOAc in Et₂O to give the title compound (1.5 g, 77 %) as a yellow solid; ¹H NMR: δ 1.05 (3H, d), 3.21 (3H, s), 3.77 (1H, s), 3.84 (1H, dt), 4.00 (1H, dd), 4.33 (1H, s), 5.13 (2H, d), 7.19 (1H, dd), 7.25 (1H, d), 7.28 – 7.43 (5H, m), 7.86 (1H, d); m/z: ES⁺ [M+H]⁺ = 404.2.

Intermediate 140b: 4-[2-Methylpiperazin-1-yl]-2-(trifluoromethyl)benzonitrile

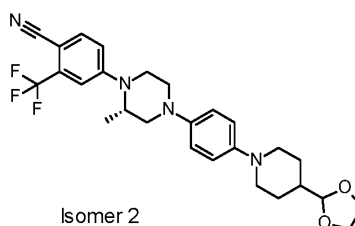
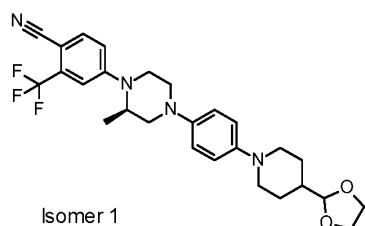
- 5 Benzyl 4-[4-cyano-3-(trifluoromethyl)phenyl]-3-methylpiperazine-1-carboxylate was reacted with hydrogen gas using the general synthetic method illustrated by intermediate 123b to give the title compound; ¹H NMR: δ 1.08 – 1.19 (3H, m), 2.57 – 2.70 (1H, m), 2.75 – 2.88 (2H, m), 2.90 – 3.03 (2H, m), 3.56 – 3.65 (1H, m), 4.12 – 4.20 (1H, m), 7.12 – 7.19 (1H, m), 7.19 – 7.27 (1H, m), 7.76 – 7.87 (1H, m); m/z: ES⁺ [M+H]⁺ = 270.1.

Intermediate 140c: 1-(4-Bromophenyl)-4-(1,3-dioxolan-2-yl)piperidine

10

- Pd₂(dba)₃ (175 mg, 0.19 mmol) was added to Xantphos (110 mg, 0.19 mmol), Cs₂CO₃ (3.1 g, 9.54 mmol), 1-bromo-4-iodobenzene (1.1 g, 4.20 mmol) and 4-(1,3-dioxolan-2-yl)piperidine (600 mg, 3.82 mmol) in 1,4-dioxane (20 mL) under nitrogen. The mixture was stirred at 80 °C for 3 h and then cooled to RT. The solvent was evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 55% EtOAc in Et₂O to give the title compound (0.30 g, 25.2 %) as a yellow solid; ¹H NMR δ 1.30 – 1.44 (2H, m), 1.59 – 1.76 (3H, m), 2.58 – 2.69 (2H, m), 3.66 – 3.74 (2H, m), 3.74 – 3.84 (2H, m), 3.81 – 3.93 (2H, m), 4.56 – 4.63 (1H, m), 6.84 – 6.91 (2H, m), 7.27 – 7.36 (2H, m); m/z: ES⁺ [M+H]⁺ = 312.1.

- 20 **Intermediate 140d and intermediate 141a: 4-[(2*R**)-4-{4-[4-(1,3-Dioxolan-2-yl)piperidin-1-yl]phenyl}-2-methylpiperazin-1-yl]-2-(trifluoromethyl)benzonitrile and 4-[(2*S**)-4-{4-[4-(1,3-Dioxolan-2-yl)piperidin-1-yl]phenyl}-2-methylpiperazin-1-yl]-2-(trifluoromethyl)benzonitrile** (absolute stereochemistry not yet confirmed)

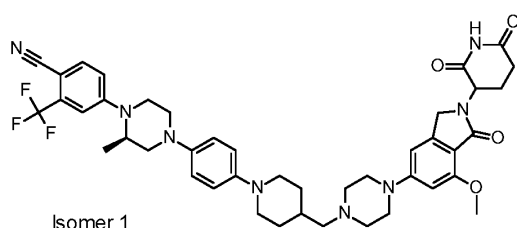


- 25 1-(4-Bromophenyl)-4-(1,3-dioxolan-2-yl)piperidine was reacted with 4-[2-methylpiperazin-1-yl]-2-(trifluoromethyl)benzonitrile using the general synthetic method illustrated by intermediate 139f to give racemic compound which was purified by preparative chiral-HPLC on a Column: CHIRALPAK IH, 3*25 cm, 5 μm; Mobile Phase A: CO₂, Mobile Phase B: MEOH (0.1% 2M NH₃-MeOH); Flow rate: 100 mL/min; Gradient: isocratic 40% B; to give the title compounds;

Intermediate 140d (isomer 1) elutes first: ^1H NMR: δ 1.21 (3H, d), 1.37–1.48 (2H, m), 1.57 (1H, s), 1.73 (2H, d), 2.67–2.74 (1H, m), 2.86 (1H, d), 3.26–3.30 (2H, m), 3.43 (1H, d), 3.54 (4H, d), 3.76–3.80 (2H, m), 3.83–3.90 (3H, m), 4.42 (1H, s), 4.60 (1H, d), 6.87 (4H, s), 7.25 (1H, d), 7.29 (1H, s), 7.85 (1H, d); m/z: $\text{ES}^+ [\text{M}+\text{H}]^+ = 501.3$, >99% ee.

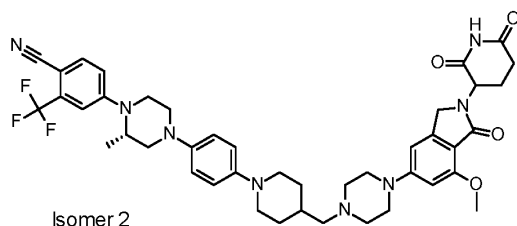
- 5 **Intermediate 141a (isomer 2):** ^1H NMR: δ 1.21 (4H, d), 1.41 (2H, q), 1.58 (1H, s), 1.73 (2H, d), 2.55 (1H, s), 2.71 (1H, d), 2.86 (1H, d), 3.43 (1H, d), 3.54 (3H, d), 3.79 (2H, d), 3.87 (3H, s), 4.42 (1H, s), 4.57–4.63 (1H, m), 6.87 (3H, d), 7.24 (1H, d), 7.29 (1H, s), 7.85 (1H, d); m/z: $\text{ES}^+ [\text{M}+\text{H}]^+ = 501.3$, >99% ee.

Example 140: 4-[(2*R)-4-{4-[4-{4-[2-(2,6-Dioxopiperidin-3-yl)-7-methoxy-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazin-1-yl}methvl]piperidin-1-yl]phenyl}-2-methylpiperazin-1-yl]-2-(trifluoromethyl)benzonitrile** (absolute stereochemistry not yet confirmed)



- 4-[(2*R**)-4-{4-[4-(1,3-Dioxolan-2-yl)piperidin-1-yl]phenyl}-2-methylpiperazin-1-yl]-2-(trifluoromethyl)benzonitrile was reacted with tert-butyl 4-[2-(2,6-dioxopiperidin-3-yl)-7-methoxy-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazine-1-carboxylate (intermediate 1e) using the general synthetic method illustrated by example 137 to give the title compound; ^1H NMR: δ 1.19–1.32 (5H, m), 1.58–1.73 (1H, m), 1.82 (2H, d), 1.88–1.95 (1H, m), 2.23 (2H, d), 2.26–2.38 (1H, m), 2.46–2.51 (4H, m), 2.53 (1H, d), 2.58 (3H, d), 2.64–2.76 (1H, m), 2.83–2.95 (2H, m), 3.23–3.33 (4H, m), 3.43 (1H, d), 3.48–3.59 (3H, m), 3.81–3.93 (4H, m), 4.11 (1H, d), 4.24 (1H, d), 4.4–4.44 (1H, m), 4.97 (1H, dd), 6.53 (2H, d), 6.88 (4H, s), 7.1–7.37 (2H, m), 7.86 (1H, d), 10.90 (1H, s); m/z: $\text{ES}^+ [\text{M}+\text{H}]^+ = 799.4$.

Example 141: 4-[(2*S)-4-{4-[4-{4-[2-(2,6-Dioxopiperidin-3-yl)-7-methoxy-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazin-1-yl}methvl]piperidin-1-yl]phenyl}-2-methylpiperazin-1-yl]-2-(trifluoromethyl)benzonitrile** (absolute stereochemistry not yet confirmed)

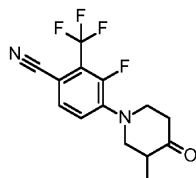


- 4-[(2*S**)-4-{4-[4-(1,3-Dioxolan-2-yl)piperidin-1-yl]phenyl}-2-methylpiperazin-1-yl]-2-(trifluoromethyl)benzonitrile was reacted with tert-butyl 4-[2-(2,6-dioxopiperidin-3-yl)-7-methoxy-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazine-1-carboxylate (intermediate 1e) using the general synthetic method illustrated by example 137 to give the title compound; ^1H NMR: δ 1.18–1.29 (6H, m), 1.66 (1H, s), 1.81 (2H,

d), 1.88–1.95 (1H, m), 2.17–2.28 (2H, m), 2.31 (2H, dd), 2.46–2.5 (4H, m), 2.53–2.76 (2H, m), 2.82–2.95 (2H, m), 3.32 (3H, s), 3.43 (2H, d), 3.48–3.55 (3H, m), 3.76–3.93 (5H, m), 4.11 (1H, d), 4.23 (1H, d), 4.42 (1H, s), 4.96 (1H, dd), 6.49 (1H, s), 6.61 (1H, s), 6.88 (4H, s), 7.21–7.27 (1H, m), 7.30 (1H, d), 7.85 (1H, d), 10.90 (1H, s); m/z: ES⁺ [M+H]⁺ = 799.4.

5

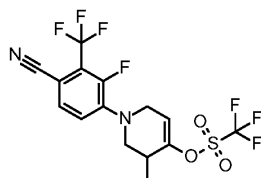
Intermediate 142a: 3-Fluoro-4-(3-methyl-4-oxopiperidin-1-yl)-2-(trifluoromethyl)benzonitrile



- Copper(I) cyanide (1.80 g, 20.12 mmol) was added to 1-bromo-3,4-difluoro-2-(trifluoromethyl)benzene (5.0 g, 19.16 mmol) in NMP (2 mL) and was stirred at 150 °C for 3 h, then cooled to 100 °C. DIPEA (6.69 mL, 38.32 mmol) and 3-methylpiperidin-4-one (2.16 g, 19.16 mmol) were added and stirred for a further 1 h. The reaction was cooled to RT and was diluted with EtOAc (200 mL) and water (200 mL), dried over Na₂SO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 30% EtOAc in Et₂O to give the title compound (3.3 g, 57.4 %) as a white solid; ¹H NMR (CDCl₃): δ 1.12 (3H, d), 2.51 – 2.64 (1H, m), 2.65 – 2.89 (2H, m), 3.04 (1H, t), 3.28 – 3.43 (1H, m), 3.75 – 3.94 (2H, m), 7.14 (1H, t), 7.52 (1H, d).

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Intermediate 142b: 1-[4-Cyano-2-fluoro-3-(trifluoromethyl)phenyl]-3-methyl-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate

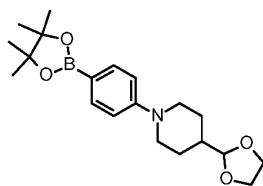


- Lithium bis(trimethylsilyl)amide (15.0 mL, 14.99 mmol) was added to 3-fluoro-4-(3-methyl-4-oxopiperidin-1-yl)-2-(trifluoromethyl)benzonitrile (1.5 g, 5.00 mmol) in THF (30 mL) under nitrogen at -65 °C for 1 h. N-(5-chloropyridin-2-yl)-1,1,1-trifluoro-N-((trifluoromethyl)sulfonyl)methanesulfonamide (3.92 g, 9.99 mmol) was added and continued to stir at -65 °C for 2 h. The reaction mixture was quenched with MeOH and evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% EtOAc in Et₂O to give the title compound (0.410 g, 18.98 %) as a yellow solid; ¹H NMR (CDCl₃): δ 1.30 (3H, t), 2.81 – 2.86 (1H, m), 3.33 (1H, dd), 3.62 (1H, dd), 3.86 – 3.95 (2H, m), 5.76 – 6.08 (1H, m), 7.11 (1H, t), 7.51 – 7.58 (1H, m); m/z: ES⁺ [M+H]⁺ = 433.1.

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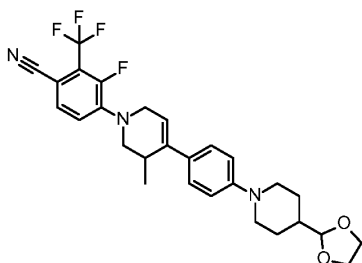
Intermediate 142c: 4-(1,3-Dioxolan-2-yl)-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine

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4-(1,3-Dioxolan-2-yl)piperidine was reacted with 2-(4-bromophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane using the general synthetic method illustrated by intermediate 139f to give the title compound; ^1H NMR (CDCl₃): δ 1.35 (12H, s), 1.50 – 1.64 (2H, m), 1.69 – 1.77 (1H, m), 1.83 – 1.90 (2H, m), 2.77 (2H, t), 3.83 – 3.87 (2H, m), 3.87 – 3.92 (2H, m), 3.92 – 4.02 (2H, m), 4.69 (1H, d), 6.92 (2H, d), 7.71 (2H, d); m/z: ES⁺ [M+H]⁺ = 360.2.

Intermediate 142d: 4-[4-{4-[4-(1,3-Dioxolan-2-yl)piperidin-1-yl]phenyl}-3-methyl-3,6-dihydropyridin-1(2H)-yl]-3-fluoro-2-(trifluoromethyl)benzonitrile



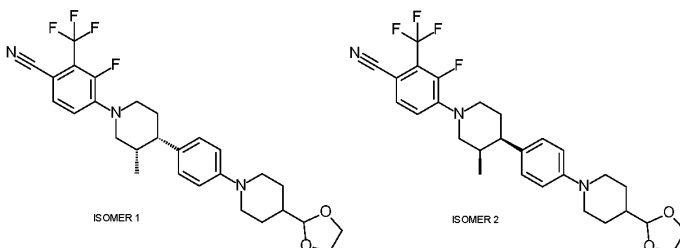
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1-[4-Cyano-2-fluoro-3-(trifluoromethyl)phenyl]-3-methyl-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate was reacted with 4-(1,3-dioxolan-2-yl)-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine using the general synthetic method illustrated by intermediate 92e to give the title compound; ^1H NMR (CDCl₃): δ 1.18 (3H, d), 1.59 – 1.73 (2H, m), 1.83 – 1.93 (3H, m), 2.70 – 2.80 (3H, m), 2.96 – 3.02 (1H, m), 3.34 – 3.46 (1H, m), 3.62 – 3.81 (4H, m), 3.85 – 3.93 (5H, m), 3.95 – 4.03 (2H, m), 4.69 (1H, d), 5.88 (1H, t), 6.90 – 6.96 (2H, m), 7.08 (1H, t), 7.29 (2H, d), 7.48 (1H, d); m/z: ES⁺ [M+H]⁺ = 516.3.

15

Intermediate 143a and intermediate 142e: 4-[(3*S,4*S**)-4-{4-[4-(1,3-dioxolan-2-yl)piperidin-1-yl]phenyl}-3-methylpiperidin-1-yl]-3-fluoro-2-(trifluoromethyl)benzonitrile and 4-[(3*R**,4*R**)-4-{4-[4-(1,3-dioxolan-2-yl)piperidin-1-yl]phenyl}-3-methylpiperidin-1-yl]-3-fluoro-2-(trifluoromethyl)benzonitrile** (absolute stereochemistry not yet confirmed)

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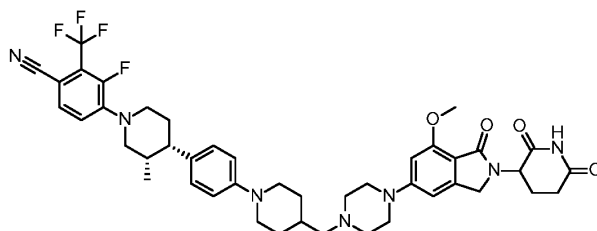


3-Ethenyl-4-fluoro-2-(trifluoromethyl)benzonitrile was reacted with hydrogen gas using the general synthetic method illustrated by intermediate 9b to give the title compound as a racemic mixture which was purified by preparative chiral-HPLC on a Column: CHIRALPAK IF, 2*25 cm, 5 µm; Mobile Phase A: Hex (0.5% 2M NH₃-MeOH), Mobile Phase B: EtOH-HPLC; Flow rate: 15 mL/min; Gradient: 50% B to 50% B in 20 mins to give the title compounds as white solids;

Intermediate 142e (cis-isomer 1) (elutes first): ¹H NMR (CDCl₃): δ 0.76 (3H, d), 1.15 (1H, s), 1.45 (2H, s), 1.73 (3H, dd), 2.06 (1H, s), 2.12 – 2.28 (1H, m), 2.57 (2H, t), 2.78 – 2.95 (2H, m), 3.00 – 3.10 (1H, m), 3.56 (4H, dd), 3.72 – 3.93 (4H, m), 4.59 (1H, d), 6.82 (2H, d), 6.93 – 7.06 (3H, m), 7.38 (1H, d); m/z: ES⁺ [M+H]⁺ = 518.2, >99% ee.

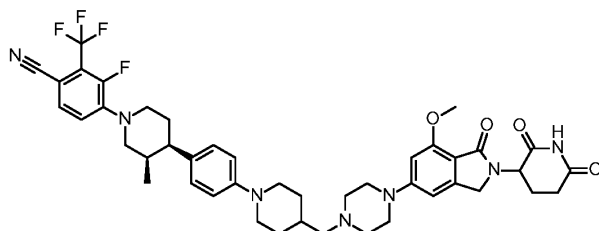
Intermediate 143a (cis-isomer 2): ¹H NMR (CDCl₃): δ 0.76 (3H, d), 1.15 (1H, s), 1.45 (2H, s), 1.56 (2H, d), 1.78 (2H, d), 2.08 – 2.27 (1H, m), 2.57 (2H, t), 2.77 – 2.95 (2H, m), 3.05 (1H, dd), 3.51 (1H, d), 3.61 (3H, d), 3.71 – 3.93 (4H, m), 4.59 (1H, d), 6.82 (2H, d), 6.93 – 7.06 (3H, m), 7.38 (1H, d); m/z: ES⁺ [M+H]⁺ = 518.2, >99% ee.

Example 142: 4-[(3*S,4*S**)-4-{4-[4-({4-[2-(2,6-dioxopiperidin-3-yl)-7-methoxy-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazin-1-yl}methvl)piperidin-1-yl]phenyl}-3-methylpiperidin-1-yl]-3-fluoro-2-(trifluoromethyl)benzonitrile** (absolute stereochemistry not yet confirmed)



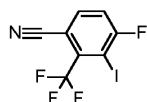
Intermediate 142e was reacted with intermediate 1e using the general synthetic method illustrated by example 137 to give the title compound; ¹H NMR (CDCl₃): δ 0.89 (3H, d), 1.43 (2H, s), 1.93 (2H, s), 2.11 – 2.38 (6H, m), 2.70 (6H, dd), 2.79 – 3.07 (5H, m), 3.18 (1H, d), 3.35 (4H, s), 3.53 – 3.79 (5H, m), 3.96 (3H, s), 4.15 – 4.54 (2H, m), 5.16 (1H, dd), 6.28 – 6.55 (2H, m), 6.95 (2H, d), 7.12 (3H, t), 7.50 (1H, d), 7.96 (1H, s); m/z: ES⁺ [M+H]⁺ = 816.4.

Example 143: 4-[(3*R,4*R**)-4-{4-[4-({4-[2-(2,6-dioxopiperidin-3-yl)-7-methoxy-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperazin-1-yl}methvl)piperidin-1-yl]phenyl}-3-methylpiperidin-1-yl]-3-fluoro-2-(trifluoromethyl)benzonitrile** (absolute stereochemistry not yet confirmed)



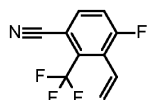
- Intermediate 143a was reacted with intermediate 1e using the general synthetic method illustrated by example 137 to give the title compound; $^1\text{H NMR}$ (CDCl_3): δ 0.89 (3H, d), 1.43 (2H, s), 1.93 (2H, s), 2.09 – 2.46 (6H, m), 2.53 – 2.85 (6H, m), 2.78 – 2.93 (2H, m), 2.87 – 3.10 (3H, m), 3.18 (1H, d), 3.36 (4H, s), 3.59 – 3.75 (5H, m), 3.97 (3H, s), 4.22 (1H, d), 4.39 (1H, d), 5.16 (1H, dd), 6.44 (2H, d), 6.95 (2H, d), 7.12 (3H, t), 7.50 (1H, d), 7.96 (1H, s); m/z : $\text{ES}^+ [\text{M}+\text{H}]^+ = 816.4$.

Intermediate 144a: 4-Fluoro-3-iodo-2-(trifluoromethyl)benzonitrile



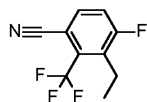
- Lithium diisopropylamide (2.91 mL, 5.82 mmol) was added to 4-fluoro-2-(trifluoromethyl)benzonitrile (1.0 g, 5.29 mmol) in THF (20 mL) and cooled to -78°C over a period of 10 mins under nitrogen. I_2 (1.47 g, 5.82 mmol) was added and the resulting mixture was stirred at -78°C for 1 h. The reaction mixture was quenched with saturated NH_4Cl solution (25 mL), extracted with EtOAc (3 x 25 mL), dried over Na_2SO_4 , filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% EtOAc in Et_2O to give the title compound (1.00 g, 60.0 %) as a yellow solid; $^1\text{H NMR}$ (CDCl_3): δ 7.31 – 7.41 (1H, m), 7.81 – 7.95 (1H, m).

Intermediate 144b: 3-Ethenyl-4-fluoro-2-(trifluoromethyl)benzonitrile

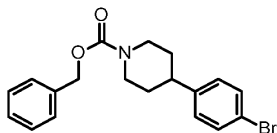


- 4-Fluoro-3-iodo-2-(trifluoromethyl)benzonitrile was reacted with 2-ethenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane using the general synthetic method illustrated by intermediate 35a to give the title compound; $^1\text{H NMR}$ (CDCl_3): δ 5.70 – 5.87 (2H, m), 6.68 (1H, m), 7.40 (1H, t), 7.74 (1H, dd).

Intermediate 144c: 3-Ethyl-4-fluoro-2-(trifluoromethyl)benzonitrile



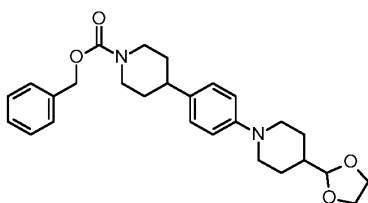
- 3-Ethenyl-4-fluoro-2-(trifluoromethyl)benzonitrile was reacted with hydrogen gas using the general synthetic method illustrated by intermediate 9b to give the title compound; $^1\text{H NMR}$ (CDCl_3): δ 1.23 (3H, t), 2.72 – 2.95 (2H, m), 7.23 – 7.40 (1H, m), 7.71 (1H, dd).

Intermediate 144d: Benzyl 4-(4-bromophenyl)piperidine-1-carboxylate

- 5 Benzyl carbonochloridate (14.27 mL, 96.17 mmol) was added dropwise over 5 mins to a solution of 4-(4-bromophenyl)piperidine (25.0 g, 100.98 mmol) and DIPEA (42.0 mL, 240.43 mmol) in 2-MeTHF (250 mL) at 0 °C. The resulting mixture was stirred at RT for 24 h and then quenched with water (250 mL). The layers were separated and the organic layer was washed with water (250 mL), NaCl solution (50 mL), dried using MgSO₄, filtered and evaporated to afford crude product as a colourless oil. The oil was diluted with IPA:water (1:1, 200 mL) and was stirred at RT for 1 h. The resulting solid was collected by filtration, washed with water (2 x 20 mL) and dried under vacuum at 50 °C for 16 h to give the title compound (32.9 g, 91 %) as a white solid; ¹H NMR δ 1.50 (2H, qd), 1.75 (2H, d), 2.72 (1H, m), 2.90 (2H, s), 4.14 (2H, d), 5.10 (2H, s), 7.18 – 7.26 (2H, m), 7.29 – 7.44 (5H, m), 7.45 – 7.53 (2H, m).
- 10

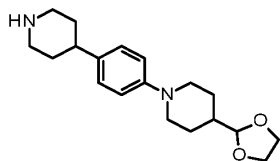
Intermediate 144e: Benzyl 4-{4-[4-(1,3-dioxolan-2-yl)piperidin-1-yl]phenyl}piperidine-1-carboxylate

15



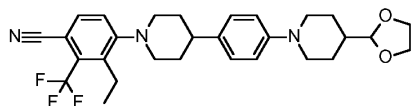
- To 4-(1,3-dioxolan-2-yl)piperidine (15.02 g, 95.52 mmol), benzyl 4-(4-bromophenyl)piperidine-1-carboxylate (32.5 g, 86.83 mmol) and Cs₂CO₃ (56.6 g, 173.67 mmol) in 1,4-dioxane (325 mL) under nitrogen was added tri-*tert*-butylphosphonium tetrafluoroborate (2.52 g, 8.68 mmol). The mixture was degassed with nitrogen followed by addition of Pd(*t*-Bu₃P)₂ (2.21 g, 4.34 mmol). The resulting mixture was stirred at 100 °C for 20 h, cooled to RT and the solid was filtered under vacuum. The solid was washed with 1,4-dioxane (3x 65 mL) and the filtrate was evaporated to afford a pale yellow solid. The solid was suspended in cyclopentyl methyl ether:heptane (1:10, 300 mL), stirred at 50 °C for 30 mins and then left to cool to RT for a further 2 h. The solid was filtered to give the title compound (28.9 g, 73.9 %) as a cream solid; ¹H NMR δ 1.43 (4H, m), 1.57 – 1.67 (1H, m), 1.73 (4H, m), 2.54 – 2.63 (3H, m), 2.89 (2H, s), 3.65 (2H, m), 3.75 – 3.93 (4H, m), 4.13 (2H, m), 4.61 (1H, d), 5.09 (2H, s), 6.85 (2H, m), 7.06 (2H, m), 7.29 – 7.44 (5H, m); *m/z*: ES⁺ [M+H]⁺ = 451.5.
- 20
- 25

Intermediate 144f: 4-(1,3-Dioxolan-2-yl)-1-[4-(piperidin-4-yl)phenyl]piperidine



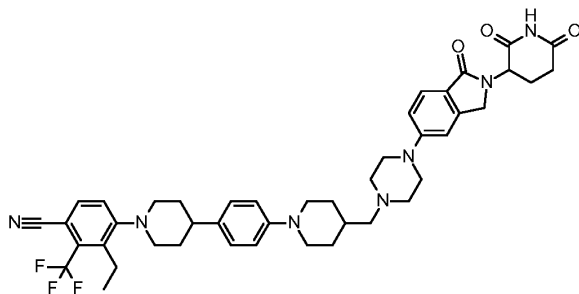
- 5 Benzyl 4-{4-[4-(1,3-dioxolan-2-yl)piperidin-1-yl]phenyl}piperidine-1-carboxylate (762 mg, 1.69 mmol) was dissolved in EtOH (20 mL) and Pd/C (10%, 180 mg, 0.17 mmol) was added under nitrogen. The reaction was stirred under an atmosphere of hydrogen at 4 bar for 16 h. The catalyst was then filtered off through a pad of Celite®, the solvent was removed under reduced pressure and azeotroped with excess MeCN. The product was dried in a vacuum oven for 2 h to give the title compound (449 mg, 84 %) as a waxy white solid; ¹H NMR δ 1.33 – 1.51 (4H, m), 1.54 – 1.68 (3H, m), 1.72 (2H, d), 2.4 – 2.46 (1H, m), 2.54 – 2.64 (4H, m), 3.01 (2H, d), 3.64 (2H, d), 3.74 – 3.94 (4H, m), 4.61 (1H, d), 6.85 (2H, d), 7.04 (2H, d); *m/z*: ES⁺ [M+H]⁺ = 317.7.

10 **Intermediate 144g: 4-(4-{4-[4-(1,3-Dioxolan-2-yl)piperidin-1-yl]phenyl}piperidin-1-yl)-3-ethyl-2-(trifluoromethyl)benzonitrile**



- 15 3-Ethyl-4-fluoro-2-(trifluoromethyl)benzonitrile was reacted with 4-(1,3-dioxolan-2-yl)-1-[4-(piperidin-4-yl)phenyl]piperidine using the general synthetic method illustrated by intermediate 140a to give the title compound; ¹H NMR (CDCl₃): δ 1.10 – 1.74 (8H, m), 1.77 – 2.05 (6H, m), 2.63 (1H, dd), 2.77 – 3.00 (4H, m), 3.15 (2H, d), 3.70 (2H, d), 3.83 – 4.05 (4H, m), 4.69 (1H, d), 6.94 (2H, s), 7.17 (2H, d), 7.37 (1H, d), 7.65 (1H, d); *m/z*: ES⁺ [M+H]⁺ = 514.3.

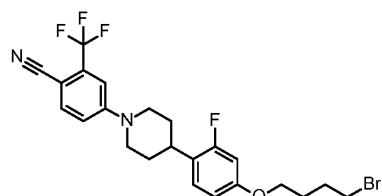
20 **Example 144: 4-(4-{4-[4-(4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl}methyl)piperidin-1-yl]phenyl}piperidin-1-yl)-3-ethyl-2-(trifluoromethyl)benzonitrile**



- 25 4-(4-{4-[4-(1,3-Dioxolan-2-yl)piperidin-1-yl]phenyl}piperidin-1-yl)-3-ethyl-2-(trifluoromethyl)benzonitrile was reacted with intermediate 2b using the general synthetic method illustrated by example 137 to give the title compound; ¹H NMR: δ 1.05 – 1.29 (5H, m), 1.59 – 2.00 (8H, m), 2.20 (2H, d), 2.29 – 2.41 (5H, m), 2.50 – 2.67 (4H, m), 2.79 – 2.92 (5H, m), 3.09 (2H, d), 3.27 (4H, t), 3.61 (2H, d), 4.03 – 4.40 (2H, m), 5.04 (1H,

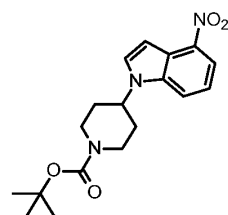
dd), 6.87 (2H, d), 6.99 – 7.15 (4H, m), 7.51 (1H, d), 7.60 (1H, d), 7.92 (1H, d), 10.93 (1H, s); m/z: ES⁺ [M+H]⁺ = 782.0.

Intermediate 145a: 4-{4-[4-(4-Bromobutoxy)-2-fluorophenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile



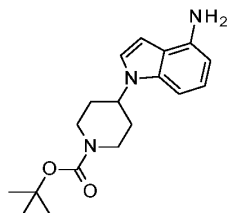
Intermediate 38d (1.0 g, 2.74 mmol), K₂CO₃ (0.759 g, 5.49 mmol) and 1,4-dibromobutane (1.63 mL, 13.72 mmol) were suspended in MeCN (20 mL) and stirred at 70 °C for 6 h. The reaction mixture was cooled to RT and filtered under vacuum. The filtrate was evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 30% EtOAc in heptane to give the title compound (1.03 g, 75 %) as a yellow oil which solidified on standing; ¹H NMR (CDCl₃): δ 1.79 (2H, qd), 1.89 – 2 (4H, m), 2.06 (2H, dtd), 3 – 3.13 (3H, m), 3.48 (2H, t), 3.96 (2H, t), 4.02 (2H, d), 6.56 – 6.67 (2H, m), 6.99 (1H, dd), 7.07 (1H, t), 7.16 (1H, d), 7.56 – 7.68 (1H, m); m/z: ES⁺ [M+H]⁺ = 499.1.

Intermediate 145b: *tert*-Butyl 4-(4-nitro-1*H*-indol-1-yl)piperidine-1-carboxylate



4-Nitro-1*H*-indole (5x 95.0 g, 585 mmol), *tert*-butyl 4-[(methanesulfonyl)oxy]piperidine-1-carboxylate (5x 409.0 g, 1.46 mol) and Cs₂CO₃ (5x 573.0 g, 1.76 mol) were added to DMF (1.5 L). The solution was degassed with nitrogen and stirred at 80 °C for 12 h. Water (10.0 L) was added to each mixture and the batches were combined by extracting with EtOAc (6.0 L). The organic layer was washed with NaCl solution (10.0 L x3) and dried with Na₂SO₄. The solvent was evaporated and the crude product was purified by re-crystallisation from MTBE:Et₂O (1:4, 500.0 mL) at RT for 20 mins. The solid was filtered and dried under vacuum to give the title compound (910.0 g) as a brown solid; ¹H NMR δ 1.39 (s, 9H), 1.82-1.93 (m, 4H), 2.85 (s, 2H), 4.08-4.11 (m, 2H), 4.69-4.75 (m, 1H), 7.02 (d, J = 3.2 Hz, 1H), 7.32 (t, J = 8.4 Hz, 1H), 7.92 (d, J = 3.6 Hz, 1H), 8.05 (d, J = 7.6 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H).

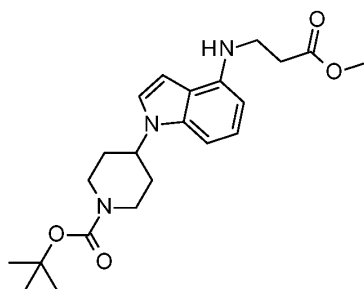
Intermediate 145c: *tert*-Butyl 4-(4-amino-1*H*-indol-1-yl)piperidine-1-carboxylate



5 *tert*-Butyl 4-(4-nitro-1*H*-indol-1-yl)piperidine-1-carboxylate (7x 140.0 g, 405 mmol) was added to 7 separate solutions of Pd/C (20.0 g, 10% purity) in MeOH:THF (1:1, 1.0 L). The solutions were degassed with nitrogen and stirred for 12 h under an atmosphere of hydrogen (30 PSI). The 7 batches were combined by filtering off Pd/C and evaporating the solvent. The resulting solid was used without further purification to give the title compound (770.0 g, 86%) as a brown solid; ¹H NMR δ 1.43 (s, 9H), 1.86-1.98 (m, 4H), 3.46-3.82 (m, 2H), 4.12 (d, J = 10.4 Hz, 2H), 4.59 (t, J = 3.6 Hz, 1H), 5.36 (s, 2H), 6.34 (d, J = 3.2 Hz, 1H), 6.89 (d, J = 7.2 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.56 (t, J = 3.6 Hz, 1H).

10

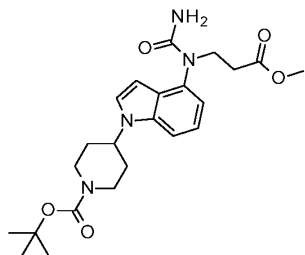
Intermediate 145d: *tert*-Butyl 4-{4-[(3-methoxy-3-oxopropyl)amino]-1*H*-indol-1-yl}piperidine-1-carboxylate



15 *tert*-Butyl 4-(4-amino-1*H*-indol-1-yl)piperidine-1-carboxylate (5x 175.0 g, 555 mmol) was added to 5 separate portions of MeOH (1.2 L). AcOH (5x 499.0 g, 8.32 mol, 476 mL) was added to each mixture followed by methyl acrylate (471.0 g, 5.47 mol, 4923 mL) and was stirred at 80 °C for 18 h. The batches were combined and the solvent was evaporated to afford crude product which was extracted with EtOAc (10.0 L) and washed with NaHCO₃ (15.0 L). The aqueous layer was back extracted with EtOAc (5.0 L x3). The combined organics were washed with NaCl solution and dried with Na₂SO₄. The solvent was evaporated to give the title compound (1.08 kg, crude) as a black oil and was used without further purification; ¹H NMR δ 1.79 (s, 9H), 1.89-1.91 (m, 2H), 1.98 (s, 1H), 2.65 (t, 6.8 Hz, 1H), 2.67 (s, 2H), 3.32-3.42 (m, 1H), 3.51 (s, 1H), 3.61 (s, 2H), 4.02-4.09 (m, 2H), 4.11-4.41 (m, 1H), 6.10 (d, 7.2 Hz, 1H), 6.39-6.54 (m, 1H), 6.78 (d, J = 8.4 Hz, 1H), 6.77-6.89 (m, 1H), 7.23 (s, 1H), 11.89 (s, 1H).

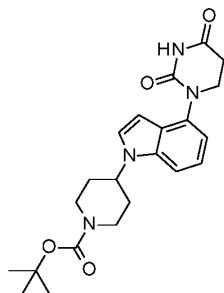
20

25 **Intermediate 145e: *tert*-Butyl 4-{4-[carbamoyl(3-methoxy-3-oxopropyl)amino]-1*H*-indol-1-yl}piperidine-1-carboxylate**



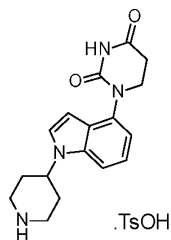
- 5 *tert*-Butyl 4-[(3-methoxy-3-oxopropyl)amino]-1*H*-indol-1-yl}piperidine-1-carboxylate (6x 200 g, 498 mmol) were added to DCM (6x 1.0 L). AcOH (6x 2.1 kg, 34.97 mol, 2.0 L) in DCM (6x 1.0 L) was added to the mixture followed by potassium cyanate (6x 40.4 g, 498 mmol) and stirred at RT for 2 h. The 6 batches
- 10 were combined and water (5.0 L) was added to the mixture. DCM (8 L x2) was added to the extraction which was washed with NaCl solution. The organic layer was dried with Na₂SO₄ and evaporated. The residue was purified by column chromatography, elution gradient 30:1 to 1:1 Et₂O:EtOAc to give the title compound (260.0 g, 19.6%) as a brown solid; ¹H NMR δ 1.82 (s, 9H), 1.93-1.98 (m, 4 H), 2.44-2.50 (m, 2H), 2.98 (s, 2H), 3.46 (s, 3H), 3.84 (s, 2H), 4.66 (d, J = 8.4 Hz, 2H), 4.66-4.78 (m, 1H), 5.36 (s, 2H), 6.34 (d, J = 3.2 Hz, 1H), 6.90 (d, J = 7.6 Hz, 1H), 7.16 (t, J = 8.4 Hz, 1 H), 7.56 (t, J = 4 Hz, 2H).

Intermediate 145f: *tert*-Butyl 4-[4-(2,4-dioxo-1,3-diazinan-1-yl)-1*H*-indol-1-yl]piperidine-1-carboxylate



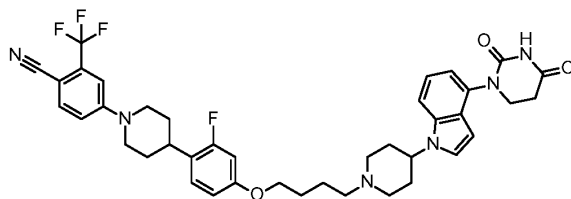
- 15 *tert*-Butyl 4-[4-[carbamoyl(3-methoxy-3-oxopropyl)amino]-1*H*-indol-1-yl}piperidine-1-carboxylate (3x 105.0 g, 236 mmol) in MeOH (3x 779.0 g, 24.3 mol, 3x 984 mL) were added to 3 separate vessels of MeOH (1.0 L) followed by MeONa/MeOH (42.5 g, 236 mmol, 30% purity). The reaction was stirred at RT for 2 h and the combined solids were collected by filtration. The filtrate was evaporated and purified by column chromatography, elution gradient 10:1 DCM:MeOH to give the title compound (180 g, 70.7%) as a white solid; ¹H NMR δ 1.43 (s, 9H), 1.92-1.81 (m, 4H), 2.75 (t, J = 6.8 Hz, 2H), 2.75 (s, 2H), 3.37-3.77 (m, 2H), 4.12 (d, J = 5.6 Hz, 2H), 4.59-4.60 (m, 1H), 6.41 (d, J = 3.2 Hz, 1 H), 6.96 (d, J = 7.6 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.52-7.54 (m, 2 H), 10.3 (s, 1H).
- 20

Intermediate 145g: 1-[1-(Piperidin-4-yl)-1*H*-indol-4-yl]-1,3-diazinane-2,4-dione TsOH



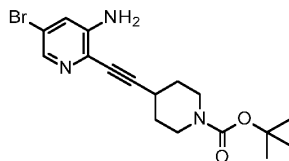
- tert*-Butyl 4-[4-(2,4-dioxo-1,3-diazinan-1-yl)-1*H*-indol-1-yl]piperidine-1-carboxylate (140.0 g, 339.41 mmol) in a solution of MeCN (300 mL) was added to *p*-toluenesulfonic acid hydrate (82.6 g, 434 mmol) in MeCN (560 mL) dropwise at RT. The reaction was stirred at 60 °C for 1 h. Additional *p*-toluenesulfonic acid hydrate (6.46 g, 33.9 mmol) was added to the mixture and stirred continued at 60 °C for a further 1 h. The reaction was then filtered and dried under vacuum to give the title compound (120.0 g, 70.8%) as a grey solid; ¹H NMR: δ 2.06-2.16 (m, 4H), 2.29 (s, 3H), 2.76 (t, *J* = 6.8 Hz, 2H), 3.19-3.45 (m, 2H), 3.45-3.48 (m, 3H), 3.77 (t, *J* = 6.4 Hz, 2H), 4.42-4.79 (m, 1H), 6.46 (d, *J* = 3.2 Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 7.10 (d, *J* = 44.0 Hz, 2H), 7.14 (t, *J* = 14.0 Hz, 1H), 7.40 (d, *J* = 3.6 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1 H), 7.56 (d, *J* = 8.4 Hz, 2H), 8.41(d, *J* = 10.0 Hz, 1H), 8.68 (d, *J* = 10.0 Hz, 1 H), 10.3 (s, 1H); *m/z*: ES⁺ [M+H]⁺ = 313.1.

Example 145: 4-{4-[4-(4-{4-[4-(2,4-Dioxo-1,3-diazinan-1-yl)-1*H*-indol-1-yl]piperidin-1-yl]butoxy)-2-fluorophenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile



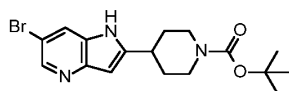
- 1-[1-(Piperidin-4-yl)-1*H*-indol-4-yl]-1,3-diazinane-2,4-dione TsOH (0.040 g, 0.13 mmol), 4-{4-[4-(4-bromobutoxy)-2-fluorophenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile (0.067 g, 0.13 mmol), potassium iodide (0.043 g, 0.26 mmol) and DIPEA (0.089 mL, 0.51 mmol) were dissolved in MeCN (2 mL) and stirred at 80 °C for 4h. The reaction mixture was cooled to RT, filtered under vacuum and the filtrate was evaporated to dryness to afford crude product. The crude product was purified by preparative HPLC (Column A, Eluent A) to give the title compound (0.03 g, 32.1 %) as a yellow solid; ¹H NMR: δ 1.62 – 1.87 (8H, m), 2.04 – 2.21 (4H, m), 2.61 (1H, s), 2.77 (2H, t), 3.01 – 3.15 (4H, m), 3.33 – 3.47 (4H, m), 3.78 (2H, t), 4.03 (2H, s), 4.19 (2H, d), 4.59 (1H, s), 6.45 (1H, d), 6.7 – 6.89 (2H, m), 6.99 (1H, d), 7.20 (2H, dt), 7.27 (1H, dd), 7.33 (1H, d), 7.43 – 7.56 (2H, m), 7.83 (1H, d), 10.33 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 731.4.

- Intermediate 146a: *tert*-Butyl 4-[(3-amino-5-bromopyridin-2-yl)ethynyl]piperidine-1-carboxylate**



- Tetrakis(triphenylphosphine)palladium(0) (1.39 g, 1.20 mmol) was added to 5-bromo-2-iodopyridin-3-amine (3.0 g, 10.04 mmol), *tert*-butyl 4-ethynylpiperidine-1-carboxylate (2.1 g, 10.04 mmol) and copper(I) iodide (0.229 g, 1.20 mmol) in triethylamine (17 mL) at RT under nitrogen. The mixture was stirred at 80 °C for 16 h, cooled to RT and the solvent was evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% EtOAc in DCM to give the title compound (3.0 g, 79 %) as a yellow solid; ¹H NMR (CDCl₃) δ 1.46 (9H, s), 1.70 (2H, m), 1.90 (2H, m), 2.86 (1H, tt), 3.19 (2H, m), 3.72–3.85 (2H, m), 4.33 (2H, s), 7.17 (1H, d), 7.98 (1H, d); *m/z*: ES⁺ [M+H]⁺ = 380.0.

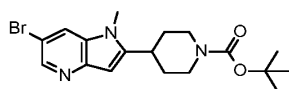
10 Intermediate 146b: *tert*-Butyl 4-(6-bromo-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl)piperidine-1-carboxylate



- Dichlorobis(MeCN)palladium(II) (0.409 g, 1.58 mmol) was added to *tert*-butyl 4-[(3-amino-5-bromopyridin-2-yl)ethynyl]piperidine-1-carboxylate (3.0 g, 7.89 mmol) in DMF (30 mL) at RT under nitrogen. The resulting mixture was stirred at 120 °C for 16 h and then cooled to RT. The reaction mixture was diluted with EtOAc (75 mL), washed with NaHCO₃ solution (100 mL), dried over Na₂SO₄, filtered and evaporated to afford crude product. The crude product was purified by flash alumina chromatography, elution gradient 0 to 50% EtOAc in Et₂O to give the title compound (1.5 g, 50.0 %) as a yellow oil; ¹H NMR δ 1.42 (9H, s), 1.96 (2H, d), 2.73 (2H, s), 2.89 (2H, s), 4.02–4.1 (3H, m), 6.35 (1H, s), 7.85 (1H, s), 8.30 (1H, s), 11.41 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 380.0.

20

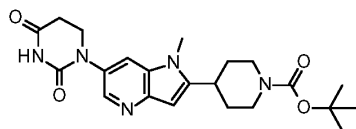
Intermediate 146c: *tert*-Butyl 4-(6-bromo-1-methyl-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl)piperidine-1-carboxylate



- Sodium hydride (60 % in mineral oil, 0.22 g, 5.52 mmol) was added to *tert*-butyl 4-(6-bromo-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl)piperidine-1-carboxylate (1.4 g, 3.68 mmol) in DMF (15 mL) at 0 °C under nitrogen. Iodomethane (0.229 mL, 3.68 mmol) was added after 15 mins. The resulting mixture was stirred at RT for 2 h. The reaction mixture was quenched with water (1 mL) and diluted with EtOAc (50 mL). The organic layer was washed with water (150 mL), dried over Na₂SO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% EtOAc in DCM to give the title compound (0.62 g, 42.7 %) as a yellow solid; ¹H NMR (CDCl₃) δ 1.50 (9H, d), 1.64–1.78 (2H, m), 1.99 (2H, d), 2.84–2.94 (3H, m), 3.72 (3H, d), 4.30 (2H, s), 6.46 (1H, s), 7.74 (1H, s), 8.45 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 394.0.

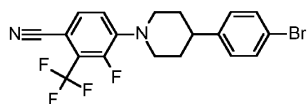
30

Intermediate 146d: *tert*-Butyl 4-[6-(2,4-dioxo-1,3-diazinan-1-yl)-1-methyl-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl]piperidine-1-carboxylate



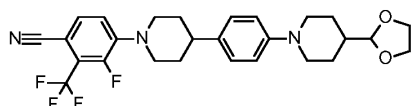
- 5 Ephos Pd G4 (280 mg, 0.30 mmol) was added to *tert*-butyl 4-(6-bromo-1-methyl-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl)piperidine-1-carboxylate (600 mg, 1.52 mmol), Cs₂CO₃ (992 mg, 3.04 mmol), Ephos (163 mg, 0.30 mmol) and 1,3-diazinane-2,4-dione (521 mg, 4.56 mmol) in 1,4-dioxane (8 mL) under nitrogen. The mixture was stirred at 100 °C for 2 h, cooled to RT and evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 4 % MeOH in DCM to give the title compound (400 mg, 61.5 %) as a red solid; ¹H NMR δ 1.43 (9H, s), 1.96 (2H, d), 2.77 (2H, t), 3.33 (5H, s), 3.83 (2H, t), 5.76 (1H, s), 6.40 (1H, s), 8.25 (1H, d), 10.42 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 428.3.
- 10

Intermediate 146e: 4-[4-(4-Bromophenyl)piperidin-1-yl]-3-fluoro-2-(trifluoromethyl)benzonitrile



- 15 1-Bromo-3,4-difluoro-2-(trifluoromethyl)benzene was reacted with 1-bromo-3,4-difluoro-2-(trifluoromethyl)benzene and copper cyanide using the general synthetic method illustrated by intermediate 137f to give the title compound; ¹H NMR: δ 1.76 (2H, qd), 1.84 – 1.92 (2H, m), 2.78 (1H, tt), 2.98 – 3.10 (2H, m), 3.68 – 3.77 (2H, m), 7.22 – 7.30 (2H, m), 7.42 – 7.54 (3H, m), 7.81 (1H, d); *m/z*: ES⁺ [M+H]⁺ = 427.1.

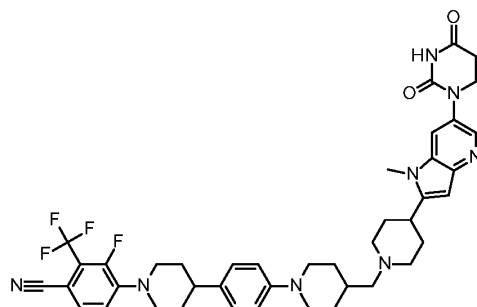
20 **Intermediate 146f: 4-(4-[4-[4-(1,3-Dioxolan-2-yl)piperidin-1-yl]phenyl]piperidin-1-yl)-3-fluoro-2-(trifluoromethyl)benzonitrile**



- 4-[4-(4-Bromophenyl)piperidin-1-yl]-3-fluoro-2-(trifluoromethyl)benzonitrile was reacted with 4-(1,3-dioxolan-2-yl)piperidine using the general synthetic method illustrated by intermediate 139f to give the title compound; ¹H NMR: δ 1.27 – 1.47 (2H, m), 1.52 – 1.68 (1H, m), 1.65 – 1.78 (4H, m), 1.78 – 1.88 (2H, m), 2.49 – 2.71 (3H, m), 2.94 – 3.08 (2H, m), 3.60 – 3.73 (4H, m), 3.74 – 3.89 (4H, m), 4.59 (1H, d), 6.80 – 6.89 (2H, m), 7.04 – 7.13 (2H, m), 7.44 (1H, t), 7.78 (1H, d); *m/z*: ES⁺ [M+H]⁺ = 504.3.
- 25

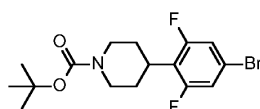
Example 146: 4-(4-[4-[4-(4-[6-(2,4-Dioxo-1,3-diazinan-1-yl)-1-methyl-1*H*-pyrrolo[3,2-*b*]pyridin-2-

- 30 **yl]piperidin-1-yl]methyl]piperidin-1-yl]phenyl]piperidin-1-yl)-3-fluoro-2-(trifluoromethyl)benzonitrile**



- 4-(4-{4-[4-(1,3-Dioxolan-2-yl)piperidin-1-yl]phenyl}piperidin-1-yl)-3-fluoro-2-(trifluoromethyl)benzonitrile (100 mg, 0.20 mmol) was added to *tert*-butyl 4-[6-(2,4-dioxo-1,3-diazinan-1-yl)-1-methyl-1*H*-pyrrolo[3,2-
 5 b]pyridin-2-yl]piperidine-1-carboxylate (85 mg, 0.20 mmol) in formic acid (2 mL) at 60 °C over a period of 1 h. The solvent was evaporated to afford a residue. The residue diluted with NMP (2 mL) and stirred at RT for 16 h. The reaction mixture was diluted with DCM (10 mL), washed with saturated NaHCO₃ solution (20 mL), saturated brine (10 mL), dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 11% MeOH in DCM and then purified by preparative TLC (DCM:MeOH, 10:1) to give the title compound (0.065 g, 42 %) as a white solid; ¹H NMR (100 °C): δ 1.17 – 1.32 (2H, m), 1.61 – 1.76 (5H, m), 1.76 – 1.96 (6H, m), 2.08 – 2.26 (4H, m), 2.60 – 2.86 (6H, m), 2.90 – 2.99 (4H, m), 3.05 (2H, td), 3.58 (2H, dt), 3.69 (2H, s), 3.73 (1H, t), 3.80 (2H, t), 6.34 (1H, s), 6.80 – 6.88 (2H, m), 7.04 – 7.11 (2H, m), 7.39 (1H, t), 7.65 – 7.74 (2H, m), 8.22 (1H, d), 9.96 (1H, s); m/z: ES⁺ [M+H]⁺ = 771.3.

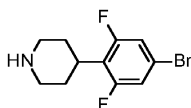
15 **Intermediate 147a: *tert*-Butyl 4-(4-bromo-2,6-difluorophenyl)piperidine-1-carboxylate**



Intermediate 138a was reacted with hydrogen gas using the general synthetic method illustrated by intermediate 137c to give the title compound; ¹H NMR (CDCl₃): δ 1.48 (9H, s), 1.65 (2H, d), 1.98 (2H, qd), 2.76 (2H, s), 3.08 (1H, qt), 4.23 (2H, s), 7 – 7.09 (2H, m).

20

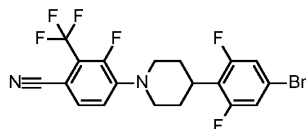
Intermediate 147b: 4-(4-Bromo-2,6-difluorophenyl)piperidine



tert-Butyl 4-(4-bromo-2,6-difluorophenyl)piperidine-1-carboxylate was reacted with HCl using the general synthetic method illustrated by intermediate 24d to give the title compound; ¹H NMR: δ 1.83 (2H, d), 2.16 (2H, q), 3.01 (2H, q), 3.25 (1H, td), 3.31 (2H, s), 7.41 – 7.52 (2H, m), 8.86 (1H, s); m/z: ES⁺ [M+H]⁺ = 276.0.

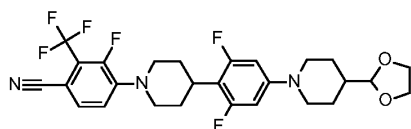
25

Intermediate 147c: 4-[4-(4-Bromo-2,6-difluorophenyl)piperidin-1-yl]-3-fluoro-2-(trifluoromethyl)benzonitrile



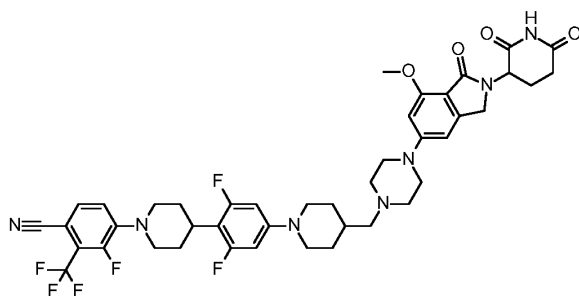
- 5 4-(4-Bromo-2,6-difluorophenyl)piperidine was reacted with 4-(4-bromophenyl)piperidine and copper cyanide using the general synthetic method illustrated by example 137d to give the title compound; ^1H NMR (CDCl_3): δ 1.78 – 1.91 (2H, m), 2.30 (2H, td), 2.98 (2H, t), 3.19 (1H, dt), 3.69 – 3.83 (2H, m), 7.02 – 7.17 (3H, m), 7.49 (1H, d); m/z: ES^+ $[\text{M}+\text{H}]^+ = 463.0$.

10 **Intermediate 147d: 4-(4-{4-[4-(1,3-Dioxolan-2-yl)piperidin-1-yl]-2,6-difluorophenyl}piperidin-1-yl)-3-fluoro-2-(trifluoromethyl)benzonitrile**



- 15 4-[4-(4-Bromo-2,6-difluorophenyl)piperidin-1-yl]-3-fluoro-2-(trifluoromethyl)benzonitrile was reacted with 4-(1,3-dioxolan-2-yl)piperidine using the general synthetic method illustrated by intermediate 139f to give the title compound; ^1H NMR (CDCl_3): δ 1.50 (2H, qd), 1.67 – 1.88 (5H, m), 2.25 (2H, qd), 2.72 (2H, td), 2.97 (2H, t), 3.07 (1H, tt), 3.6 – 3.79 (4H, m), 3.79 – 4.02 (4H, m), 4.67 (1H, d), 6.26 – 6.5 (2H, m), 7.11 (1H, t), 7.48 (1H, d); m/z: ES^+ $[\text{M}+\text{H}]^+ = 540.2$.

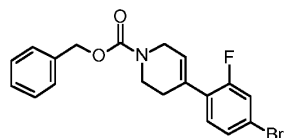
20 **Example 147: 4-(4-{4-[4-(4-[2-(2,6-Dioxopiperidin-3-yl)-7-methoxy-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl]methyl}piperidin-1-yl)-2,6-difluorophenyl}piperidin-1-yl)-3-fluoro-2-(trifluoromethyl)benzonitrile**



- 25 4-(4-{4-[4-(1,3-Dioxolan-2-yl)piperidin-1-yl]-2,6-difluorophenyl}piperidin-1-yl)-3-fluoro-2-(trifluoromethyl)benzonitrile was reacted with intermediate 1e using the general synthetic method illustrated by example 138 and purified by preparative HPLC (Column A, Eluent D) to give the title compound; ^1H NMR: δ 1.16 (2H, d), 1.71 – 1.82 (5H, m), 1.88 – 1.97 (1H, m), 2.06 (2H, d), 2.21 (2H, d), 2.26 – 2.33 (1H, m), 2.52 – 2.53 (4H, m), 2.57 (1H, d), 2.73 (2H, d), 2.82 – 2.96 (1H, m), 3.04 (3H, t), 3.37 (4H, s), 3.64 – 3.77

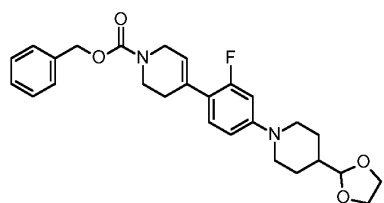
(4H, m), 3.84 (3H, s), 4.11 (1H, d), 4.24 (1H, d), 4.97 (1H, dd), 6.49 (1H, s), 6.54 – 6.64 (3H, m), 7.46 (1H, t), 7.81 (1H, d), 10.90 (1H, s); m/z: ES⁺ [M+H]⁺ = 838.4.

Intermediate 148a: Benzyl 4-(4-bromo-2-fluorophenyl)-3,6-dihydropyridine-1(2H)-carboxylate



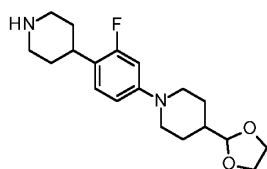
5
4-Bromo-2-fluoro-1-iodobenzene was reacted with benzyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate using the general synthetic method illustrated by intermediate 35a to give the title compound; ¹H NMR: δ 2.11 (2H, dt), 3.42 (2H, s), 3.96 (2H, s), 4.08 (2H, s), 5.10 (4H, d), 5.76 (1H, s), 6.03 (2H, s), 6.40 (1H, s), 7.54 (1H, dd); m/z: ES⁺ [M+H]⁺ = 390.1.

Intermediate 148b: Benzyl 4-{4-[4-(1,3-dioxolan-2-yl)piperidin-1-yl]-2-fluorophenyl}-3,6-dihydropyridine-1(2H)-carboxylate



15
Pd-PEPPSI-IHep^{Cl} (0.312 g, 0.32 mmol) was added to benzyl 4-(4-bromo-2-fluorophenyl)-3,6-dihydropyridine-1(2H)-carboxylate (2.5 g, 6.41 mmol), 4-(1,3-dioxolan-2-yl)piperidine (1.1 g, 7.05 mmol) and Cs₂CO₃ (5.2 g, 16.02 mmol) in dioxane (50 mL) under nitrogen and stirred at 80 °C for 24h. The reaction was cooled to RT and the solvent was evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 35% EtOAc in Et₂O followed by 0 to 10% EtOAc in DCM to give the title compound (0.950 g, 31.8 %) as a yellow solid; ¹H NMR: δ 1.28 – 1.42 (2H, m), 1.61 – 1.75 (3H, m), 2.22 – 2.26 (1H, m), 2.35 – 2.43 (1H, m), 2.67 (2H, td), 3.58 (2H, s), 3.70 (1H, t), 3.71 – 3.83 (4H, m), 3.80 – 3.92 (2H, m), 4.59 (1H, d), 5.04 – 5.15 (3H, m), 5.88 (1H, s), 6.64 – 6.75 (2H, m), 7.14 (1H, t), 7.37 – 7.40 (5H, m); m/z: ES⁺ [M+H]⁺ = 467.3.

Intermediate 148c: 4-(1,3-Dioxolan-2-yl)-1-[3-fluoro-4-(piperidin-4-yl)phenyl]piperidine

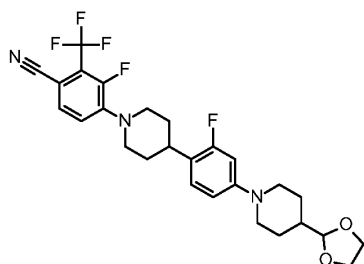


25
Benzyl 4-{4-[4-(1,3-dioxolan-2-yl)piperidin-1-yl]-2-fluorophenyl}-3,6-dihydropyridine-1(2H)-carboxylate was reacted with hydrogen gas using the general synthetic method illustrated by intermediate 9b to give the title compound; ¹H NMR: δ 1.08 – 1.27 (1H, m), 1.28 – 1.42 (2H, m), 1.42 – 1.67 (4H, m), 1.70 (2H, d), 2.24

(1H, t), 2.52 – 2.66 (3H, m), 2.62 – 2.76 (1H, m), 2.87 – 3.02 (2H, m), 3.20 – 3.56 (2H, m), 3.69 (2H, d), 3.73 – 3.92 (4H, m), 4.60 (1H, d), 6.60 – 6.72 (2H, m), 7.06 (1H, t); m/z: ES⁺ [M+H]⁺ = 335.3.

Intermediate 148d: 4-(4-{4-[4-(1,3-Dioxolan-2-yl)piperidin-1-yl]-2-fluorophenyl}piperidin-1-yl)-3-fluoro-2-(trifluoromethyl)benzonitrile

5

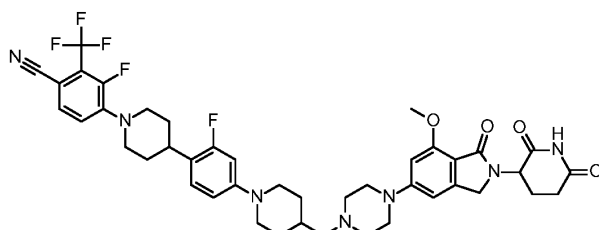


4-(1,3-Dioxolan-2-yl)-1-[3-fluoro-4-(piperidin-4-yl)phenyl]piperidine was reacted with 1-bromo-3,4-difluoro-2-(trifluoromethyl)benzene and copper cyanide using the general synthetic method illustrated by example 137f to give the title compound; ¹H NMR: δ 1.27 – 1.43 (2H, m), 1.61 – 1.75 (3H, m), 1.77 – 1.84 (4H, m), 2.58 – 2.68 (2H, m), 2.88 – 2.96 (1H, m), 3.03 – 3.07 (2H, m), 3.74 (4H, dd), 3.75 – 3.84 (2H, m), 3.84 – 3.91 (2H, m), 4.60 (1H, d), 6.62 – 6.74 (2H, m), 7.13 (1H, t), 7.45 (1H, t), 7.81 (1H, d); m/z: ES⁺ [M+H]⁺ = 522.2.

10

Example 148: 4-(4-{4-[4-(1,3-Dioxolan-2-yl)piperidin-1-yl]-2-fluorophenyl}piperidin-1-yl)-3-fluoro-2-(trifluoromethyl)benzonitrile

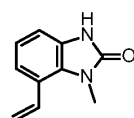
15



4-(4-{4-[4-(1,3-Dioxolan-2-yl)piperidin-1-yl]-2-fluorophenyl}piperidin-1-yl)-3-fluoro-2-(trifluoromethyl)benzonitrile was reacted with intermediate 1e using the general synthetic method illustrated by example 146 to give the title compound; ¹H NMR: δ 1.18 – 1.27 (2H, m), 1.72 – 1.82 (8H, m), 1.91 (1H, s), 2.20 (2H, d), 2.25 – 2.36 (1H, m), 2.56 – 2.64 (2H, m), 2.70 (1H, dd), 2.77 – 2.96 (2H, m), 3.00 – 3.06 (2H, m), 3.30 (8H, s), 3.61 – 3.74 (4H, m), 3.82 (3H, s), 4.15 (2H, q), 4.94 (1H, dd), 6.47 (1H, s), 6.59 (1H, s), 6.62 – 6.73 (2H, m), 7.12 (1H, t), 7.44 (1H, t), 7.79 (1H, d), 10.88 (1H, s); m/z: ES⁺ [M+H]⁺ = 820.4.

20

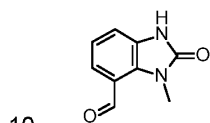
Intermediate 149a: 7-Ethenyl-1-methyl-1,3-dihydro-2H-benzimidazol-2-one



25

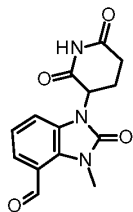
- 5 Pd(dppf)₂Cl₂-DCM (0.575 g, 0.70 mmol) was added to 7-bromo-1-methyl-1,3-dihydro-2H-benzimidazol-2-one (2.0 g, 8.81 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (2.03 g, 13.21 mmol) and K₂CO₃ (3.04 g, 22.02 mmol) in 1,4-dioxane:water (4:1, 48 mL) under nitrogen. The resulting mixture was stirred at 80 °C for 18 h. The reaction was cooled to RT and evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% EtOAc in Et₂O to give the title compound (1.1 g, 71.7 %) as a white solid; ¹H NMR δ 3.36 (3H, s), 5.24 (1H, dd), 5.57 (1H, dd), 6.74 – 6.94 (2H, m), 7.00 (1H, m), 7.26 (1H, dd), 10.80 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 175.2.

Intermediate 149b: 3-Methyl-2-oxo-2,3-dihydro-1H-benzimidazole-4-carbaldehyde



- 15 Potassium osmate dihydrate (0.212 g, 0.57 mmol) was added to 7-ethenyl-1-methyl-1,3-dihydro-2H-benzimidazol-2-one (1.0 g, 5.74 mmol), sodium meta periodate (3.68 g, 17.22 mmol) and 2,6-lutidine (1.33 mL, 11.48 mmol) in 1,4-dioxane:water (3:1, 40 mL) at RT and stirred for 2 h. The reaction mixture was quenched with water (100 mL), extracted with EtOAc (3 x 100 mL), dried over Na₂SO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 4% MeOH in DCM to give the title compound (0.95 g, 94 %) as a grey solid; ¹H NMR δ 3.58 (3H, s), 7.11 (1H, t), 7.19 – 7.28 (1H, m), 7.51 (1H, dd), 10.34 (1H, s), 11.30 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 177.2.

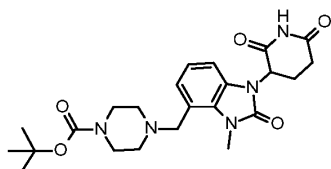
- 20 **Intermediate 149c: 1-(2,6-Dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-4-carbaldehyde**



- 25 LHMDS (153 mL, 153.26 mmol) was added to 3-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-4-carbaldehyde (9.0 g, 51.09 mmol) in THF (80 mL) at 0 °C under nitrogen. The resulting mixture was stirred at RT for 1h. This mixture was added dropwise to a solution of 3-bromopiperidine-2,6-dione (19.62 g, 102.17 mmol) in THF (80 mL) at RT. The mixture was stirred at 60 °C for 3 h, then was cooled to 10 °C and quenched with saturated NH₄Cl solution (20 mL), water (200 mL) and the resulting solid was collected by filtration. The solid was washed with water (50 mL) and EtOAc (50 mL). The aqueous was extracted with EtOAc (300 mL) and the solvent was evaporated to afford a brown solid. The brown solid was triturated with water to give a solid which was collected by filtration and dried under vacuum to give crude product. The two solid batches were combined, triturated with Et₂O, collected by filtration and dried under vacuum to give the

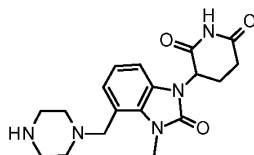
title compound (10.0 g, 68.1 %) as a grey solid; ^1H NMR δ 2.64 (2H, d), 2.89 (2H, d), 3.54 (3H, s), 5.39 – 5.48 (1H, m), 7.07 (1H, d), 7.13 (1H, t), 7.27 (1H, d), 9.27 (1H, s), 10.41 (1H, s); m/z : ES^+ $[\text{M}+\text{H}]^+ = 288.2$.

Intermediate 149d: *tert*-Butyl 4-([1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-4-yl]methyl)piperazine-1-carboxylate



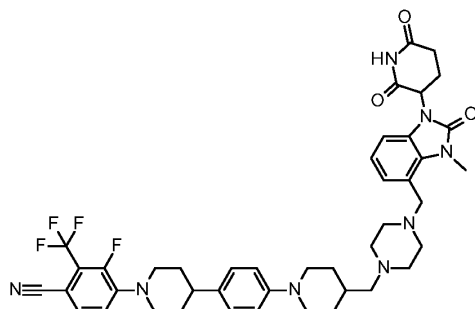
Sodium triacetoxyborohydride (3.69 g, 17.40 mmol) was added to 1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazole-4-carbaldehyde (2.0 g, 3.48 mmol) and *tert*-butyl piperazine-1-carboxylate (1.94 g, 10.44 mmol) in DCM:MeOH (1:2, 24 mL) and stirred at RT for 16 h. The solvent was reduced in volume, poured into NaCl Solution (25 mL), extracted with EtOAc (300 mL) and the layers were separated. The organic layer was dried over Na_2SO_4 , filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 50 to 100% EtOAc in Et_2O to give the title compound (0.800 g, 50.2 %) as a yellow solid; ^1H NMR δ 1.40 (9H, s), 1.95 – 2.08 (1H, m), 2.29 – 2.41 (4H, m), 2.56 – 2.95 (3H, m), 3.24 – 3.32 (4H, m), 3.59 – 3.65 (2H, m), 3.68 (3H, s), 5.30 – 5.44 (1H, m), 6.86 – 6.93 (1H, m), 6.94 – 7.01 (1H, m), 7.06 – 7.12 (1H, m), 11.11 (1H, s); m/z : ES^+ $[\text{M}+\text{H}]^+ = 458.3$.

Intermediate 149e: 3-{3-Methyl-2-oxo-4-[(piperazin-1-yl)methyl]-2,3-dihydro-1H-benzimidazol-1-yl}piperidine-2,6-dione



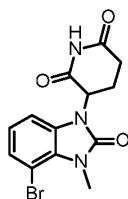
TFA (2.5 mL) was added to *tert*-butyl 4-([1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-4-yl]methyl)piperazine-1-carboxylate (750 mg, 1.64 mmol) in DCM (10 mL) and stirred at RT for 1 h. The solvent was evaporated to give the title compound (1.1 g, 96 %) as yellow oil which was used without further purification; ^1H NMR δ 1.92 – 2.06 (2H, m), 2.62 – 2.94 (9H, m), 3.65 (3H, s), 3.83 – 4.13 (3H, m), 5.36 – 5.45 (1H, m), 6.96 – 7.02 (2H, m), 7.15 (1H, d), 11.11 (1H, s); m/z : ES^+ $[\text{M}+\text{H}]^+ = 358.2$.

Example 149: 4-[4-(4-{4-([1-(2,6-Dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-4-yl]methyl)piperazin-1-yl)methyl}piperidin-1-yl)phenyl]piperidin-1-yl]-3-fluoro-2-(trifluoromethyl)benzonitrile



- 3-{3-Methyl-2-oxo-4-[(piperazin-1-yl)methyl]-2,3-dihydro-1H-benzimidazol-1-yl}piperidine-2,6-dione was reacted with intermediate 146f using the general synthetic method illustrated by example 138 to give the title compound; ^1H NMR (CDCl_3): δ 1.44 (2H, qd), 1.75 – 2.04 (8H, m), 2.13 – 2.28 (1H, m), 2.58 – 3.12 (17H, m), 3.55 – 3.84 (9H, m), 5.22 (1H, dd), 6.79 (1H, d), 6.86 – 6.93 (3H, m), 6.94 – 7 (1H, m), 7.07 – 7.16 (3H, m), 7.48 (1H, d), 8.38 (1H, s); m/z : $\text{ES}^+ [\text{M}+\text{H}]^+ = 801.5$.

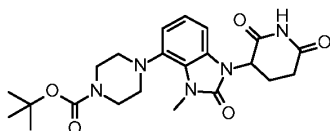
Intermediate 150a: 3-(4-Bromo-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidine-2,6-dione



- 10 Lithium bis(trimethylsilyl)amide (1M in THF, 11.01 mL, 11.01 mmol) was added dropwise over 5 mins to a suspension of 7-bromo-1-methyl-1,3-dihydro-2H-benzimidazol-2-one (1.0 g, 4.40 mmol) in THF (5.00 mL) at RT under nitrogen for 20 minutes at RT. This solution was then added portionwise over 5 mins to a separate flask containing a solution of 3-bromopiperidine-2,6-dione (1.78 g, 8.81 mmol) in THF (10 mL) and was stirred at 60 °C for 4 h. The reaction was cooled to RT and was diluted with saturated NH_4Cl solution (10 mL), water (10 mL), saturated brine solution (5 mL), dried with MgSO_4 and was evaporated to dryness to afford crude product. The crude product was triturated with IPA:Heptane (1:1 20 mL) and was heated to 50 °C for 30 mins. The mixture was cooled to RT and filtered under vacuum to give the title compound (743 mg, 50 %)
- 15 as a grey solid; ^1H NMR (CDCl_3): δ 2.23 (1H, m), 2.67 – 3 (3H, m), 3.79 (3H, s), 5.19 (1H, dd), 6.73 (1H, dd), 6.92 (1H, t), 7.24 (1H, dd), 8.08 (1H, s); m/z : $\text{ES}^+ [\text{M}+\text{H}]^+ = 338.0$.

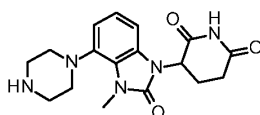
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Intermediate 150b: *tert*-Butyl 4-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-4-yl]piperazine-1-carboxylate



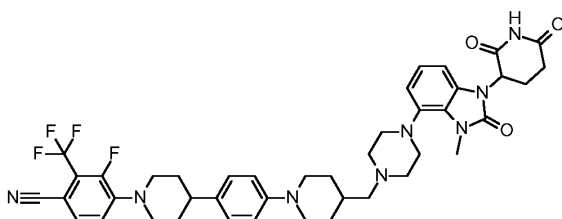
3-(4-Bromo-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidine-2,6-dione (2.21 g, 6.55 mmol), Pd-PEPPSI-IPent (0.550 g, 0.65 mmol), *tert*-butyl piperazine-1-carboxylate (3.05 g, 16.37 mmol) and sodium *tert*-butoxide (1.88 g, 19.64 mmol) were suspended in 1,4-dioxane (60 mL) under nitrogen. The reaction was stirred at 50 °C for 1 h. The reaction was cooled to RT, diluted with DCM (100 mL), washed with NH₄Cl solution (50 mL), water (50 mL), NaHCO₃ solution (50 mL) and NaCl solution (50 mL). The organic layer was dried with Na₂SO₄, filtered and evaporated to afford crude product. The crude product was triturated with Hexane:EtOAc (1:1, 100 mL) and filtered under vacuum. The solid was then slurried in EtOH (50 mL) for 20 mins, filtered under vacuum and then slurried in MeCN (50 mL). The solid was filtered under vacuum to give the title compound (1.48 g, 51.2 %) as a beige solid; ¹H NMR: δ 1.42 (9H, s), 1.98 (1H, br t), 2.56 - 2.76 (4H, m), 2.79 - 2.96 (2H, m), 2.96 - 3.20 (4H, m), 3.62 (3H, s), 3.94 (1H, br s), 5.30 - 5.40 (1H, m), 6.88 - 6.94 (2H, m), 6.94 - 7.00 (1H, m), 11.09 (1H, br s); *m/z*: ES⁺ [M+Na] = 466.1.

Intermediate 150c: 3-[3-Methyl-2-oxo-4-(piperazin-1-yl)-2,3-dihydro-1H-benzimidazol-1-yl]piperidine-2,6-dione

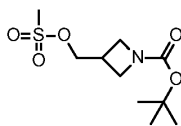


tert-Butyl 4-[1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-4-yl]piperazine-1-carboxylate was reacted with HCl using the general synthetic method illustrated by intermediate 34d to give the title compound isolated as an HCl salt; ¹H NMR: δ 1.95 - 2.04 (1H, m), 2.59 - 2.77 (2H, m), 2.84 - 2.96 (1H, m), 2.99 - 3.30 (7H, m), 3.33 - 3.41 (2H, m), 3.63 (3H, s), 5.33 - 5.43 (1H, m), 6.89 - 7.09 (3H, m), 11.11 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 344.3.

Example 150: 4-(4-{4-[4-{1-(2,6-Dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-4-yl]piperazin-1-yl}methvl)piperidin-1-yl}phenyl)piperidin-1-yl)-3-fluoro-2-(trifluoromethyl)benzonitrile

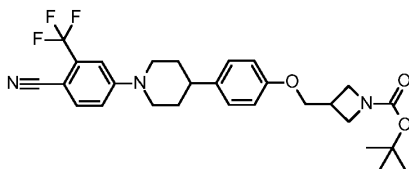


3-[3-Methyl-2-oxo-4-(piperazin-1-yl)-2,3-dihydro-1H-benzimidazol-1-yl]piperidine-2,6-dione was reacted with intermediate 146f using the general synthetic method illustrated by example 138 and purified by preparative HPLC (Column A, Eluent D) to give the title compound; ¹H NMR (CDCl₃): δ 1.44 (2H, qd), 1.74 - 2.05 (7H, m), 2.12 - 2.3 (1H, m), 2.47 - 3.3 (18H, m), 3.67 (2H, d), 3.71 - 3.8 (5H, m), 5.21 (1H, dd), 6.61 (1H, dd), 6.88 - 7.04 (4H, m), 7.08 - 7.19 (3H, m), 7.48 (1H, d), 8.32 (1H, s), 8.57 - 8.77 (1H, m); *m/z*: ES⁺ [M+H]⁺ = 787.5.

Intermediate 151a: *tert*-Butyl 3-[(methanesulfonyl)oxy]methylazetidine-1-carboxylate

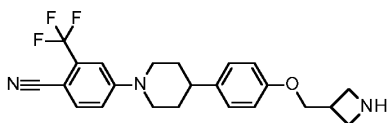
5 Methanesulfonyl chloride (9.1 mL, 117.50 mmol) was dissolved in DCM (40 mL) and added to a solution of *tert*-butyl 3-(hydroxymethyl)azetidine-1-carboxylate (20.0 g, 106.82 mmol), triethylamine (22.33 mL, 160.22 mmol) and DMAP (0.652 g, 5.34 mmol) in DCM (236 mL) at 0 °C and was stirred to RT for 2 h. The reaction was then washed with citric acid (1M, 2x 100 mL), saturated NaHCO₃ solution (100 mL), saturated brine (100 mL), dried over MgSO₄ and evaporated to dryness to give the title compound (28.0 g, 99 %) as a light brown oil, which was used without further purification; ¹H NMR (CDCl₃): δ 1.44 (9H, s), 2.93 (1H, dddd), 3.05 (3H, s), 3.72 (2H, dd), 3.98 – 4.11 (2H, m), 4.35 (2H, d).

10

Intermediate 151b: *tert*-Butyl 3-[(4-{1-[4-cyano-3-(trifluoromethyl)phenyl]piperidin-4-yl}phenoxy)methyl]azetidine-1-carboxylate

15 Intermediate 1g (1.9 g, 4.50 mmol) was stirred with K₂CO₃ (1.865 g, 13.49 mmol) and *tert*-butyl 3-[(methanesulfonyl)oxy]methylazetidine-1-carboxylate (1.45 g, 5.5 mmol) in MeCN (45.0 mL) at RT for 48 h. The reaction was then cooled to RT and evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% EtOAc in heptane to give the title compound (2.2 g, 95 %) as a colourless gum; ¹H NMR (CDCl₃): δ 1.45 (9H, s), 1.76 (2H, qd), 1.98 (2H, d), 2.75 (1H, tt), 2.95 (1H, dddd), 3.06 (2H, td), 3.78 (2H, dd), 3.95 – 4.11 (6H, m), 6.84 – 6.89 (2H, m), 6.99 (1H, dd), 7.11 – 7.18 (3H, m), 7.61 (1H, d); m/z: ES⁺ [M+H]⁺ = 516.3.

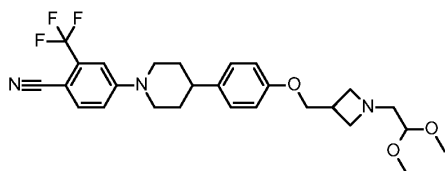
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Intermediate 151c: 4-(4-{4-[(Azetidin-3-yl)methoxy]phenyl}piperidin-1-yl)-2-(trifluoromethyl)benzonitrile

25 TFA (0.6 mL, 7.79 mmol) was added to *tert*-butyl 3-[(4-{1-[4-cyano-3-(trifluoromethyl)phenyl]piperidin-4-yl}phenoxy)methyl]azetidine-1-carboxylate (230 mg, 0.45 mmol) in DCM (6 mL) and was stirred at RT for 2 h. The solvent was evaporated to dryness to give the title compound in the form of a TFA salt (0.23 g, 97 %) as a yellow oil and was used without further purification; ¹H NMR (CDCl₃): δ 1.80 (2H, qd), 1.95 – 2.07 (2H, m), 2.71 – 2.87 (1H, m), 3.09 (2H, td), 3.31 – 3.46 (1H, m), 4.02 – 4.10 (2H, m), 4.13 (2H, d), 4.20 – 4.32

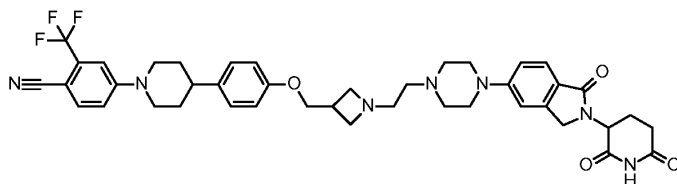
(2H, m), 4.34 – 4.52 (2H, m), 6.96 (2H, d), 7.04 (1H, dd), 7.15 – 7.24 (3H, m), 7.66 (1H, d), 8.21 (1H, s); m/z: ES⁺ [M+H]⁺ = 416.0.

Intermediate 151d: 4-[4-(4-{[1-(2,2-Dimethoxyethyl)azetidin-3-yl]methoxy}phenyl)piperidin-1-yl]-2-(trifluoromethyl)benzonitrile



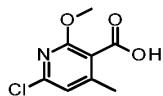
2-Bromo-1,1-dimethoxyethane (0.206 mL, 1.74 mmol), 4-(4-{[1-(2,2-Dimethoxyethyl)azetidin-3-yl]methoxy}phenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile (0.602 g, 1.45 mmol) and DIPEA (0.631 mL, 3.63 mmol) were stirred in NMP (10 mL) under nitrogen at RT for 8 h. The reaction mixture was purified by preparative HPLC (Column A, Eluent D). The product was extracted with DCM (300 mL), dried over a phase separating cartridge and evaporated to give the title compound (0.055 g, 6.37 %) as a dry film; ¹H NMR (CDCl₃): δ 1.76 (2H, qd), 1.98 (2H, d), 2.75 (1H, tt), 3.01 – 3.12 (3H, m), 3.16 – 3.28 (1H, m), 3.43 (6H, s), 3.76 (2H, dd), 3.97 – 4.13 (6H, m), 4.61 (1H, t), 6.84 – 6.9 (2H, m), 6.99 (1H, dd), 7.14 (3H, dd), 7.61 (1H, d), 8.48 (1H, s); m/z: ES⁺ [M+H]⁺ = 504.4.

Example 151: 4-[4-(4-{[1-(2-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-indol-5-yl]piperazin-1-yl}ethyl)azetidin-3-yl]methoxy}phenyl)piperidin-1-yl]-2-(trifluoromethyl)benzonitrile



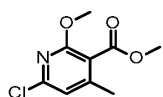
4-[4-(4-{[1-(2,2-Dimethoxyethyl)azetidin-3-yl]methoxy}phenyl)piperidin-1-yl]-2-(trifluoromethyl)benzonitrile (55 mg, 0.11 mmol) was stirred in 2-MeTHF (1 mL) and HCl (1M, 1 mL) at 60 °C for 1 h, cooled to RT and evaporated to dryness. The residue was redissolved in NMP (1 mL) and intermediate 2c (47.8 mg, 0.13 mmol) was added followed by sodium triacetoxymethylborohydride (57.9 mg, 0.27 mmol) and was stirred at RT for 1 h. The reaction mixture was purified by preparative HPLC (Column A, Eluent A) to give the title compound in the form of a formate salt (0.013 g, 14.59 %) as a colourless film; ¹H NMR (CDCl₃): δ 1.76 (2H, qd), 1.98 (2H, d), 2.19 (1H, ddq), 2.32 (1H, qd), 2.63 – 2.7 (4H, m), 2.72 (2H, t), 2.75 – 2.86 (2H, m), 2.90 (1H, ddd), 3.06 (2H, td), 3.24 (2H, t), 3.28 – 3.41 (5H, m), 3.88 – 3.99 (2H, m), 3.99 – 4.07 (4H, m), 4.25 (1H, d), 4.32 (2H, t), 4.40 (1H, d), 5.18 (1H, dd), 6.82 – 6.93 (3H, m), 6.98 (2H, ddd), 7.14 – 7.2 (3H, m), 7.62 (1H, d), 7.72 (1H, d), 8.39 (2H, s); m/z: ES⁺ [M+H]⁺ = 770.4.

Intermediate 152a: 6-Chloro-2-methoxy-4-methylpyridine-3-carboxylic acid



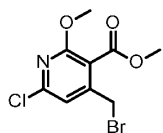
- 5 To a stirred solution sodium methoxide (20.67 mL, 112 mmol) in THF (50.0 mL) was added 2,6-dichloro-4-methylpyridine-3-carboxylic acid (10.0 g, 48.5 mmol) in THF (50.0 mL) at 0 °C and was then stirred at 70 °C for 16 h. The reaction was then cooled to RT and acidified with a HCl (2M, aq) to pH 3-4, then extracted with EtOAc (160 mL). The organic layer was washed with water (100 mL), NaCl solution (100 mL), dried over Na₂SO₄, filtered and evaporated to dryness to give the title compound (8.0 g, 78 % yield) which was used without further purification; ¹H NMR δ 2.27 (3H, s), 3.87 (3H, s), 7.10 (1H, s), 13.42 (1H, s).

Intermediate 152b: Methyl 6-chloro-2-methoxy-4-methylpyridine-3-carboxylate



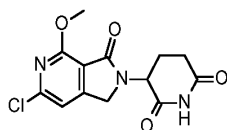
- 10 To a stirred solution of 6-chloro-2-methoxy-4-methylpyridine-3-carboxylic acid (8.0 g, 39.7 mmol) in DMF (80 mL) was added K₂CO₃ (6.58 g, 47.6 mmol) and methyl iodide (8.45 g, 59.5 mmol) which was stirred at RT for 16 h. The reaction mixture was diluted with water (80 mL) and extracted with MTBE (240 mL). The organic layer was washed with NaCl solution (160 mL), dried over Na₂SO₄, filtered and evaporated to dryness to give the title compound (8.5 g, 37.1 mmol, 93 % yield) as pale yellow solid; ¹H NMR δ 2.26 (3H, s), 3.84 (3H, s), 3.87 (3H, s), 7.13 (1H, s).

Intermediate 152c: Methyl 4-(bromomethyl)-6-chloro-2-methoxypyridine-3-carboxylate



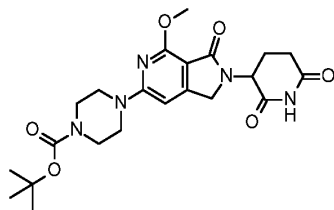
- 20 Methyl 6-chloro-2-methoxy-4-methylpyridine-3-carboxylate (8.0 g, 37.1 mmol) was added to *tert*-butyl acetate (150 mL) under nitrogen. NBS (9.24 g, 51.9 mmol) and benzoyl peroxide (1.79 g, 7.42 mmol) were added at RT and was then stirred at 110 °C for 14 h. Additional NBS (2.64 g, 14.84 mmol) was added and was continued to stir at 110 °C for 12 h. The reaction mixture was cooled to RT and diluted with NaHCO₃ solution (10%, 50 mL) and extracted with EtOAc (120 mL). The organic layer was washed with NaCl solution (80 mL), dried over Na₂SO₄, filtered and evaporated to dryness to give the title compound (11.0 g, 10.01 mmol, 27.0 % yield) as brown liquid which was used without further purification; *m/z*: ES⁺ [M+H]⁺ = 294.0.
- 25

Intermediate 152d: 3-(6-Chloro-4-methoxy-3-oxo-1,3-dihydro-2H-pyrrolo[3,4-c]pyridin-2-yl)piperidine-2,6-dione



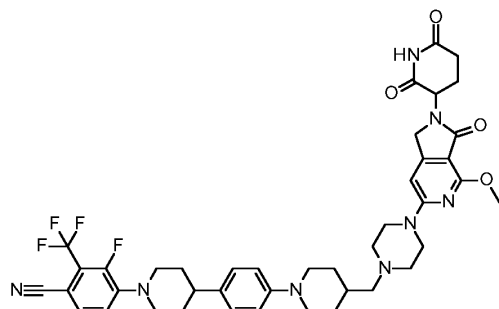
- Methyl 4-(bromomethyl)-6-chloro-2-methoxypyridine-3-carboxylate (11.0 g, 10.01 mmol) was dissolved in MeCN (80 mL). 3-Aminopiperidine-2,6-dione hydrochloride (1.65 g, 10.01 mmol) and DIPEA (5.17 g, 40.0 mmol) were added and the reaction was stirred at 85 °C for 16 h. The reaction mixture was then cooled to RT, diluted with DCM (200 mL), washed AcOH (5%, aq 200 mL), water (200 mL), NaHCO₃ solution (200 mL), NaCl solution (200 mL), dried with Na₂SO₄, filtered and evaporated to afford crude product. The crude product was triturated with EtOAc (10 mL) and washed with MTBE (30 mL) to afford solid which was collected by filtration and dried under vacuum to give the title compound (1.6 g, 4.35 mmol, 43.5 % yield) as brown solid; ¹H NMR δ 1.89 - 2.02 (1H, m), 2.30 - 2.35 (1H, m), 2.50 - 2.59 (1H, m), 2.84 - 2.98 (1H, m), 3.99 (3H, s), 4.26 - 4.39 (1H, m), 4.40 - 4.53 (1H, m), 5.05 (1H, dd), 7.40 (1H, s), 10.99 (1H, br s); *m/z*: ES⁺ [M+H]⁺ = 310.2.

Intermediate 152c: *tert*-Butyl 4-[2-(2,6-dioxopiperidin-3-yl)-4-methoxy-3-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl]piperazine-1-carboxylate



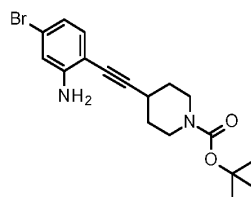
- Pd-PEPPSI-IPent (47.1 mg, 0.048 mmol) was added to *tert*-butyl piperazine-1-carboxylate (541 mg, 2.91 mmol), Cs₂CO₃ (947 mg, 2.91 mmol) and 3-(6-chloro-4-methoxy-3-oxo-1,3-dihydro-2H-pyrrolo[3,4-c]pyridin-2-yl)piperidine-2,6-dione (300 mg, 0.969 mmol) in 1,4-dioxane (10 mL) at RT under nitrogen. The resulting suspension was stirred at 120 °C for 2 h. The reaction mixture was cooled to RT and diluted with DCM (20 mL), washed with AcOH (5%, aq 20 mL), water (20 mL), NaHCO₃ solution (20 mL), NaCl solution (20 mL), dried with Na₂SO₄, filtered and evaporated to afford crude product. The crude product was triturated with EtOAc (4 mL) and washed with MTBE (16 mL) to afford solid which was collected by filtration and dried under vacuum to give the title compound (260 mg, 0.485 mmol, 50.1 % yield) as brown solid; ¹H NMR: δ 1.43 (9H, s), 1.88 - 2.00 (1H, m), 2.29 - 2.39 (1H, m), 2.58 - 2.68 (1H, m), 2.86 - 2.96 (1H, m), 3.34 - 3.44 (4H, m), 3.53 - 3.63 (4H, m), 3.90 (3H, s), 4.09 - 4.18 (1H, m), 4.24 - 4.34 (1H, m), 4.97 (1H, br dd), 6.50 (1H, s), 10.92 (1H, br s); *m/z*: ES⁺ [M+H]⁺ = 460.2.

Example 152: 4-(4-{4-[4-(4-[2-(2,6-Dioxopiperidin-3-yl)-4-methoxy-3-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl]piperazin-1-yl)methyl]piperidin-1-yl}phenyl)piperidin-1-yl)-3-fluoro-2-(trifluoromethyl)benzonitrile



tert-Butyl 4-[2-(2,6-dioxopiperidin-3-yl)-4-methoxy-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-yl]piperazine-1-carboxylate was reacted with intermediate 146f using the general synthetic method illustrated by example 138 to give the title compound; ¹H NMR (CDCl₃): δ 1.38 (2H, qd), 1.63 – 2 (7H, m), 2.12 – 2.34 (4H, m), 2.51 – 2.59 (4H, m), 2.6 – 2.75 (3H, m), 2.76 – 2.93 (2H, m), 2.98 (2H, td), 3.61 – 3.81 (8H, m), 4.02 (3H, s), 4.17 (1H, d), 4.35 (1H, d), 5.14 (1H, dd), 6.15 (1H, s), 6.92 (2H, d), 7.07 – 7.16 (3H, m), 7.49 (1H, d), 7.86 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 803.4.

Intermediate 153a: *tert*-Butyl 4-[(2-amino-4-bromophenyl)ethynyl]piperidine-1-carboxylate

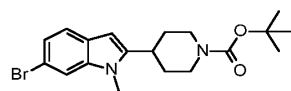


10

PdCl₂(PPh₃)₂ (3.36 g, 4.78 mmol) was added in to *tert*-butyl 4-ethynylpiperidine-1-carboxylate (10.01 g, 47.83 mmol), 5-bromo-2-iodoaniline (14.25 g, 47.83 mmol), copper(I) iodide (1.36 g, 7.17 mmol) and triethylamine (19.97 mL, 143.49 mmol) in DMF (145 mL) under nitrogen. The dark brown solution was stirred at RT for 18 h. The reaction mixture was diluted with water (150 mL) and extracted into MTBE (150 mL). The organic layer was washed with water (150 mL), NaCl solution (50 mL), dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 5 to 20% EtOAc in heptane to give the title compound (24.1 g, 70 %) as an orange oil; ¹H NMR (CDCl₃): δ 1.46 (9H, s), 1.68 (2H, m), 1.88 (2H, m), 2.83 (1H, m), 3.18 – 3.26 (2H, m), 3.76 (2H, m), 4.18 (2H, s), 6.78 (1H, m), 6.84 (1H, m), 7.08 (1H, d); *m/z*: ES⁺ [M+H]⁺ = 379.1.

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Intermediate 153b: *tert*-Butyl 4-(6-bromo-1-methyl-1*H*-indol-2-yl)piperidine-1-carboxylate

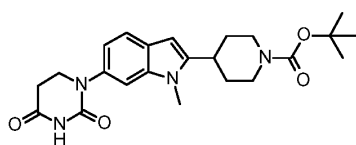


Potassium *tert*-butoxide (13.3 g, 118.48 mmol) was added to *tert*-butyl 4-[(2-amino-4-bromophenyl)ethynyl]piperidine-1-carboxylate (21.4 g, 39.49 mmol) in NMP (200 mL) at RT and was stirred for 3 h. Iodomethane (7.38 mL, 118.48 mmol) was then added over 10 mins to the reaction flask, keeping the

25

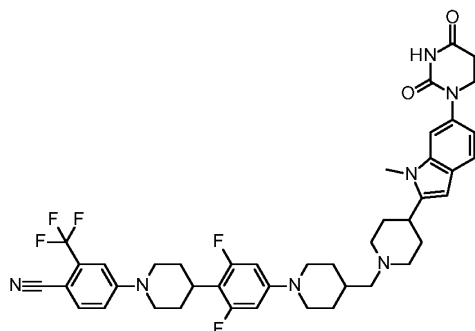
- internal temperature below 35 °C which was then left to stir for 1 h. The reaction mixture was quenched with NH₄Cl solution (100 mL) and water (100 mL). The product was extracted with 2-MeTHF (400 mL), washed with water (2 x 100 mL), NaCl solution (100 mL), dried over MgSO₄, filtered and evaporated to afford crude. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% EtOAc in heptane to give the title compound (13.74 g, 88 %) as a white solid; ¹H NMR (CDCl₃): δ 1.51 (9H, s), 1.68 (2H, qd), 1.99 (2H, d), 2.79 – 2.96 (3H, m), 3.70 (3H, s), 4.28 (2H, d), 6.24 (1H, s), 7.19 (1H, dd), 7.39 – 7.44 (1H, m), 7.45 (1H, d); *m/z*: ES⁺ [M+H]⁺ = 393.3.

Intermediate 153c: *tert*-Butyl 4-[6-(2,4-dioxo-1,3-diazinan-1-yl)-1-methyl-1*H*-indol-2-yl]piperidine-1-carboxylate



- tert*-Butyl 4-(6-bromo-1-methyl-1*H*-indol-2-yl)piperidine-1-carboxylate (10.82 g, 27.51 mmol) was dissolved in 1,4-dioxane (180 mL) and added to a flask containing 1,3-diazinane-2,4-dione (9.42 g, 82.53 mmol), K₂CO₃ (11.41 g, 82.53 mmol) and *tert*-butylBrettPhos (1.33 g, 2.75 mmol). The mixture was degassed with nitrogen followed by the addition of *tert*-butylBrettPhos Pd G3 (2.35 g, 2.75 mmol). The mixture stirred at 100 °C for 42 h and then cooled to RT. Water (180 mL) and 2-MeTHF (180 mL) was added and stirred for 5 mins. The layers were separated and the organic layer was washed with water (180 mL), NaCl solution (50 mL), dried with MgSO₄, filtered and evaporated to afford crude product. The crude product was slurried in EtOAc (30 mL) and the resulting brown suspension was filtered, the solid was washed with EtOAc (10 mL) to give the title compound (6.59 g, 56.2 %) as a pale brown solid; ¹H NMR: δ 1.43 (11H, s), 1.94 (2H, d), 2.73 (2H, t), 2.82 – 3.07 (3H, m), 3.70 (3H, s), 3.79 (2H, t), 4.06 (2H, dd), 6.24 (1H, s), 6.94 (1H, dd), 7.37 (1H, d), 7.43 (1H, d), 10.26 (1H, s).

Example 153: 4-(4-{4-[4-(4-[6-(2,4-Dioxo-1,3-diazinan-1-yl)-1-methyl-1*H*-indol-2-yl]piperidin-1-yl)methyl]piperidin-1-yl}-2,6-difluorophenyl)piperidin-1-yl)-2-(trifluoromethyl)benzonitrile

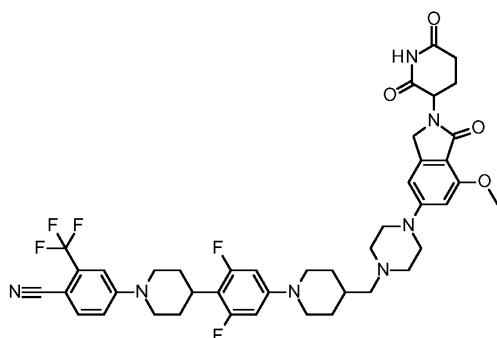


tert-Butyl 4-[6-(2,4-dioxo-1,3-diazinan-1-yl)-1-methyl-1*H*-indol-2-yl]piperidine-1-carboxylate was reacted with intermediate 138e using the general synthetic method illustrated by example 138 to give the title

compound; ^1H NMR (CDCl_3): δ 1.22 – 1.36 (2H, m), 1.62 – 1.98 (9H, m), 2.03 – 2.19 (4H, m), 2.25 (2H, d), 2.53 – 2.81 (3H, m), 2.86 (2H, t), 2.96 – 3.07 (4H, m), 3.12 (1H, tt), 3.6 – 3.67 (2H, m), 3.69 (3H, s), 3.90 (2H, t), 4.00 (2H, d), 6.28 (1H, s), 6.31 – 6.44 (2H, m), 6.92 – 6.99 (2H, m), 7.14 (1H, d), 7.23 (1H, d), 7.40 (1H, s), 7.55 (1H, d), 7.61 (1H, d); m/z : ES^+ $[\text{M}+\text{H}]^+ = 788.5$.

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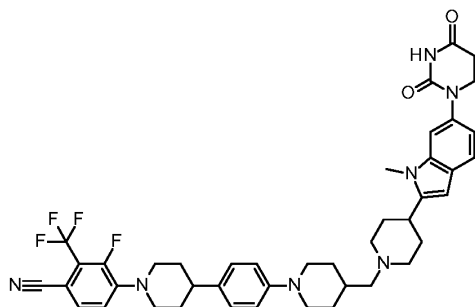
Example 154: 4-(4-{4-[4-({4-[2-(2,6-Dioxopiperidin-3-yl)-7-methoxy-1-oxo-2,3-dihydro-1H-indol-5-yl]piperazin-1-yl}methyl)piperidin-1-yl]-2,6-difluorophenyl}piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



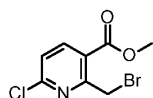
- 10 Intermediate 138e was reacted with intermediate 1e using the general synthetic method illustrated by example 138 to give the title compound; ^1H NMR (CDCl_3): δ 1.24 – 1.38 (2H, m), 1.68 – 1.79 (1H, m), 1.86 (3H, dd), 2.05 – 2.22 (3H, m), 2.23 – 2.38 (3H, m), 2.62 – 2.67 (4H, m), 2.7 – 2.94 (5H, m), 3.03 (2H, t), 3.13 (1H, tt), 3.3 – 3.43 (4H, m), 3.64 (2H, d), 3.94 (3H, s), 4.00 (2H, d), 4.20 (1H, d), 4.36 (1H, d), 5.14 (1H, dd), 6.32 – 6.41 (3H, m), 6.47 (1H, s), 6.97 (1H, dd), 7.14 (1H, d), 7.61 (1H, d), 7.99 (1H, s); m/z : ES^+ $[\text{M}+\text{H}]^+ = 820.5$.

15

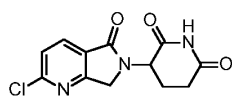
Example 155: 4-(4-{4-[4-({4-[6-(2,4-Dioxo-1,3-diazinan-1-yl)-1-methyl-1H-indol-2-yl]piperidin-1-yl}methyl)piperidin-1-yl]phenyl}piperidin-1-yl)-3-fluoro-2-(trifluoromethyl)benzonitrile



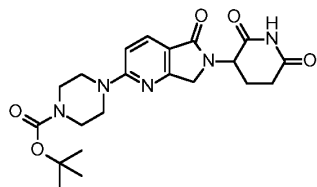
- 20 Intermediate 146f was reacted with intermediate 153c using the general synthetic method illustrated by example 138 and purified by preparative HPLC (Column A, Eluent D) to give the title compound; ^1H NMR (CDCl_3): δ 1.36 (2H, qd), 1.62 – 1.71 (1H, m), 1.74 – 2.02 (10H, m), 2.04 – 2.14 (2H, m), 2.27 (2H, d), 2.58 – 2.76 (4H, m), 2.86 (2H, t), 2.94 – 3.07 (4H, m), 3.61 – 3.79 (7H, m), 3.90 (2H, t), 6.28 (1H, s), 6.89 – 6.97 (3H, m), 7.07 – 7.16 (3H, m), 7.23 (1H, d), 7.44 (1H, s), 7.48 (1H, d), 7.55 (1H, d); m/z : ES^+ $[\text{M}+\text{H}]^+ = 770.5$.

Intermediate 156a: Methyl 2-(bromomethyl)-6-chloropyridine-3-carboxylate

- 5 AIBN (88 mg, 0.54 mmol) was added to methyl 6-chloro-2-methylpyridine-3-carboxylate (1.0 g, 5.39 mmol) and NBS (1.05 g, 5.93 mmol) in chloroform (12 mL) and was stirred at 80 °C for 6 h. The reaction was cooled to RT, filtered through Celite® and evaporated to afford crude product. The crude product was purified by silica gel chromatography (0-8% EtOAc/Hexane) to give the title compound (0.350 g, 24.5 %); m/z: ES⁺ [M+H]⁺ = 264.0.

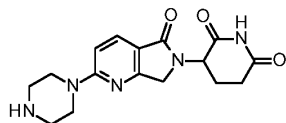
Intermediate 156b: 3-(2-Chloro-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione

- 10 DIPEA (475 µL, 2.72 mmol) was added to methyl 2-(bromomethyl)-6-chloropyridine-3-carboxylate (240 mg, 0.91 mmol) and 3-aminopiperidine-2,6-dione, HCl (119 mg, 0.73 mmol) in DMF (2 mL). The mixture was stirred at 40 °C for 2 h followed by 100 °C for 16 h. The reaction was cooled to RT and evaporated to dryness to afford crude product. The crude product was purified by silica gel chromatography (0-10% MeOH:DCM) followed by crystallisation from EtOAc to give the title compound (0.140 g, 55.2 %) as a purple solid; ¹H NMR: δ 2.02 - 2.08 (1H, m), 2.43 (1H, br dd), 2.62 (1H, br d), 2.91 - 2.97 (1H, m), 4.36 - 4.46 (1H, m), 4.56 (1H, br d), 5.18 (1H, br dd), 7.69 (1H, d), 8.21 (1H, dd), 11.03 (1H, br s); m/z: ES⁺ [M+H]⁺ = 280.0.

Intermediate 156c: *tert*-Butyl 4-[6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl]piperazine-1-carboxylate

- 20 DIPEA (1.27 mL, 7.15 mmol) was added to 3-(2-chloro-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione (1.0 g, 3.58 mmol) and *tert*-butyl piperazine-1-carboxylate (0.66 g, 3.58 mmol) in DMSO (8 mL). The mixture was stirred at 120 °C for 5 h and then poured into ice water. The precipitate was collected by filtration, dried under vacuum for 48 h to give the title compound (1.06 g, 69.5 %) as a beige solid; ¹H NMR: δ 1.43 (9H, s), 1.91 - 2.04 (1H, m), 2.3 - 2.44 (1H, m), 2.55 - 2.65 (1H, m), 2.91 (1H, ddd), 3.39 - 3.54 (4H, m), 3.62 - 3.74 (4H, m), 4.12 (1H, d), 4.29 (1H, d), 5.08 (1H, dd), 6.91 (1H, d), 7.80 (1H, d), 10.93 (1H, s); m/z: ES⁻ [M-H]⁻ = 428.4.

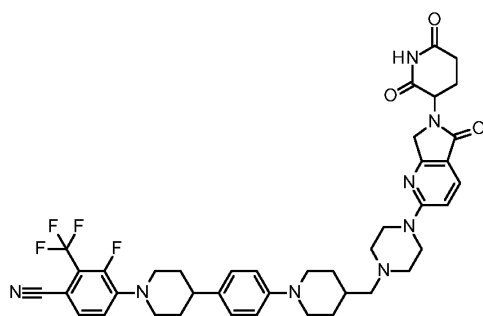
- 30 **Intermediate 156d: 3-[5-Oxo-2-(piperazin-1-yl)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl]piperidine-2,6-dione**



HCl (4M in dioxane, 2 mL, 8.00 mmol) was added to *tert*-butyl 4-[6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl]piperazine-1-carboxylate (92 mg, 0.21 mmol) at RT and was stirred for 2 h. The reaction was evaporated to dryness to give the title compound as a HCl salt which was used without further purification.

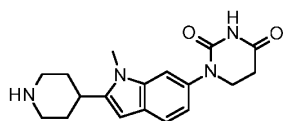
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Example 156: 4-(4-{4-[4-(4-[6-(2,6-Dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl]piperazin-1-yl]methyl}piperidin-1-yl]phenyl}piperidin-1-yl)-3-fluoro-2-(trifluoromethyl)benzonitrile



- 10 Intermediate 146f (0.075g, 0.13 mmol) was stirred in formic acid (2 mL) at 60 °C for 2 h. The mixture was evaporated and the residue was redissolved in NMP (2 mL) with 3-[5-oxo-2-(piperazin-1-yl)-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl]piperidine-2,6-dione (0.060 g, 0.17 mmol) at RT. Sodium triacetoxyborohydride (0.067 g, 0.32 mmol) was added after 5 mins and suspension was stirred at RT for 10 mins. The reaction mixture was purified by preparative HPLC (Column A, Eluent A) gave the title compound in the form of a
- 15 formate salt (0.054 g, 51.9 %) as pale solid; ¹H NMR (CDCl₃): δ 1.29 – 1.5 (2H, m), 1.81 – 2.02 (6H, m), 2.16 – 2.25 (2H, m), 2.26 – 2.4 (3H, m), 2.55 – 2.75 (7H, m), 2.76 – 3.03 (4H, m), 3.6 – 3.84 (8H, m), 4.18 (1H, d), 4.32 (1H, d), 5.20 (1H, dd), 6.66 (1H, d), 6.87 – 6.96 (2H, m), 7.08 – 7.16 (3H, m), 7.49 (1H, d), 7.86 (1H, d), 7.92 (1H, s), 8.09 (1H, s); m/z: ES⁺ [M+H]⁺ = 773.4.

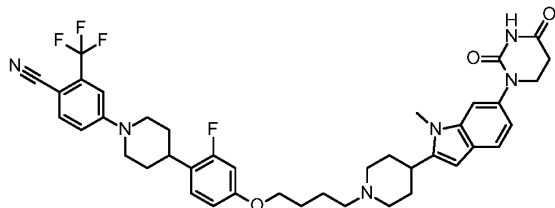
- 20 **Intermediate 157a: 1-[1-Methyl-2-(piperidin-4-yl)-1H-indol-6-yl]-1,3-diazinane-2,4-dione**



Intermediate 153c was reacted with TFA using the general synthetic method illustrated by intermediate 149e to give the title compound in the form of a TFA salt and was used without further purification; ¹H NMR: δ 1.71 – 1.87 (2H, m), 2.07 – 2.15 (2H, m), 2.69 – 2.77 (2H, m), 3.02 – 3.23 (3H, m), 3.41 (2H, d), 3.71 (3H, s), 3.75 – 3.83 (2H, m), 6.25 (1H, s), 6.92 – 6.99 (1H, m), 7.38 (1H, s), 7.46 (1H, d), 10.28 (1H, s); m/z: ES⁺ [M+H]⁺ = 327.1.

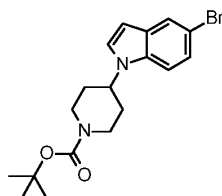
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Example 157: 4-{4-[4-(4-{4-[6-(2,4-Dioxo-1,3-diazinan-1-yl)-1-methyl-1*H*-indol-2-yl]piperidin-1-yl}butoxy)-2-fluorophenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile



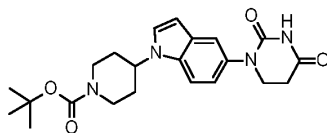
- 1-[1-Methyl-2-(piperidin-4-yl)-1*H*-indol-6-yl]-1,3-diazinane-2,4-dione was reacted with intermediate 145a in the general synthetic method illustrated by example 12 to give the title compound; ¹H NMR: δ 1.62 – 1.88 (10H, m), 2.04 (2H, d), 2.74 (3H, t), 2.9 – 3 (1H, m), 3.01 – 3.15 (3H, m), 3.31 (5H, s), 3.70 (3H, s), 3.79 (2H, t), 4.02 (2H, t), 4.18 (2H, d), 6.24 (1H, s), 6.75 (1H, dd), 6.80 (1H, dd), 6.95 (1H, dd), 7.22 (1H, t), 7.27 (1H, dd), 7.35 (2H, dd), 7.44 (1H, d), 7.82 (1H, d), 10.28 (1H, s); m/z: ES⁺ [M+H]⁺ = 745.4.

Intermediate 158a: *tert*-Butyl 4-(5-bromo-1*H*-indol-1-yl)piperidine-1-carboxylate



- tert*-Butyl 4-[(methanesulfonyl)oxy]piperidine-1-carboxylate (534 g, 1912.81 mmol) and potassium *tert*-butoxide (258 g, 2295.37 mmol) were added portion wise to 5-bromo-1*H*-indole (150 g, 765.12 mmol) in heptane (2400 mL) and stirred at 80 °C for 3 h. The reaction mixture cooled to RT and was diluted with MTBE. The solid was filtered and the filtrate was evaporated to dryness. The residue was redissolved in EtOAc, washed with water, dried over Na₂SO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 30% EtOAc in Et₂O to give a colourless foam which was crystallised from MTBE:Et₂O (1:5) to give the title compound (85 g, 29.3 %) as a white solid; ¹H NMR (CDCl₃) δ 1.36 – 1.42 (9H, s), 1.69 – 1.89 (2H, m), 1.92 – 2.02 (2H, d), 2.73 – 2.89 (2H, m), 4.14 – 4.29 (3H, m), 6.33 – 6.40 (1H, m), 7.04 – 7.12 (1H, d), 7.09 – 7.23 (2H, m), 7.60 – 7.69 (1H, m); m/z: ES⁺ [M-tBu]⁺ = 323.0.

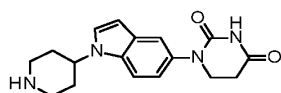
Intermediate 158b: *tert*-Butyl 4-[5-(2,4-dioxo-1,3-diazinan-1-yl)-1*H*-indol-1-yl]piperidine-1-carboxylate



- [Pd(cinnamyl)Cl]₂ (0.913 g, 1.65 mmol) was added to *tert*-butyl 4-(5-bromo-1*H*-indol-1-yl)piperidine-1-carboxylate (25 g, 65.91 mmol), 1,3-diazinane-2,4-dione (15.04 g, 131.82 mmol), *tert*-butylBrettPhos (1.59 g, 3.30 mmol) and Cs₂CO₃ (43 g, 131.82 mmol) in 1,4-dioxane (750 mL) at RT under nitrogen. The resulting

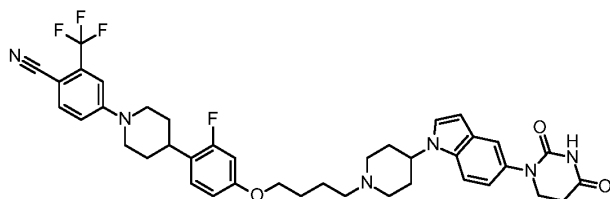
- mixture was stirred at 90 °C for 16 h. The reaction mixture was cooled to RT and diluted with EtOAc (2 L) and water (2 L). The organic layer was dried over Na₂SO₄, filtered and evaporated to afford crude product. The crude product was purified by crystallisation from MTBE to give the title compound (44.0 g, 57.1 %) as a white solid; ¹H NMR (CDCl₃) δ 1.49 – 1.54 (9H, s), 1.85 – 2.00 (2H, qd), 2.04 – 2.13 (2H, m), 2.84 – 3.00 (4H, m), 3.88 – 3.95 (2H, m), 4.32 – 4.44 (3H, m), 6.52 – 6.58 (1H, m), 7.12 – 7.19 (1H, m), 7.22 – 7.27 (1H, d), 7.38 – 7.46 (2H, m), 7.52 – 7.57 (1H, d); *m/z*: ES⁺ [M+H]⁺ = 413.0.

Intermediate 158c: 1-[1-(Piperidin-4-yl)-1*H*-indol-5-yl]-1,3-diazinane-2,4-dione



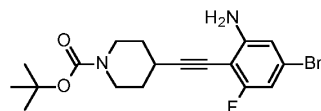
- The title compound was prepared using methodology described in intermediate 145g using *tert*-butyl 4-[5-(2,4-dioxo-1,3-diazinan-1-yl)-1*H*-indol-1-yl]piperidine-1-carboxylate to give the title compound as a tosylate salt (73 g, 82 %) as a white solid; ¹H NMR δ 2.05 – 2.20 (4H, m), 2.27 – 2.32 (3H, d), 2.69 – 2.77 (2H, m), 3.15 – 3.20 (2H, s), 3.44 – 3.51 (2H, d), 3.73 – 3.81 (2H, m), 4.71 – 4.75 (1H, s), 6.48 – 6.54 (1H, m), 7.08 – 7.16 (3H, m), 7.39 – 7.47 (1H, m), 7.47 – 7.53 (3H, m), 7.53 – 7.63 (1H, m), 8.37 – 8.42 (1H, s), 8.61 – 8.65 (1H, s), 10.24 – 10.29 (1H, d); *m/z*: ES⁺ [M+H]⁺ = 313.0.

Example 158: 4-{4-[4-(4-{4-[5-(2,4-Dioxo-1,3-diazinan-1-yl)-1*H*-indol-1-yl]piperidin-1-yl}butoxy)-2-fluorophenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile



- 1-[1-(Piperidin-4-yl)-1*H*-indol-5-yl]-1,3-diazinane-2,4-dione was reacted with intermediate 145a in the general synthetic method illustrated by example 12 to give the title compound; ¹H NMR: δ 1.62 – 1.86 (8H, m), 2 – 2.16 (5H, m), 2.73 (3H, t), 2.78 – 3.14 (5H, m), 3.31 (3H, s), 3.77 (2H, t), 4.02 (2H, t), 4.18 (2H, d), 4.44 – 4.61 (1H, m), 6.49 (1H, d), 6.75 (1H, dd), 6.80 (1H, dd), 7.10 (1H, dd), 7.22 (1H, t), 7.26 – 7.3 (1H, m), 7.33 (1H, d), 7.46 – 7.52 (2H, m), 7.56 (1H, s), 7.82 (1H, d), 8.14 (0H, s), 10.26 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 731.4.

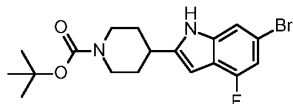
Intermediate 159a: *tert*-Butyl 4-[(2-amino-4-bromo-6-fluorophenyl)ethynyl]piperidine-1-carboxylate



- Tetrakis(triphenylphosphine)palladium(0) (1.46 g, 1.27 mmol) was added to 5-bromo-3-fluoro-2-iodoaniline (4.0 g, 12.66 mmol), *tert*-butyl 4-ethynylpiperidine-1-carboxylate (2.91 g, 13.93 mmol) and copper(I) iodide

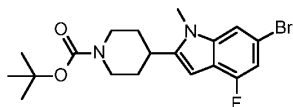
- (0.241 g, 1.27 mmol) in triethylamine (60 mL) at RT under nitrogen. The mixture was stirred at 100 °C for 2 h, cooled to RT and then evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 35% EtOAc in Et₂O to give the title compound (4.0 g, 80 %) as a yellow solid; ¹H NMR: δ 1.40 (9H, s), 1.49 – 1.62 (2H, m), 1.77 – 1.88 (2H, m), 2.84 – 2.95 (1H, m), 3.10 (2H, t), 3.60 – 3.70 (2H, m), 5.85 (2H, s), 6.58 (1H, dd), 6.69 – 6.74 (1H, m); m/z: ES⁺ [M-*t*Bu]⁺ = 341.1.

Intermediate 159b: *tert*-Butyl 4-(6-bromo-4-fluoro-1*H*-indol-2-yl)piperidine-1-carboxylate



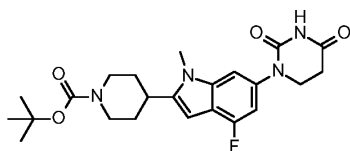
- Bis(MeCN)palladium(II) chloride (0.496 g, 1.91 mmol) was added to *tert*-butyl 4-[(2-amino-4-bromo-6-fluorophenyl)ethynyl]piperidine-1-carboxylate (3.8 g, 9.56 mmol) in DMF (40 mL) under nitrogen. The mixture was stirred at 120 °C for 3 h and then cooled to RT. The mixture was diluted with water (125 mL), and EtOAc (300 mL), washed with saturated brine (100 mL), dried over MgSO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 35% EtOAc in Et₂O to give the title compound (1.35 g, 35.5 %) as a yellow solid; ¹H NMR: δ 1.42 (9H, d), 1.48 – 1.62 (2H, m), 1.92 – 2.02 (2H, m), 2.85 – 2.96 (3H, m), 4.01 – 4.09 (2H, m), 6.26 (1H, s), 6.96 (1H, d), 7.32 (1H, s), 11.47 (1H, s); m/z: ES⁺ [M-*t*Bu+H]⁺ = 343.1.

Intermediate 159c: *tert*-Butyl 4-(6-bromo-4-fluoro-1-methyl-1*H*-indol-2-yl)piperidine-1-carboxylate



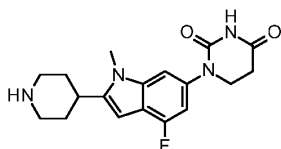
- NaH (60% in mineral oil, 0.196 g, 4.91 mmol) was added to *tert*-butyl 4-(6-bromo-4-fluoro-1*H*-indol-2-yl)piperidine-1-carboxylate (1.3 g, 3.27 mmol) in THF (20 mL) at 0 °C under nitrogen. Iodomethane (0.204 mL, 3.27 mmol) was added after 15 mins and was stirred to RT for 2 h. The reaction mixture was quenched with water (1 mL), diluted with EtOAc (50 mL), washed with water (3x 50 mL), dried over Na₂SO₄, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 100% EtOAc in Et₂O to give the title compound (1.15 g, 85 %) as a red solid; ¹H NMR: δ 1.42 (9H, s), 1.44 – 1.55 (2H, m), 1.92 (2H, d), 2.89 – 3.00 (3H, m), 3.73 (3H, s), 4.03 – 4.13 (2H, m), 6.32 (1H, s), 7.01 (1H, dd), 7.57 (1H, s); m/z: ES⁺ [M-*t*Bu]⁺ = 355.0.

Intermediate 159d: *tert*-Butyl 4-[6-(2,4-dioxo-1,3-diazinan-1-yl)-4-fluoro-1-methyl-1*H*-indol-2-yl]piperidine-1-carboxylate



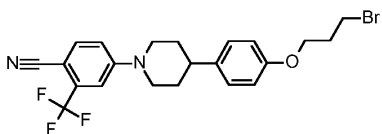
tert-Butyl 4-(6-bromo-4-fluoro-1-methyl-1*H*-indol-2-yl)piperidine-1-carboxylate was reacted using the general synthetic method illustrated by intermediate 146d to give the title compound; *m/z*: ES⁺ [M-*t*Bu+H]⁺ = 389.3.

5 Intermediate 159e: 1-[4-Fluoro-1-methyl-2-(piperidin-4-yl)-1*H*-indol-6-yl]-1,3-diazinane-2,4-dione



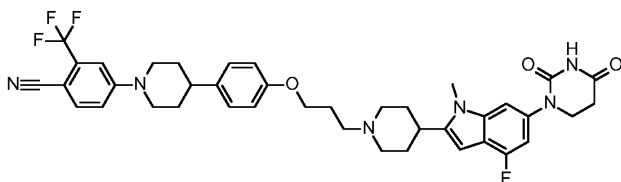
- tert*-Butyl 4-[6-(2,4-dioxo-1,3-diazinan-1-yl)-4-fluoro-1-methyl-1*H*-indol-2-yl]piperidine-1-carboxylate (500 mg, 1.12 mmol) was added to formic acid (1 mL) and was stirred at RT for 1 h. The reaction mixture was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH₃/MeOH to give the title compound (0.300 g, 77 %) as a yellow solid; ¹H NMR: δ 1.44 – 1.52 (1H, m), 1.50 – 1.58 (1H, m), 1.86 (2H, d), 2.61 – 2.77 (4H, m), 2.86 – 2.91 (1H, m), 3.00 – 3.07 (2H, m), 3.70 (3H, s), 3.80 (2H, t), 6.24 (1H, s), 6.82 (1H, dd), 7.26 (1H, t), 10.33 (1H, s); *m/z*: ES⁺ [M+H]⁺ = 345.3.

15 Intermediate 159f: 4-{4-[4-(3-Bromopropoxy)phenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile



- Intermediate 1g (2.0 g, 5.77 mmol) was added to 1,3-dibromopropane (3.5 g, 17.32 mmol) and K₂CO₃ (1.59 g, 11.55 mmol) in MeCN (30 mL) at RT. The mixture was stirred at 80 °C for 16 h and then cooled to RT and evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 25% EtOAc in Et₂O to give the title compound (1.9 g, 70.4 %) as a white solid; ¹H NMR: δ 1.52 – 1.72 (2H, m), 1.79 – 1.90 (2H, m), 2.23 (2H, p), 2.70 – 2.83 (1H, m), 2.96 – 3.12 (2H, m), 3.66 (2H, t), 4.05 (2H, t), 4.18 (2H, d), 6.82 – 6.93 (2H, m), 7.11 – 7.22 (2H, m), 7.22 – 7.36 (2H, m), 7.81 (1H, d); *m/z*: ES⁺ [M+H]⁺ = 467.2.

25 Example 159: 4-{4-[4-(3-{4-[6-(2,4-Dioxo-1,3-diazinan-1-yl)-4-fluoro-1-methyl-1*H*-indol-2-yl]piperidin-1-yl}propoxy)phenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile

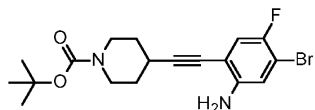


4-{4-[4-(3-Bromopropoxy)phenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile was reacted with 1-[4-fluoro-1-methyl-2-(piperidin-4-yl)-1*H*-indol-6-yl]-1,3-diazinane-2,4-dione in the general synthetic method

illustrated by example 12 to give the title compound; ^1H NMR: δ 1.55 – 1.69 (4H, m), 1.78 – 1.97 (6H, m), 2.07 (4H, s), 2.74 (4H, q), 2.95 – 3.09 (4H, m), 3.70 (3H, s), 3.79 (2H, t), 3.99 (2H, t), 4.17 (2H, d), 6.28 (1H, s), 6.84 (3H, dd), 7.16 (2H, d), 7.26 (2H, s), 7.32 (1H, d), 7.81 (1H, d), 10.34 (1H, s); m/z : ES^+ $[\text{M}+\text{H}]^+ = 731.4$.

5

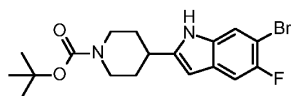
Intermediate 160a: *tert*-Butyl 4-[(2-amino-4-bromo-5-fluorophenyl)ethynyl]piperidine-1-carboxylate



5-Bromo-4-fluoro-2-iodoaniline and *tert*-butyl 4-ethynylpiperidine-1-carboxylate were reacted using the general synthetic method illustrated by intermediate 159a to give the title compound; ^1H NMR: δ 1.40 (9H, s), 1.46 – 1.64 (2H, m), 1.75 – 1.90 (2H, m), 2.80 – 2.94 (1H, m), 3.01 – 3.20 (2H, m), 3.60 – 3.73 (2H, m), 5.36 (2H, s), 6.95 (1H, d), 7.11 (1H, d); m/z : ES^+ $[\text{M}-t\text{Bu}]^+ = 341.1$.

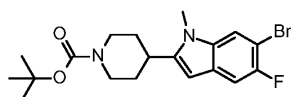
10

Intermediate 160b: *tert*-Butyl 4-(6-bromo-5-fluoro-1*H*-indol-2-yl)piperidine-1-carboxylate



15 *tert*-Butyl 4-[(2-amino-4-bromo-5-fluorophenyl)ethynyl]piperidine-1-carboxylate was reacted using the general synthetic method illustrated by intermediate 159b to give the title compound; ^1H NMR: δ 1.42 (9H, s), 1.46 – 1.61 (2H, m), 1.90 – 2.02 (2H, m), 2.71 – 3.00 (3H, m), 3.99 – 4.09 (2H, m), 6.20 (1H, d), 7.38 (1H, d), 7.52 (1H, d), 11.20 (1H, s); m/z : ES^+ $[\text{M}-t\text{Bu}]^+ = 341.1$.

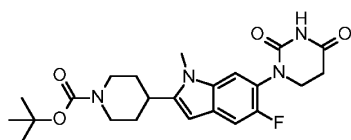
20 **Intermediate 160c: *tert*-Butyl 4-(6-bromo-5-fluoro-1-methyl-1*H*-indol-2-yl)piperidine-1-carboxylate**



tert-Butyl 4-(6-bromo-5-fluoro-1*H*-indol-2-yl)piperidine-1-carboxylate was reacted using the general synthetic method illustrated by intermediate 159c to give the title compound; ^1H NMR: δ 1.42 (9H, s), 1.42 – 1.53 (2H, m), 1.91 (2H, d), 2.92 – 3.04 (1H, m), 3.17 (1H, d), 3.31 (1H, s), 3.71 (3H, s), 4.00 – 4.12 (2H, m), 6.25 (1H, s), 7.39 (1H, d), 7.77 (1H, d); m/z : ES^+ $[\text{M}-t\text{Bu}]^+ = 355.1$.

25

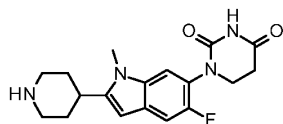
Intermediate 160d: *tert*-Butyl 4-[6-(2,4-dioxo-1,3-diazinan-1-yl)-5-fluoro-1-methyl-1*H*-indol-2-yl]piperidine-1-carboxylate



tert-Butyl 4-(6-bromo-5-fluoro-1-methyl-1*H*-indol-2-yl)piperidine-1-carboxylate was reacted using the general synthetic method illustrated by intermediate 146d to give the title compound; ¹H NMR: δ 1.44 (9H, s), 1.73 – 1.84 (3H, m), 1.84 – 1.91 (1H, m), 2.87 (3H, s), 3.16 – 3.28 (4H, m), 3.33 (1H, s), 4.04 – 4.12 (2H, m), 4.54 – 4.60 (2H, m), 7.07 – 7.17 (1H, m), 7.46 – 7.57 (1H, m), 7.67 (1H, s); m/z: ES⁺ [M-*t*Bu]⁺ = 389.2.

5

Intermediate 160e: 1-[5-Fluoro-1-methyl-2-(piperidin-4-yl)-1*H*-indol-6-yl]-1,3-diazinane-2,4-dione

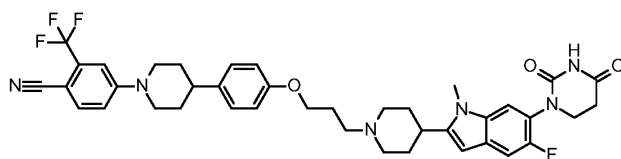


tert-Butyl 4-[6-(2,4-dioxo-1,3-diazinan-1-yl)-5-fluoro-1-methyl-1*H*-indol-2-yl]piperidine-1-carboxylate was reacted using the general synthetic method illustrated by intermediate 80g to give the title compound; ¹H NMR: δ 1.69 – 1.77 (2H, m), 2.03 (2H, d), 2.76 (2H, d), 2.95 (2H, t), 3.07 – 3.12 (1H, m), 3.29 (2H, d), 3.63 – 3.80 (5H, m), 6.25 (1H, s), 7.34 (1H, d), 7.48 – 7.54 (1H, m), 8.35 (1H, s), 10.44 (1H, s); m/z: ES⁺ [M+H]⁺ = 345.2.

10

Example 160: 4-{4-[4-(3-{4-[6-(2,4-Dioxo-1,3-diazinan-1-yl)-5-fluoro-1-methyl-1*H*-indol-2-yl]piperidin-1-yl}propoxy)phenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile

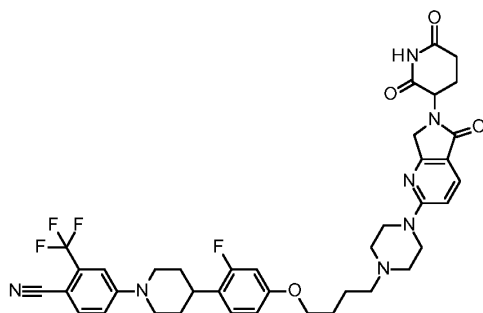
15



Intermediate 159f was reacted with 1-[5-fluoro-1-methyl-2-(piperidin-4-yl)-1*H*-indol-6-yl]-1,3-diazinane-2,4-dione in the general synthetic method illustrated by example 12 to give the title compound; ¹H NMR: δ 1.58 – 1.65 (4H, m), 1.84 – 1.92 (6H, m), 2.03 – 2.13 (2H, m), 2.69 – 2.85 (5H, m), 2.90 – 3.15 (5H, m), 3.66 – 3.75 (5H, m), 3.98 (2H, t), 4.17 (2H, d), 6.24 (1H, s), 6.82 – 6.89 (2H, m), 7.12 – 7.19 (2H, m), 7.22 – 7.34 (3H, m), 7.45 – 7.51 (1H, m), 7.81 (1H, d), 10.41 (1H, s); m/z: ES⁺ [M+H]⁺ = 731.3.

20

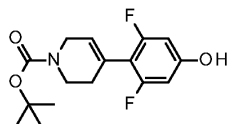
Example 161: 4-{4-[4-(4-{4-[6-(2,6-Dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]piperidin-2-yl]piperazin-1-yl}butoxy)-2-fluorophenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile



25

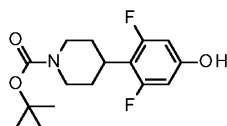
- Intermediate 156d was reacted with intermediate 38e in the general synthetic method illustrated by example 138 to give the title compound in the form of a formate salt; ^1H NMR (CDCl_3): δ 1.7 – 1.88 (6H, m), 1.95 (2H, d), 2.21 (1H, ddq), 2.33 (1H, qd), 2.74 – 2.97 (8H, m), 3 – 3.13 (3H, m), 3.79 – 3.98 (6H, m), 4.02 (2H, d), 4.19 (1H, d), 4.32 (1H, d), 5.20 (1H, dd), 6.60 (1H, dd), 6.64 (1H, dd), 6.69 (1H, s), 6.99 (1H, dd), 7.07 (1H, t), 7.16 (1H, d), 7.61 (1H, d), 7.89 (1H, d), 8.19 – 8.44 (2H, m); m/z : ES^+ $[\text{M}+\text{H}]^+ = 748.4$.

Intermediate 162a: *tert*-Butyl 4-(2,6-difluoro-4-hydroxyphenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate



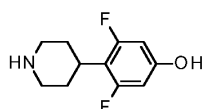
- tert*-Butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate was reacted with 4-bromo-3,5-difluorophenol in the general synthetic method illustrated by intermediate 9a to give the title compound; ^1H NMR: δ 1.43 (9H, s), 2.26 (2H, brs), 3.50 (2H, t), 3.96 (2H, br s), 5.75 (1H, brs), 6.4 – 6.5 (2H, m), 10.33 (1H, s); m/z : ES^+ $[\text{M}-t\text{Bu}]^+ = 256.1$.

Intermediate 162b: *tert*-Butyl 4-(2,6-difluoro-4-hydroxyphenyl)piperidine-1-carboxylate



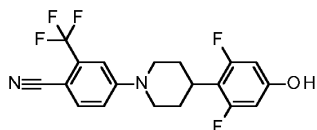
- tert*-Butyl 4-(2,6-difluoro-4-hydroxyphenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate was reacted with hydrogen gas in the general synthetic method illustrated by intermediate 9b to give the title compound; ^1H NMR (CDCl_3): δ 0.96 (1H, d), 1.15 (2H, d), 1.26 (2H, d), 1.48 (9H, s), 1.57 – 1.69 (2H, m), 1.69 – 1.86 (2H, m), 1.86 – 2.03 (3H, m), 2.32 – 2.46 (1H, m), 2.69 – 2.8 (2H, m), 3.00 (1H, tt), 4.21 (2H, d), 6.32 (2H, d); m/z : ES^+ $[\text{M}-t\text{Bu}]^+ = 258.1$.

Intermediate 162c: 3,5-Difluoro-4-(piperidin-4-yl)phenol



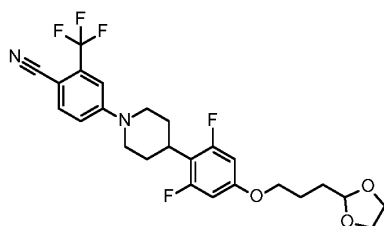
- tert*-Butyl 4-(2,6-difluoro-4-hydroxyphenyl)piperidine-1-carboxylate (130 mg, 0.41 mmol) was suspended in DCM (2 mL) and TFA (317 μL , 4.15 mmol) and was stirred at RT for 1 h. The solution was evaporated to dryness to afford crude product. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 1M NH_3/MeOH to give the title compound (0.083 g, 94 %) as a white solid; m/z : ES^+ $[\text{M}+\text{H}]^+ = 214.1$.

- Intermediate 162d: 4-[4-(2,6-Difluoro-4-hydroxyphenyl)piperidin-1-yl]-2-(trifluoromethyl)benzonitrile**



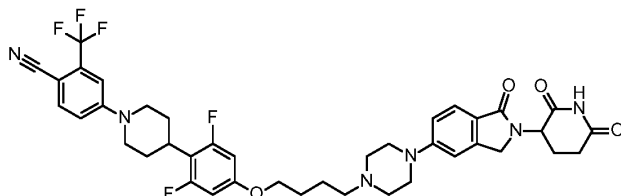
- 3,5-Difluoro-4-(piperidin-4-yl)phenol (83 mg, 0.39 mmol), 4-fluoro-2-(trifluoromethyl)benzonitrile (77 mg, 0.41 mmol) and DIPEA (74.6 μ L, 0.43 mmol) in NMP (1 mL) were stirred at 100 °C for 1 h. The reaction was cooled to RT and diluted with EtOAc (10 mL) and water (10 mL). The organic phase was washed with brine (10 mL), dried with MgSO_4 , filtered and evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% EtOAc in heptane to give the title compound (0.143 g, 96 %) as a white solid; ^1H NMR: δ 1.78 – 1.89 (2H, m), 1.99 – 2.07 (2H, m), 2.07 – 2.21 (2H, m), 2.40 (2H, t), 2.86 (3H, t), 2.96 – 3.08 (2H, m), 3.14 (1H, ddd), 3.36 – 3.45 (2H, m), 3.93 – 4.04 (2H, m), 6.35 – 6.44 (2H, m), 6.97 (1H, dd), 7.05 (1H, s), 7.15 (1H, d), 7.57 – 7.64 (1H, m); m/z: ES^- $[\text{M}-\text{H}]^- =$

Intermediate 162c: 4-(4-{4-[3-(1,3-Dioxolan-2-yl)propoxy]-2,6-difluorophenyl}piperidin-1-yl)-2-(trifluoromethyl)benzonitrile



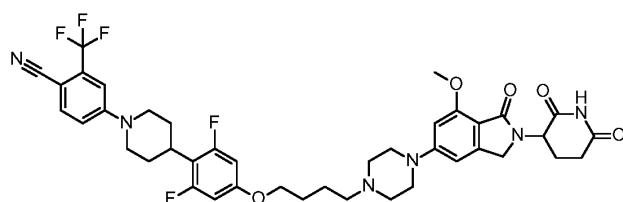
- To 4-[4-(2,6-difluoro-4-hydroxyphenyl)piperidin-1-yl]-2-(trifluoromethyl)benzonitrile (140 mg, 0.37 mmol) in MeCN (5 mL) was added K_2CO_3 (253 mg, 1.83 mmol) and 2-(3-bromopropyl)-1,3-dioxolane (99 μ L, 0.73 mmol). The reaction was stirred at 80 °C for 2 h. The mixture was cooled to RT, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% EtOAc in heptane to give the title compound (0.127 g, 69.9 %) as a white solid; ^1H NMR: δ 1.61 – 1.82 (6H, m), 1.85 – 2.01 (2H, m), 3.06 (2H, t), 3.12 – 3.22 (1H, m), 3.73 – 3.8 (2H, m), 3.85 – 3.92 (2H, m), 3.99 (2H, t), 4.11 – 4.24 (2H, m), 4.84 (1H, t), 6.67 (2H, d), 7.27 (1H, dd), 7.33 (1H, d), 7.81 (1H, d); m/z: ES^+ $[\text{M}+\text{H}]^+ = 497.4$.

Example 162: 4-{4-[4-(4-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl}butoxy)-2,6-difluorophenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile



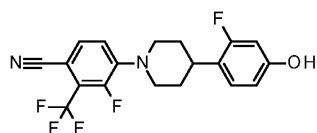
- 4-(4-{4-[3-(1,3-Dioxolan-2-yl)propoxy]-2,6-difluorophenyl}piperidin-1-yl)-2-(trifluoromethyl)benzonitrile was reacted with intermediate 2b in the general synthetic method illustrated by example 138 to give the title compound in the form of a formate salt; ^1H NMR (CDCl_3): δ 1.77 – 1.92 (6H, m), 2.07 – 2.26 (3H, m), 2.35 (1H, qd), 2.69 – 2.99 (8H, m), 3.06 (2H, t), 3.18 (1H, ddd), 3.43 – 3.56 (4H, m), 3.9 – 3.99 (2H, m), 3.99 – 4.07 (2H, m), 4.29 (1H, d), 4.44 (1H, d), 5.22 (1H, dd), 5.29 – 5.98 (1H, m), 6.43 (2H, d), 6.87 – 6.95 (1H, m), 6.96 – 7.06 (2H, m), 7.17 (1H, d), 7.64 (1H, d), 7.78 (1H, d), 8.11 (1H, s), 8.24 (1H, s); m/z: $\text{ES}^+ [\text{M}+\text{H}]^+ = 765.4$.

Example 163: 4-{4-[4-(4-{4-[2-(2,6-Dioxopiperidin-3-yl)-7-methoxy-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl}butoxy)-2,6-difluorophenyl]piperidin-1-yl}-2-(trifluoromethyl)benzonitrile



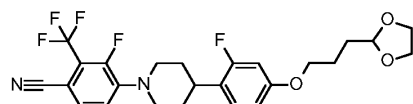
- Intermediate 162e was reacted with intermediate 1e in the general synthetic method illustrated by example 138 to give the title compound in the form of a formate salt; ^1H NMR (CDCl_3): δ 1.75 – 1.9 (6H, m), 2.05 – 2.21 (3H, m), 2.29 (1H, qd), 2.68 – 2.78 (2H, m), 2.78 – 2.88 (2H, m), 2.88 – 2.97 (4H, m), 3.03 (2H, t), 3.09 – 3.22 (1H, m), 3.39 – 3.52 (4H, m), 3.88 – 3.98 (5H, m), 4.01 (2H, d), 4.20 (1H, d), 4.35 (1H, d), 5.12 (1H, dd), 5.9 – 6.28 (1H, m), 6.41 (4H, dd), 6.97 (1H, dd), 7.14 (1H, d), 7.61 (1H, d), 8.13 – 8.34 (2H, m); m/z: $\text{ES}^+ [\text{M}+\text{H}]^+ = 795.3$.

Intermediate 164a: 3-Fluoro-4-[4-(2-fluoro-4-hydroxy-phenyl)-1-piperidyl]-2-(trifluoromethyl)benzonitrile



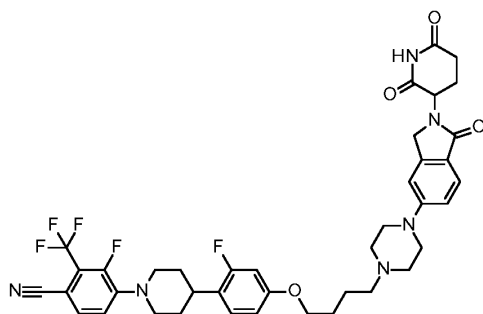
- Intermediate 38c was reacted with 1-bromo-3,4-difluoro-2-(trifluoromethyl)benzene in the general synthetic method illustrated by intermediate 137f to give the title compound; ^1H NMR (CDCl_3): δ 1.85 – 1.97 (4H, m), 2.92 – 3.11 (3H, m), 3.68 – 3.8 (2H, m), 6.54 – 6.65 (2H, m), 7.09 (2H, dt), 7.46 – 7.53 (1H, m); m/z: $\text{ES}^+ [\text{M}+\text{H}]^+ = 383.2$.

Intermediate 164b: 4-(4-{4-[3-(1,3-Dioxolan-2-yl)propoxy]-2-fluorophenyl}piperidin-1-yl)-3-fluoro-2-(trifluoromethyl)benzonitrile



3-Fluoro-4-[4-(2-fluoro-4-hydroxy-phenyl)-1-piperidyl]-2-(trifluoromethyl)benzonitrile was reacted with 2-(3-bromopropyl)-1,3-dioxolane in the general synthetic method illustrated by intermediate 38e to give the title compound; m/z: ES⁺ [M+H]⁺ = 497.3.

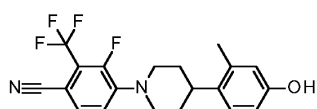
5 **Example 164: 4-{4-[4-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isindol-5-yl]piperazin-1-yl]butoxy}-2-fluorophenyl]piperidin-1-yl}-3-fluoro-2-(trifluoromethyl)benzonitrile**



4-(4-{4-[3-(1,3-Dioxolan-2-yl)propoxy]-2-fluorophenyl]piperidin-1-yl)-3-fluoro-2-(trifluoromethyl)benzonitrile was reacted with intermediate 2b in the general synthetic method illustrated by example 138 to give the title compound in the form of a formate salt; ¹H NMR (CDCl₃): δ 1.68 – 1.79 (2H, m), 1.8 – 1.98 (6H, m), 2.19 (1H, dtd), 2.32 (1H, qd), 2.49 – 2.57 (2H, m), 2.65 – 2.72 (4H, m), 2.75 – 3.1 (5H, m), 3.29 – 3.47 (4H, m), 3.73 (2H, d), 3.97 (2H, t), 4.25 (1H, d), 4.41 (1H, d), 5.19 (1H, dd), 6.61 (1H, dd), 6.67 (1H, dd), 6.88 (1H, d), 6.99 (1H, dd), 7.11 (2H, td), 7.49 (1H, d), 7.73 (1H, d), 7.99 – 8.11 (1H, m); m/z: ES⁺ [M+H]⁺ = 765.4.

15

Intermediate 165a: 3-Fluoro-4-[4-(4-hydroxy-2-methylphenyl)piperidin-1-yl]-2-(trifluoromethyl)benzonitrile

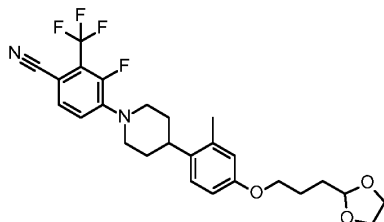


Intermediate 123c was reacted with 1-bromo-3,4-difluoro-2-(trifluoromethyl)benzene in the general synthetic method illustrated by intermediate 137f to give the title compound; ¹H NMR: δ 1.64 – 1.8 (4H, m), 2.25 (3H, s), 2.78 – 2.91 (1H, m), 3 – 3.13 (2H, m), 3.72 (2H, d), 6.53 – 6.58 (2H, m), 7.01 (1H, d), 7.46 (1H, t), 7.80 (1H, d), 9.02 (1H, s); m/z: ES⁺ [M+H]⁺ = 379.2.

20

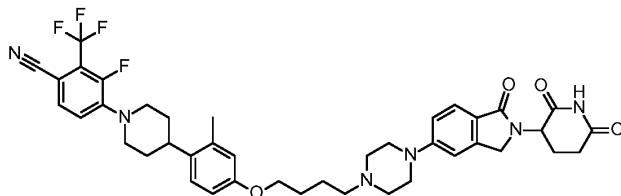
Intermediate 165b: 4-(4-{4-[3-(1,3-Dioxolan-2-yl)propoxy]-2-methylphenyl]piperidin-1-yl}-3-fluoro-2-(trifluoromethyl)benzonitrile

25



3-Fluoro-4-[4-(4-hydroxy-2-methylphenyl)piperidin-1-yl]-2-(trifluoromethyl)benzonitrile was reacted with 2-(3-bromopropyl)-1,3-dioxolane in the general synthetic method illustrated by intermediate 38e to give the title compound; ^1H NMR: δ 1.63 – 1.83 (8H, m), 2.30 (3H, s), 2.79 – 2.94 (1H, m), 3.01 – 3.13 (2H, m), 3.66 – 3.8 (4H, m), 3.85 – 3.98 (4H, m), 4.84 (1H, t), 6.67 – 6.75 (2H, m), 7.11 (1H, d), 7.45 (1H, t), 7.80 (1H, d); m/z: $\text{ES}^+ [\text{M}+\text{H}]^+ = 493.3$.

Example 165: 4-{4-[4-(4-{4-[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl]butoxy}-2-methylphenyl)piperidin-1-yl]-3-fluoro-2-(trifluoromethyl)benzonitrile

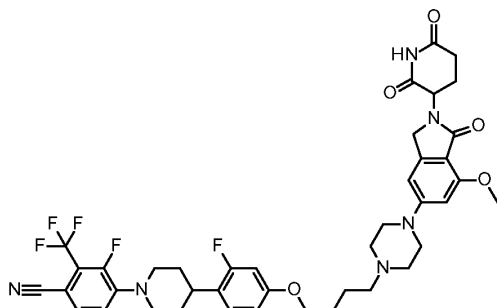


10

4-(4-{4-[3-(1,3-Dioxolan-2-yl)propoxy]-2-methylphenyl}piperidin-1-yl)-3-fluoro-2-(trifluoromethyl)benzonitrile was reacted with intermediate 2b in the general synthetic method illustrated by example 138 to give the title compound in the form of a formate salt; ^1H NMR (CDCl_3): δ 1.8 – 1.97 (8H, m), 2.15 – 2.27 (1H, m), 2.27 – 2.43 (4H, m), 2.75 – 2.97 (5H, m), 2.97 – 3.08 (6H, m), 3.45 – 3.56 (4H, m), 3.72 – 3.83 (2H, m), 4.00 (2H, t), 4.29 (1H, d), 4.44 (1H, d), 5.22 (1H, dd), 6.75 (2H, d), 6.92 (1H, d), 7.02 (1H, dd), 7.14 (2H, t), 7.52 (1H, d), 7.77 (1H, d), 8.21 (1H, s), 8.27 (1H, s); m/z: $\text{ES}^+ [\text{M}+\text{H}]^+ = 761.5$.

15

Example 166: 4-{4-[4-(4-{4-[2-(2,6-Dioxopiperidin-3-yl)-7-methoxy-1-oxo-2,3-dihydro-1H-isoindol-5-yl]piperazin-1-yl]butoxy}-2-fluorophenyl)piperidin-1-yl]-3-fluoro-2-(trifluoromethyl)benzonitrile

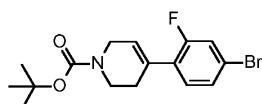


20

Intermediate 164b was reacted with intermediate 1e in the general synthetic method illustrated by example 138 to give the title compound in the form of a formate salt; ^1H NMR (CDCl_3): δ 1.66 – 2.01 (8H, m), 2.1 – 2.22

(1H, m), 2.30 (1H, qd), 2.48 – 2.6 (2H, m), 2.64 – 2.7 (4H, m), 2.75 – 3.1 (5H, m), 3.27 – 3.42 (4H, m), 3.74 (2H, d), 3.94 (3H, s), 3.97 (2H, t), 4.20 (1H, d), 4.36 (1H, d), 5.13 (1H, dd), 6.36 (1H, d), 6.45 – 6.49 (1H, m), 6.61 (1H, dd), 6.66 (1H, dd), 7.12 (2H, td), 7.49 (1H, d), 7.84 (1H, s), 8.09 (1H, s); m/z: ES⁺ [M+H]⁺ = 795.3.

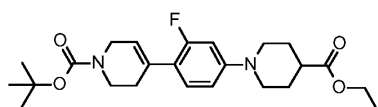
5 **Intermediate 167a: *tert*-Butyl 4-(4-bromo-2-fluorophenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate**



4-bromo-2-fluoro-1-iodobenzene was reacted with *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate in the general synthetic method illustrated by intermediate 8a to give the title compound; ¹H NMR: δ 1.43 (9H, s), 2.41 (2H, br s), 3.52 (2H, t), 3.99 (2H, br s), 6.02 (1H, br s), 7.30 – 7.35 (1H, m), 7.39 – 7.43 (1H, m), 7.54 (1H, dd).

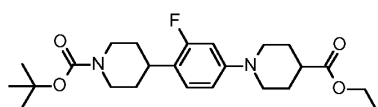
10

Intermediate 167b: *tert*-Butyl 4-{4-[4-(ethoxycarbonyl)piperidin-1-yl]-2-fluorophenyl}-3,6-dihydropyridine-1(2*H*)-carboxylate



- 15 To *tert*-butyl 4-(4-bromo-2-fluorophenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (1.0 g, 2.81 mmol) in toluene (30 mL) was added ethyl piperidine-4-carboxylate (0.883 g, 5.61 mmol) and sodium *tert*-butoxide (0.540 g, 5.61 mmol) at RT and was degassed for 5 mins followed by addition of Pd₂(dba)₃ (0.129 g, 0.140 mmol) and BINAP (0.175 g, 0.281 mmol). The mixture was stirred for 6 h at 120 °C and was then cooled to RT and quenched with water. The product was extracted with EtOAc (200 mL), washed with saturated brine
- 20 (50 mL), dried over Na₂SO₄, filtered and evaporated to dryness to afford crude product. The crude product was purified by flash column chromatography using EtOAc:Hexane (0-20 %) to give the title compound (0.5 g, 37 %) as yellow solid; m/z: ES⁺ [M+H]⁺ = 433.2.

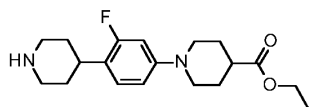
25 **Intermediate 167c: *tert*-Butyl 4-{4-[4-(ethoxycarbonyl)piperidin-1-yl]-2-fluorophenyl}piperidine-1-carboxylate**



tert-Butyl 4-{4-[4-(ethoxycarbonyl)piperidin-1-yl]-2-fluorophenyl}-3,6-dihydropyridine-1(2*H*)-carboxylate was reacted with hydrogen gas in the general synthetic method illustrated by intermediate 123b to give the title compound; m/z: ES⁺ [M+H]⁺ = 435.0.

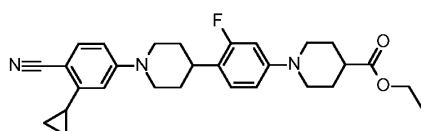
30

Intermediate 167d: Ethyl 1-[3-fluoro-4-(piperidin-4-yl)phenyl]piperidine-4-carboxylate



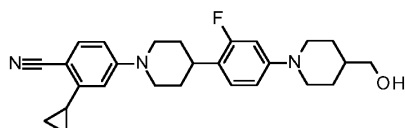
- To *tert*-butyl 4-{4-[4-(ethoxycarbonyl)piperidin-1-yl]-2-fluorophenyl}piperidine-1-carboxylate (0.4 g, 0.920 mmol) in DCM (20 mL) was added HCl (4M in dioxane, 10 mL, 40.0 mmol) dropwise at 0 °C. The reaction was stirred at RT for 4 h and then evaporated to dryness to afford crude product. The crude product was trituted in MTBE (30 mL) and filtered under vacuum to give the title compound in the form of an HCl salt and was used without further purification; m/z: ES⁺ [M+H]⁺ = 335.5.

Intermediate 167e: Ethyl 1-{4-[1-(4-cyano-3-cyclopropylphenyl)piperidin-4-yl]-3-fluorophenyl}piperidine-4-carboxylate



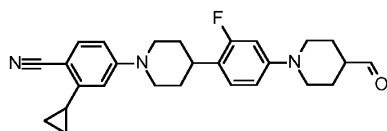
- To ethyl 1-[3-fluoro-4-(piperidin-4-yl)phenyl]piperidine-4-carboxylate hydrochloride (0.518 g, 1.396 mmol) in DMSO (7 mL) was added K₂CO₃ (0.386 g, 2.79 mmol) and 2-cyclopropyl-4-fluorobenzonitrile (0.15g, 0.931 mmol) and stirred at 120 °C for 16 h. The reaction was then cooled to RT and quenched with water. The product was extracted with EtOAc (200 mL), washed with saturated brine (50 mL), dried over Na₂SO₄, filtered and evaporated to dryness to afford crude product. The crude product was purified by flash column chromatography using EtOAc:Hexane (0-20 %) to give the title compound (0.3 g, 66.4 %) as yellow solid; m/z: ES⁺ [M+H]⁺ = 476.0.

Intermediate 167f: 2-Cyclopropyl-4-{4-[2-fluoro-4-[4-(hydroxymethyl)piperidin-1-yl]phenyl]piperidin-1-yl}benzonitrile



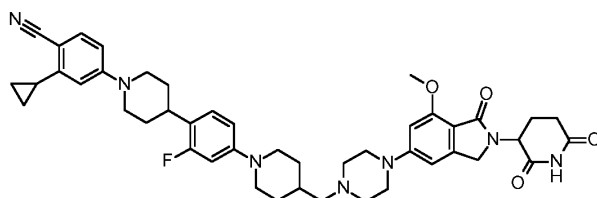
- To ethyl 1-{4-[1-(4-cyano-3-cyclopropylphenyl)piperidin-4-yl]-3-fluorophenyl}piperidine-4-carboxylate (0.3 g, 0.631 mmol) in methanol (15 mL) was added NaBH₄ (0.239 g, 6.31 mmol) at 0 °C and was stirred to RT for 4h. the reaction was quenched with saturated NH₄Cl solution and extracted with DCM (10 mL). The organic layer was washed with saturated brine (50 mL), dried over Na₂SO₄, filtered and evaporated to dryness to afford crude product. The crude product was purified by flash column chromatography using EtOAc:Hexane (0-50 %) to give the title compound (0.1 g, 35.8 %) as a white solid; ¹H NMR: δ 0.76 - 0.92 (2H, m), 0.97 - 1.11 (2H, m), 1.11 - 1.28 (2H, m), 1.45 - 1.56 (1H, m), 1.61 - 1.83 (6H, m), 2.08 (1H, tt), 2.55 - 2.72 (2H, m), 2.81 - 3.00 (3H, m), 3.19 - 3.41 (2H, m), 3.68 (2H, d), 4.03 (2H, d), 4.46 (1H, t), 6.46 (1H, d), 6.62 - 6.72 (2H, m), 6.85 (1H, dd), 6.98 - 7.16 (1H, m), 7.48 (1H, d); m/z: ES⁺ [M+H]⁺ = 434.0.

Intermediate 167g: 2-Cyclopropyl-4-{4-[2-fluoro-4-(4-formylpiperidin-1-yl)phenyl]piperidin-1-yl}benzonitrile



- 5 2-Cyclopropyl-4-(4-{2-fluoro-4-[4-(hydroxymethyl)piperidin-1-yl]phenyl}piperidin-1-yl)benzonitrile was reacted with Dess-Martin periodinane in the general synthetic method illustrated by intermediate 53b to give the title compound which was isolated crude and used without further purification.

Example 167: 2-Cyclopropyl-4-(4-{4-[4-{4-[2-(2,6-dioxopiperidin-3-yl)-7-methoxy-1-oxo-2,3-dihydro-1H-isindol-5-yl]piperazin-1-yl}methvl]piperidin-1-yl]-2-fluorophenyl}piperidin-1-yl)benzonitrile



- To intermediate 1f (0.16 g, 0.405 mmol) and 2-cyclopropyl-4-{4-[2-fluoro-4-(4-formylpiperidin-1-yl)phenyl]piperidin-1-yl}benzonitrile (0.175 g, 0.405 mmol) in DCM (10 mL) was added sodium acetate (0.066 g, 0.810 mmol) and was stirred at RT for 3 h followed by the addition of sodium triacetoxyborohydride (0.172 g, 0.810 mmol). The mixture was stirred at RT for 16 h and was extracted with DCM (80 mL). The solution was washed with water (100 mL), dried over Na₂SO₄, filtered and evaporated to afford crude product.
- 15 Purification by preparative HPLC (Column A, Eluent A) was performed and the fractions containing product were evaporated followed by neutralization with saturated NaHCO₃ solution and extracted with DCM (2x 50 mL). The organic layer was dried with Na₂SO₄, filtered and evaporated to dryness to give the title compound
- 20 (0.025 g, 7.81 %) as a white solid; ¹H NMR: δ 0.80 - 0.90 (2H, m), 0.98 - 1.09 (2H, m), 1.15 - 1.25 (2H, m), 1.65 - 1.83 (7H, m), 2.06 - 2.12 (1H, m), 2.22 (1H, d), 2.30 - 2.36 (3H, m), 2.59 - 2.71 (7H, m), 2.90 (4H, t), 3.43 (4H, br s), 3.68 (2H, d), 3.84 (3H, s), 3.98 - 4.09 (3H, m), 4.19 - 4.27 (1H, m), 4.97 (1H, dd), 6.44 - 6.52 (2H, m), 6.61 (1H, s), 6.65 - 6.73 (2H, m), 6.85 (1H, dd), 7.01 - 7.13 (1H, m), 7.48 (1H, d), 10.91 (1H, s); m/z: ES⁺ [M+H]⁺ = 774.5.

25

LNCaP Androgen Receptor Imaging Assay

- This cell-based imaging assay uses immuno-fluorescence to measure both cell number and endogenous nuclear AR staining in the prostate cancer cell line LNCaP (expressing AR-full length). The purpose of the assay is to identify compounds that regulate AR protein level according to the protocol laid out
- 30 in the steps below.

All work was performed in a sterile tissue culture hood up to the point of cell fixation. LNCaP cells were cultured at 6-8 × 10⁶ per T175 flask and split every 3-4 days. Medium: RPMI 1640 (VWR Sigma)

containing 10% FCS and 1% glutamine. Cells were plated in assay ready plates at a density of 12,000 cells (CedexTM Cell counter, Beckmann & Coulter), 40µL per well, using a Multidrop (ThermoFisher).

Cells were dosed with test compound diluted in DMSO using an Echo 555TM (Labcyte) and the final concentration of DMSO in the well was 0.3%. A neutral control (DMSO) and a positive AR degrader control at 3µM (a prior art AR PROTAC) were included. The Echo uses acoustic technology to perform direct microplate-to-microplate transfers of DMSO compound solutions to assay plates. The system can be programmed to transfer volumes as low as 2.5 nL in multiple increments between microplates and in so doing generates a serial dilution of compound in the assay plate which is then back-filled to normalise the DMSO concentration across the dilution range. Compounds were dispensed onto the cell plates with a compound source plate prepared as above producing a 12 point dose response curve with 3-fold dilutions and one final 10-fold dilution, and a top concentration of 3 or 30µM using the Integrated Echo workcell. The plates were incubated at 37°C / 5% CO₂ for 24h and then fixed and stained as below.

40µL of 8% paraformaldehyde solution (v/v) in phosphate buffered saline (PBS) was added on top of the media already in the well using a Multidrop to fix plates giving a final concentration of 4% PFA (v/v) for 20-30 minutes (keep in fume hood to minimise PFA exposure). After 20-30 mins, the plates were washed with 3 × PBS using a BioTek washer.

The cells were incubated with a Mouse monoclonal Anti-AR antibody AR441 (DAKO M3562) (1:1000), diluted in modified blocking buffer (PBS+1% BSA+0.1% TritonX); 15 µL / well for 2h at RT. The plates were then washed with 3 × PBS using a BioTek washer. Cells were then incubated with Goat anti-mouse secondary antibody 488 (Invitrogen A11001) (1:500) and nuclear stain, DRAQ5 (Abcam Ab108410) (1:2000) diluted in modified blocking buffer for 45 mins at room temperature 15 µL / well. Plates are then washed with 3 × PBS using a BioTek washer and sealed with black plate seals.

Plates are read using a Cellomics Cellinsight to measure the Androgen Receptor level in each well. The data is exported into Genedata to perform curve fitting analysis. All data are normalized as % of positive control and any data points that fall on the hook of the curve are masked before fitting. Down-regulation of AR is expressed as a DC₅₀ value and determined by calculation of the concentration of compound that is required to give 50% of maximum degradation of AR as per the curve fit for that compound. The maximum degradation observed for each compound is expressed as D_{max}. The AR degradation data for compounds is shown in the table below and may be a result from a single experiment or an average of two or more experiments.

Example No.	LNCaP AR Degradation DC ₅₀ (nM)	LNCaP AR Degradation D _{max} (%)
1	11.8	94
2	8.6	95
3	61.2	85
4	24.7	91
5	42.8	90
6	23.6	97
7	17.3	92

Example No.	LNCaP AR Degradation DC ₅₀ (nM)	LNCaP AR Degradation D _{max} (%)
8	15.7	84
9	17.5	72
10	20.2	83
11	22.2	75
12	58.0	82
13	22.2	79
14	133.8	92

Example No.	LNCaP AR Degradation DC ₅₀ (nM)	LNCaP AR Degradation D _{max} (%)
15	72.9	84
16	17.8	97
17	13.2	68
18	30.9	64
19	26.2	95
20	27.9	97
21	14.9	92
22	17.5	79
23	60.6	100
24	20.4	92
25	22.1	95
26	11.0	89
27	107.3	73
28	48.6	78
29	6.6	92
30	24.5	99
31	154.1	88
32	21.6	93
33	12.9	96
34	10.3	93
35	22.2	90
36	13.1	94
37	57.2	82
38	9.0	99
39	25.2	93
40	19.1	89
41	10.4	98
42	58.4	87
43	20.1	93
44	19.3	92
45	23.0	87
46	31.7	93
47	40.2	98
48	6.4	87
49	27.0	81
50	32.0	86
51	30.1	93
52	21.6	79
53	12.5	88
54	13.2	97
55	47.8	70

Example No.	LNCaP AR Degradation DC ₅₀ (nM)	LNCaP AR Degradation D _{max} (%)
56	37.7	74
57	18.5	80
58	11.4	84
59	28.3	99
60	14.0	94
61	22.0	95
62	21.1	97
63	106.9	82
64	62.7	69
65	368.7	62
66	17.1	63
67	45.4	85
68	19.5	88
69	81.9	59
70	555.1	78
71	89.4	64
72	80.6	95
73	34.9	90
74	23.2	83
75	26.7	84
76	11.4	92
77	30.4	52
78	911.2	67
79	61.7	63
80	91.5	100
81	88.1	88
82	46.4	67
83	38.6	80
84	56.3	82
85	91.6	99
86	4.9	83
87	113.1	68
88	101.4	88
89	63.0	87
90	54.9	68
91	13.6	90
92	53.8	85
93	30.1	79
94	48.3	86
95	29.0	79
96	26.0	78

Example No.	LNCaP AR Degradation DC ₅₀ (nM)	LNCaP AR Degradation D _{max} (%)
97	91.5	67
98	119.0	83
99	137.8	75
100	69.5	79
101	40.8	96
102	15.1	95
103	10.8	81
104	68.4	86
105	28.6	99
106	80.7	98
107	53.1	45
108	25.2	66
109	26.3	95
110	34.9	74
111	23.9	55
112	18.1	82
113	28.7	89
114	24.3	88
115	17.7	81
116	7.0	68
117	12.7	90
118	21.0	88
119	22.0	94
120	15.7	90
121	11.7	97
122	4.1	98
123	13.5	97
124	23.4	79
125	15.1	98
126	10.9	99
127	16.6	89
128	14.2	88
129	25.2	93
130	6.3	91
131	20.0	90
132	42.8	93
133	12.8	91
134	8.6	95
135	14.7	96
136	35.5	88

LNCaP Androgen Receptor L702H Imaging Assay

- While treatment with AR antagonists has been shown to be of patient benefit, most cancers eventually progress to castration resistant prostate cancer (CRPC). At this stage, anti-androgen therapy is largely ineffective due to AR amplification, overexpression or point mutation. One of the point mutations observed in patient populations is L702H in the AR Ligand Binding Domain. LNCaP cells have been engineered to introduce the mutation L702H into the AR gene using CRISPR/Cas9. The previously described imaging-based AR assay will monitor nuclear AR (L702H) levels in these cells to identify compounds that regulate AR (L702H). Down-regulation of AR (L702H) is expressed as a DC_{50} value and determined by calculation of the concentration of compound that is required to give 50% of maximum degradation of AR (L702H) as per the curve fit for that compound. The maximum degradation observed for each compound is expressed as D_{max} . The AR and AR (L702H) degradation data for compounds is shown in the table below and may be a result from a single experiment or an average of two or more experiments.

Example No.	LNCaP AR Degradation DC_{50} (nM)	LNCaP AR Degradation D_{max} (%)	LNCaP AR (L702H) Degradation DC_{50} (nM)	LNCaP AR (L702H) Degradation D_{max} (%)
6	24	97	92	74
24	20	92	152	65
25	22	95	482	72
46	32	93	265	66
54	13	97	107	78
126	11	99	683	84
133	13	91	462	76
137	15	99	542	83
138	6	100	81	76
139	54	86	330	100
140	30	77	49	79
141	>3000		>3000	
142	32	96	92	91
143	>3000		>3000	
144	87	92	103	89
145	5	101	1000	100
146	13	98	13	73
147	18	104	633	80
148	74	101	469	100
149	62	90	73	94
150	25	88	169	80
151	5	99	>3000	
152	24	100	172	93
153	20	104	923	94
154	7	101	>3000	
155	47	99	511	92
156	30	94	103	75

Example No.	LNCaP AR Degradation DC ₅₀ (nM)	LNCaP AR Degradation D _{max} (%)	LNCaP AR (L702H) Degradation DC ₅₀ (nM)	LNCaP AR (L702H) Degradation D _{max} (%)
157	6	102	1400	100
158	4	101	2800	100
159	39	97	>3000	
160	22	95	-	-
161	5	94	2200	100
162	5	104	132	84
163	4	104	82	74
164	15	95	433	88
165	35	102	>3000	
166	7	104	266	74
167	27	101	573	60

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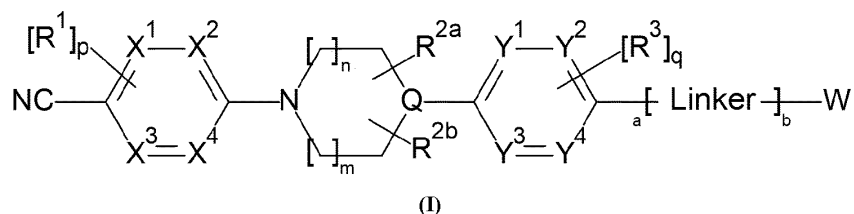
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STATEMENTS

1. A compound of Formula (I):



or a pharmaceutically acceptable salt thereof,

wherein:

X^1 is C & 0, 1 or 2 of X^2 , X^3 & X^4 is/are N, and are otherwise C;

or

X^3 & X^4 are both C and are substituted by $-X^5=X^6-X^7=X^8-$ with X^5 attached to X^3 and with X^8 attached to X^4 , where 1 or 2 of X^1 , X^2 , X^5 , X^6 , X^7 & X^8 is/are N, and are otherwise C;

p is 1 or 2 and X^1 is C attached to R^1 when X^3 & X^4 are not substituted by $-X^5=X^6-X^7=X^8-$; and otherwise p is 0, 1 or 2;

where:

each R^1 is a substituent on any C atom at X^1 , X^2 , X^3 & X^4 , (or at X^1 , X^2 , X^5 , X^6 , X^7 & X^8 when X^3 & X^4 are substituted by $-X^5=X^6-X^7=X^8-$), and is independently selected from F, Cl, C_{1-3} alkyl and C_{1-3} alkoxy, wherein said C_{1-3} alkyl and C_{1-3} alkoxy may be independently optionally substituted by one or more F;

n is 0, 1 or 2;

m is 0 or 1;

Q is CH or N when n & m are both other than 0 and otherwise Q is CH;

R^{2a} and R^{2b} are substituents on the same or different C atoms other than at Q , each independently selected from H, F and C_{1-3} alkyl, or R^{2a} & R^{2b} together form a $-(CH_2)_r-$ group where r is 1, 2 or 3;

0, 1 or 2 of Y^1 , Y^2 , Y^3 & Y^4 is/are N, and are otherwise C;

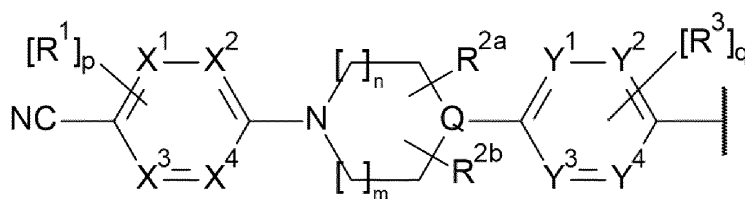
each R^3 is a substituent on any C atom at Y^1 , Y^2 , Y^3 & Y^4 , and is independently selected from F, Cl, CN, C_{1-3} alkyl and C_{1-3} alkoxy, wherein said C_{1-3} alkyl and C_{1-3} alkoxy may be independently optionally substituted by one or more F;

q is 0, 1 or 2;

Linker is a saturated or a partially or fully unsaturated framework comprising C and H atoms and at least one heteroatom, wherein said framework has end points of attachment 'a' and

- ‘b’ and a minimum length of from 6 to 26 atoms between ‘a’ and ‘b’; wherein said framework may include one or more straight and/or branched chains and/or rings and is optionally substituted on any available C atom(s) by one or more F; and is an E3 ubiquitin ligase cereblon binder unit.
- 5 **W**
2. The compound of **Formula (I)**, or pharmaceutically acceptable salt thereof, according to statement 1 wherein the **Linker** is a saturated or partially unsaturated framework.
- 10 3. The compound of **Formula (I)**, or pharmaceutically acceptable salt thereof, according to statement 1 or statement 2 wherein the **Linker** comprises C and H atoms and at least two heteroatoms.
4. The compound of **Formula (I)**, or pharmaceutically acceptable salt thereof, according to statement 1 or statement 2 wherein the **Linker** comprises C and H atoms and at least one nitrogen heteroatom in the form of a secondary or tertiary amine.
- 15
5. The compound of **Formula (I)**, or pharmaceutically acceptable salt thereof, according to statement 1 or statement 2 wherein the **Linker** includes at least one nitrogen-containing saturated or partially unsaturated heterocyclic group having from 4 to 12 ring atoms, or a $A^1-CH_2-CH_2-A^2$ unit where A^1 and A^2 are each independently selected from N and O.
- 20
6. The compound of **Formula (I)**, or pharmaceutically acceptable salt thereof, according to any one of statements 1 to 5 wherein the **Linker** has the **Formula**:
- ‘a’ - $Q^A-Q^B-Q^C$ - ‘b’
- 25 wherein:
- ‘a’ and ‘b’ represent the end points of attachment;
- Q^A is -G- Q^H - or -G-(C₁₋₅alkylene)-;
- Q^B is a direct bond, - $Q^{B1}-Q^{B2}-Q^{B3}$ - or C₁₋₃alkylene optionally substituted by one or more F (e.g. 1 or 2);
- where:
- 30 Q^{B1} & Q^{B3} each independently represent a direct bond or C₁₋₂alkylene;
- Q^{B2} is Q^H , -O-CH₂CH₂-O-, -O- or -N(R^J)- where R^J is H or C₁₋₃alkyl;
- Q^C is - Q^H -G- or -(C₁₋₅alkylene)-G-;
- each G is independently a direct bond, -CH₂-, -O-, or -N(R^G)- where R^G is H or C₁₋₃alkyl;
- each Q^H is independently a 4-12-membered nitrogen-containing saturated or partially unsaturated heterocyclic group;
- 35 where the values of Q^A , Q^B and Q^C are selected so that the **Linker** does not contain any N-N or N-O bonds.

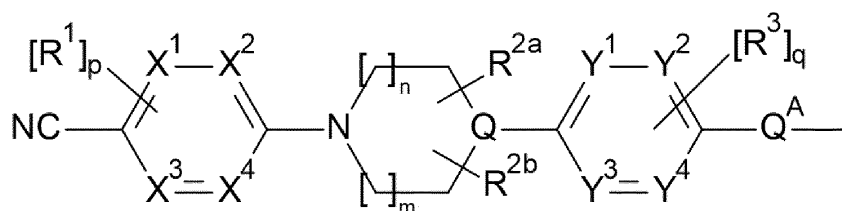
7. The compound of **Formula (I)**, or pharmaceutically acceptable salt thereof, according to statement 6 wherein Q^{B2} is Q^H , $-O-CH_2CH_2-O-$ or $-N(R^J)-$ where R^J is $C_{1-3}alkyl$.
8. The compound of **Formula (I)**, or pharmaceutically acceptable salt thereof, according to statement 6 or statement 7 wherein Q^C is $-Q^H-G-$ or $-(C_{1-2}alkylene)-G-$.
9. The compound of **Formula (I)**, or pharmaceutically acceptable salt thereof, according to any one of statements 6 to 8, wherein each Q^H is independently selected from piperazin-1,4-diyl, azetidin-1,3-diyl, piperidin-1,4-diyl, 1,4-diazepan-1,4-diyl, 12-oxa-3,9-diazaspiro[5.6]dodecan-3,9-diyl, pyrrolidin-1,3-diyl, 3,9-diazaspiro[5.5]undecan-3,9-diyl, 2,5-diazabicyclo[2.2.1]heptan-2,5-diyl, 1,3,3a,4,6,6a-hexahydropyrrolo[3,4-*c*]pyrrol-2,5-diyl, 3,6-dihydro-2*H*-pyridin-1,4-diyl and 9-azaspiro[5.5]undecan-3,9-diyl.
10. The compound of **Formula (I)**, or pharmaceutically acceptable salt thereof, according to any one of statements 1 to 9, wherein the **Linker** is selected from any of **Linkers** 1 to 46 or 1 to 48 as shown in the description.
11. A PROTAC compound or a pharmaceutically acceptable salt thereof, containing an E3 ubiquitin ligase cereblon binder unit and an AR binding unit of **Formula (Ia)**:



(Ia)

where R^1 , p , X^1 , X^2 , X^3 , X^4 , n , m , R^{2a} , R^{2b} , Q , Y^1 , Y^2 , Y^3 , Y^4 , R^3 and q are as defined in statement 1.

12. The PROTAC compound or a pharmaceutically acceptable salt thereof, according to statement 11, containing an E3 ubiquitin ligase cereblon binder unit and an AR binding unit of **Formula (Ia)** of **Formula (Ib)**:



(Ib)

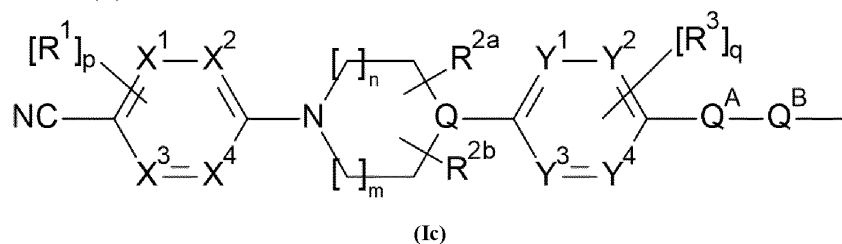
where:

Q^A is $-G-Q^H-$ or $-G-(C_{1-5}\text{alkylene})-$;

G is a direct bond, $-\text{CH}_2-$, $-\text{O}-$, or $-\text{N}(\text{R}^G)-$ where R^G is H or $\text{C}_{1-3}\text{alkyl}$; and

Q^H is a 4-12-membered nitrogen-containing saturated or partially unsaturated heterocyclic group.

- 5 13. The PROTAC compound or a pharmaceutically acceptable salt thereof, according to statement 12, containing an E3 ubiquitin ligase cereblon binder unit and an AR binding unit of **Formula (Ia)** of **Formula (Ic)**:



- 10 where:

Q^B is a direct bond, $-Q^{B1}-Q^{B2}-Q^{B3}-$ or $\text{C}_{1-3}\text{alkylene}$ optionally substituted by one or more F (e.g. 1 or 2);

where:

Q^{B1} & Q^{B3} each independently represent a direct bond or $\text{C}_{1-2}\text{alkylene}$;

Q^{B2} is Q^H , $-\text{O}-\text{CH}_2\text{CH}_2-\text{O}-$, $-\text{O}-$ or $-\text{N}(\text{R}^J)-$ where R^J is H or $\text{C}_{1-3}\text{alkyl}$;

- 15 and each Q^H is independently a 4-12-membered nitrogen-containing saturated or partially unsaturated heterocyclic group;

where the values of Q^A and Q^B are selected so that **Formula (Ic)** does not contain any N-N or N-O bonds.

- 20 14. The PROTAC compound or a pharmaceutically acceptable salt thereof, according to statement 12 or statement 13, where:

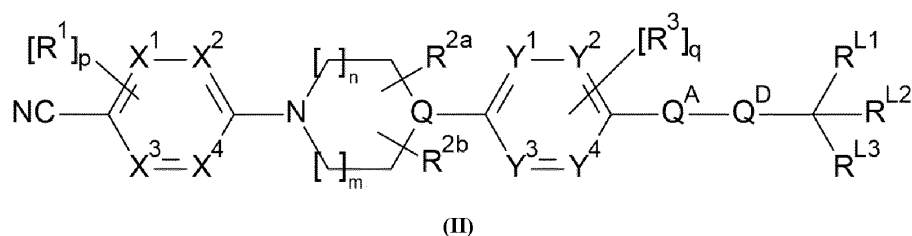
Q^A is $-G^A-Q^{HA}-$ or $-G^A-(C_{1-5}\text{alkylene})-$ where:

G^A is selected from a direct bond, $-\text{CH}_2-$, $-\text{O}-$ or $-\text{N}(\text{R}^G)-$;

R^G is H or $\text{C}_{1-3}\text{alkyl}$; and

- 25 Q^{HA} is a 4 to 11-membered nitrogen-containing saturated heterocyclic group.

15. A compound of **Formula (II)**:



- 30 or a salt thereof, wherein:

Q^A is $-G-Q^H-$ or $-G-(C_{1-5}\text{alkylene})-$;

G is a direct bond, -CH₂-, -O-, or -N(**R^G**)- where **R^G** is H or C₁₋₃alkyl;

Q^H is a 4-12-membered nitrogen-containing saturated or partially unsaturated heterocyclic group;

Q^D is a direct bond or C₁₋₂alkylene optionally substituted by one or more F (for example 1 or 2 F); and

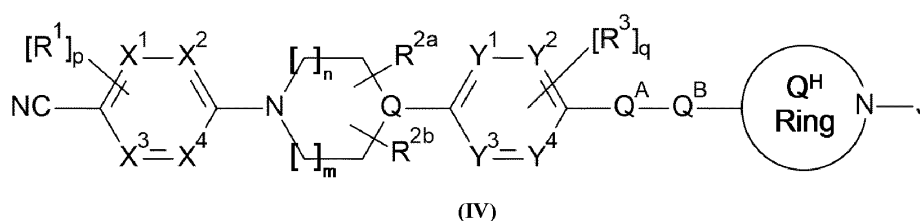
- 5 (i) **R^{L1}** & **R^{L2}** together form “=O” and **R^{L3}** is H or C₁₋₆alkoxy;
 (ii) **R^{L1}** & **R^{L2}** are each independently C₁₋₆alkoxy, and **R^{L3}** is H;
 (iii) **R^{L1}** & **R^{L2}** together form -O-(CH₂)_k-O- where **k** is 2 or 3, and **R^{L3}** is H; or
 (iv) **R^{L1}** is OH or **LG¹** where **LG¹** is a leaving group, and **R^{L2}** & **R^{L3}** are both H;

where when **Q^D** is a direct bond and **Q^A** is -**G-Q^H**-, the value of **Q^H** is selected so that **Q^D** connects to a C atom of **Q^H**;

10 and **R¹**, **p**, **X¹**, **X²**, **X³**, **X⁴**, **n**, **m**, **Q**, **R^{2a}**, **R^{2b}**, **Y¹**, **Y²**, **Y³**, **Y⁴**, **R³** and **q** are as defined in statement 1.

16. The compound of **Formula (II)** or a salt thereof, according to statement 15, wherein **LG¹** is selected from Cl, Br, I, trifluoromethanesulfonate and C₁₋₇hydrocarbysulfonate.

- 15 17. A compound of **Formula (IV)**:



or a salt thereof, wherein:

J is H or **PG²** where **PG²** is a nitrogen protecting group (for example a *tert*-butoxycarbonyl group);

20 **Q^A** is -**G-Q^H**-, or -**G-(C₁₋₅alkylene)**-;

G is a direct bond, -CH₂-, -O-, or -N(**R^G**)- where **R^G** is H or C₁₋₃alkyl;

Q^B is a direct bond, -**Q^{B1}-Q^{B2}-Q^{B3}**- or C₁₋₃alkylene optionally substituted by one or more F (e.g. 1 or 2);

where:

Q^{B1} & **Q^{B3}** each independently represent a direct bond or C₁₋₂alkylene;

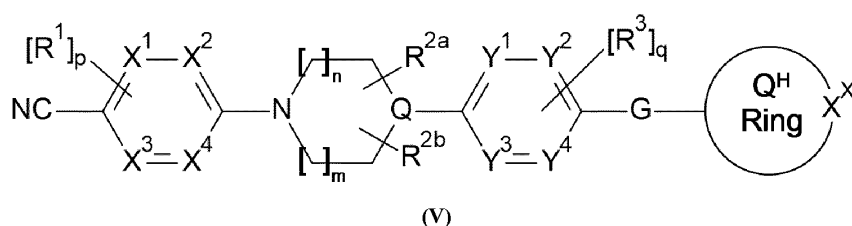
25 **Q^{B2}** is **Q^H**, -O-CH₂CH₂-O-, -O- or -N(**R^J**)- where **R^J** is H or C₁₋₃alkyl;

and each **Q^H** (including the “**Q^H Ring**” attached to **J**) is independently a 4-12-membered nitrogen-containing saturated or partially unsaturated heterocyclic group;

where the values of **Q^A**, **Q^B** and **Q^H Ring** are selected so that **Formula (IV)** does not contain any N-N or N-O bonds; and **R¹**, **p**, **X¹**, **X²**, **X³**, **X⁴**, **n**, **m**, **R^{2a}**, **R^{2b}**, **Q**, **Y¹**, **Y²**, **Y³**, **Y⁴**, **R³** and **q** are as defined in statement 1.

18. The compound of **Formula (IV)**, or a salt thereof, as stated in statement 17, wherein **PG²** is C₁₋₆alkoxycarbonyl.

- 35 19. A compound of **Formula (V)**:



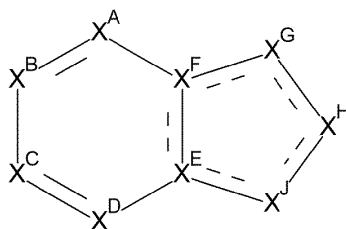
or a salt thereof, wherein:

X^X is selected from:

- 5 (i) N substituted by **J** where **J** is H or **PG³** where **PG³** is a protecting group; and
 (ii) C substituted by oxo, or by **R^{U1}** and **R^{U2}**; where **R^{U1}** and **R^{U2}** are each C₁₋₆alkoxy;
 or **R^{U1}** and **R^{U2}** together represent $-O-(CH_2)_u-O-$ where **u** is 2 or 3;
G is a direct bond, $-CH_2-$, $-O-$, or $-N(R^G)-$ where **R^G** is H or C₁₋₃alkyl;
Q^H Ring is a 4-12-membered nitrogen-containing saturated or partially unsaturated heterocyclic group;
 10 where the values of **G** and **Q^H Ring** are selected so that **Formula (V)** does not contain any N-N or N-O bonds; and **R¹**, **p**, **X¹**, **X²**, **X³**, **X⁴**, **n**, **m**, **R^{2a}**, **R^{2b}**, **Q**, **Y¹**, **Y²**, **Y³**, **Y⁴**, **R³** and **q** are as defined in statement 1.

20. The compound of **Formula (V)**, or a salt thereof, according to statement 19, wherein **PG³** is
 15 C₁₋₆alkoxycarbonyl.

21. The compound of **Formula (I)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1 to 10, wherein **W** is **W1** which is: $-Z-(R^A)_h$
 where **Z** is:



20

wherein:

represents a single covalent bond or a double covalent bond;

0, 1 or 2 of **X^A**, **X^B**, **X^C**, **X^D**, **X^E** & **X^F**

is/are N, where **X^E** & **X^F** are not both N, and are otherwise C;

25

1 of **X^G**, **X^H** & **X^J**

is C(O);

1 of **X^G**, **X^H** & **X^J**

is N-(2,6-dioxopiperidin-3-yl) (**Y**); and

1 of **X^G**, **X^H** & **X^J**

is selected from C(**R^T**)₂, $-CH_2CH_2-$, C(O), N(C₁₋₃alkyl), $-O-$ and $-N=$, wherein each **R^T** is selected from H, F, Me

or together with the carbon of $C(R^T)_2$ forms a cycloprop-1,1-diyl group;

where $\mathbf{X}^G$, $\mathbf{X}^H$ & $\mathbf{X}^J$ are selected such that there are not two C(O) groups present at adjacent positions, and that the N-(2,6-dioxopiperidin-3-yl) is not at an adjacent position to either N(C₁₋₃alkyl) or O;

is independently a substituent on any available C atom at **X^A**, **X^B**, **X^C** or **X^D** selected from F, Cl, C₁₋₃alkyl,

C₁₋₃alkoxy wherein said C₁₋₃alkyl and C₁₋₃alkoxy is

independently optionally substituted by one or more F;

is 0, 1 or 2; and

is attached to any C atom at $\mathbf{X}^A$, $\mathbf{X}^B$, $\mathbf{X}^C$ or $\mathbf{X}^D$.

5

each $\mathbf{R}^A$

10

h

wherein the **Linker**

15

22. The compound of **Formula (I)**, or a pharmaceutically acceptable salt thereof, according to statement 21 where each **R^A** is a substituent on any available C at **X^A**, **X^B**, **X^C** or **X^D** selected from F, Cl and C₁₋₃alkoxy optionally substituted by one or more F.

20

23. The compound of **Formula (I)**, or a pharmaceutically acceptable salt thereof, according to statement 21 or statement 22 where X^G - X^H - X^J is:

(i) $\mathbf{X}^G\text{-NY-C(O)}$ where $\mathbf{X}^G$ is $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $=\text{N-}$ or C(O)- ;

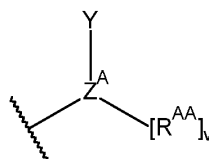
(ii) $\text{X}^{\text{G}}\text{-C(O)-NY}$ where X^{G} is -O- or $\text{N}(\text{C}_{1-3}\text{alkyl})$; or

(iii) C(O)-NY-CH_2 .

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24. The compound of **Formula (I)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 21 to 23 where $-Z-(R^A)_h$ together represent any of the groups 1 to 21 as shown in the description.

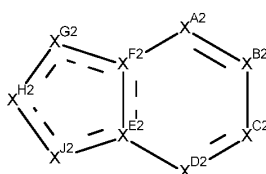
25. The compound of **Formula (I)**, or a pharmaceutically acceptable salt thereof, according to any one of



statements 1 to 10, wherein **W** is **W2** which is

30

$\mathbf{Z}^A$ is:



wherein:

1 of X^{A2} , X^{B2} , X^{C2} & X^{D2}

represents a single covalent bond or a double covalent bond;

is C and covalently bound to **Y**;

0, 1 or 2 of X^{A2} , X^{B2} , X^{C2} , X^{D2} , X^{E2} & X^{F2} is/are N (where X^{E2} & X^{F2} are not both N) and are

otherwise C;

1 or 2 of X^{G2} , X^{H2} & X^{J2}

is/are N; and are otherwise C;

each R^{AA}

is a substituent on any available C or N atom of **Z** – in each case

independently selected from R^{AA1} optionally substituted by one

or more R^{AA2} ; where R^{AA} is further selected from R^{AA2} when

R^{AA} is a substituent on an available C atom of Z^A ;

each R^{AA1}

is independently C₁₋₄alkyl, C₂₋₃alkenyl, C₂₋₃alkynyl,

C₁₋₃alkoxyC₁₋₃alkyl, carboxyC₁₋₃alkyl, C₅₋₇carbocyclyl or a 4-6

membered heterocyclyl;

each R^{AA2}

is independently selected from F, Cl, Br, CN, NH₂, C₁₋₃alkyl,

O(C₁₋₃alkyl), NH(C₁₋₃alkyl) and N(C₁₋₃alkyl)₂; wherein said

C₁₋₃alkyls are optionally substituted by one or more F;

v

is 0, 1 or 2;

Y

is N-(2,6-dioxopiperidin-3-yl).

26. The compound or salt thereof according to statement 25, wherein

1 of X^{A2} & X^{B2} is C and covalently bound to **Y** and the other of X^{A2} & X^{B2} is C;

0 or 1 of X^{C2} & X^{D2}

is N and is/are otherwise C;

1 of X^{G2} & X^{J2}

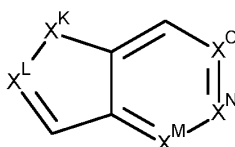
is N and the other of X^{G2} & X^{J2} is C; and

X^{H2} , X^{E2} & X^{F2}

are all C.

25

27. The compound or salt thereof according to statement 25, wherein **W** is **W2-1**



wherein:

X^K and X^L

are either N-linker and CH or NMe and C-linker respectively;

1 of X^M and X^O

is N-(2,6-dioxopiperidin-3-yl) (**Y**);

0 or 1 of X^M and X^N

is C-F;

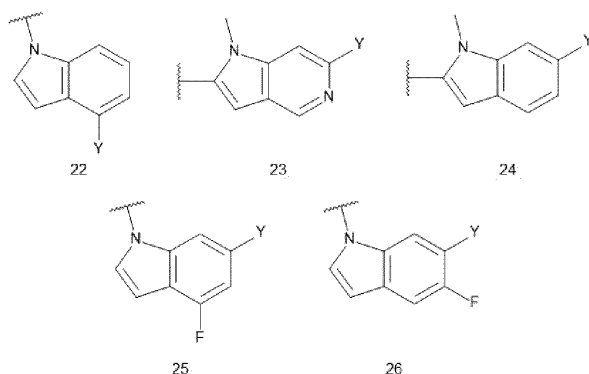
X^N

may be N if X^M is not C-F;

the remainder of X^N , X^M and X^O

are CH.

28. The compound or salt thereof according to statement 27, wherein **W** represents any of the groups 22 to 26 shown below:



29. The compound or salt thereof, according to any preceding statement wherein X^1 is C and 0 or 1 of X^2 , X^3 & X^4 is N and are otherwise C; or X^3 & X^4 are both C and are substituted by $-X^5=X^6-X^7=X^8-$ with X^5 attached to X^3 and X^8 attached to X^5 , where 1 of X^1 , X^2 , X^5 , X^6 , X^7 & X^8 is N, and are otherwise C.
30. The compound or salt thereof, according to any preceding statement wherein R^{2a} and R^{2b} are substituents on the same or different C atoms adjacent Q.
31. The compound or salt thereof according to any preceding statement wherein R^{2a} and R^{2b} are substituents on the same or different C atoms, each independently selected from H and C_{1-3} alkyl.
32. The compound or salt thereof according to any preceding statement wherein Y^1 , Y^2 , Y^3 & Y^4 are respectively selected from (C, C, C, C), (N, C, C, C), (C, N, C, C) and (N, C, N, C).
33. The compound or salt thereof according to any preceding statement wherein q is 0, 1 or 2 and R^3 (when present) is a substituent on any C atom at Y^1 , Y^2 , Y^3 & Y^4 selected from F and C_{1-3} alkyl.
34. The compound or salt thereof according to any preceding statement wherein p is 1; X^3 & X^4 are not substituted by $-X^5=X^6-X^7=X^8-$; X^1 , X^2 , X^3 & X^4 are all C and R^1 is a substituent on X^1 and is CF_3 .
35. The compound or salt thereof according to any one of statements 1 to 33 wherein p is 2; X^3 & X^4 are not substituted by $-X^5=X^6-X^7=X^8-$; X^1 , X^2 , X^3 & X^4 are all C; one R^1 substituent is on X^1 and is CF_3 , and the other R^1 substituent is on X^2 and is F or ethyl.
36. The compound or salt thereof according to any preceding statement wherein n is 1, m is 1, Q is CH, R^{2a} is H and R^{2b} is H.

37. The compound of salt thereof according to any preceding statement wherein 0 or 1 of Y^1 , Y^2 , Y^3 & Y^4 is N and are otherwise C.
38. The compound of salt thereof according to any preceding statement wherein Y^1 , Y^2 , Y^3 & Y^4 are all C.
39. The compound of salt thereof according to any preceding statement wherein q is 0.
40. The compound of salt thereof according to any one of statements 1 to 38, wherein q is 1 and R^3 is attached to C at Y^1 , and R^3 is selected from F, CN and Me.
41. The compound of salt thereof according to any one of statements 1 to 38, wherein q is 2 and each R^3 group is F, which are attached to C at Y^1 and Y^3 .
42. A pharmaceutical composition, which comprises a compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof according to one of statements 1-14 or 21-41, in association with a pharmaceutically acceptable excipient.
43. A pharmaceutical composition, which comprises a compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41, for use in the treatment of cancer.
44. A pharmaceutical composition, which comprises a compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41, for use in the treatment of a solid tumour.
45. A pharmaceutical composition, which comprises a compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41, for use in the treatment of an AR-sensitive tumour type.
46. A pharmaceutical composition, which comprises a compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41, for use in the treatment of tumour types that harbour one or more mutated forms of the androgen receptor.
47. A pharmaceutical composition, which comprises a compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41, for use in the treatment of prostate cancer.

48. A pharmaceutical composition, which comprises a compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41, for use in the treatment of castrate-resistant prostate cancer.
- 5 49. A pharmaceutical composition, which comprises a compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41, for use in the treatment of metastatic castrate-resistant prostate cancer.
- 10 50. A pharmaceutical composition, which comprises a compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41, for use in the treatment of AR-mutated cancer.
- 15 51. The compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41, for use as a medicament.
52. The compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41, for use in therapy.
- 20 53. The compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41, for use in a method of treatment of the human or animal body by therapy.
- 25 54. The compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41, for use in the production of an anti-proliferative effect in a warm-blooded animal such as man.
- 30 55. Use of a compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41, for the manufacture of a medicament for the production of an anti-proliferative effect in a warm-blooded animal such as man.
- 35 56. A method for producing an anti-proliferative effect in a warm-blooded animal, such as man, in need of such effect, which comprises administering to said animal an effective amount of a compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41.

57. A compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41, for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.
- 5 58. Use of a compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41, for the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.
- 10 59. A method for producing an anti-invasive effect by the containment and/or treatment of solid tumour disease, in a warm-blooded animal, such as man, in need of such effect, which comprises administering to said animal an effective amount of a compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41.
- 15 60. A compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41, for use in the prevention or treatment of cancer.
- 20 61. Use of a compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41, for the manufacture of a medicament for the prevention or treatment of cancer.
- 25 62. A method for the prevention or treatment of cancer in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41.
- 30 63. A compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41, for use in the prevention or treatment of solid tumour(s).
64. Use of a compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41, for the manufacture of a medicament for the prevention or treatment of solid tumour(s).
- 35 65. A method for the prevention or treatment of solid tumour(s) in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a

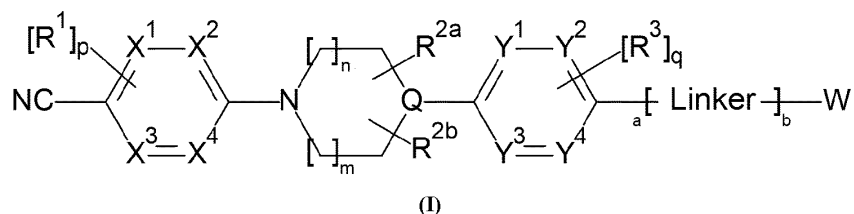
compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41.

- 5 66. A compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41, for use in the prevention or treatment of tumour types that are sensitive to degradation of androgen receptors.
- 10 67. Use of a compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41, for the manufacture of a medicament for the prevention or treatment of those tumour types that are sensitive to degradation of androgen receptors.
- 15 68. A method for the prevention or treatment of those tumour types that are sensitive to degradation of androgen receptors in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41.
- 20 69. A compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41, for use in providing a degrading effect on androgen receptors in a warm-blooded animal such as man.
- 25 70. Use of a compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41, for the manufacture of a medicament for providing a degrading effect on androgen receptors in a warm-blooded animal such as man.
- 30 71. A method for providing a degrading effect on androgen receptors in a warm-blooded animal, such as man, in need of such effect, which comprises administering to said animal an effective amount of a compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41.
72. A compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41, for use in providing a selective degrading effect on androgen receptors in a warm-blooded animal such as man.
- 35 73. Use of a compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41, for the manufacture of a medicament for providing a selective degrading effect on androgen receptors in a warm-blooded animal such as man.

74. A method for providing a selective degrading effect on androgen receptors in a warm-blooded animal, such as man, in need of such effect, which comprises administering an effective amount of a compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41.
75. A compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41, for use in the treatment of tumour types that harbour androgen receptor mutations.
76. Use of a compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41, for the manufacture of a medicament for the prevention or treatment of those tumour types that harbour androgen receptor mutations.
77. A method for the prevention or treatment of those tumour types that harbour androgen receptor mutations in a warm-blooded animal, such as man, in need of such prevention or treatment, which comprises administering to said animal an effective amount of a compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41.
78. A compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41, for use in the treatment of prostate cancer (for example castrate-resistant prostate cancer (CRPC), for example metastatic CRPC)).
79. Use of a compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41, for the manufacture of a medicament for the treatment of prostate cancer (for example castrate-resistant prostate cancer (CRPC), for example metastatic CRPC).
80. A method for treating prostate cancer (for example castrate-resistant prostate cancer (CRPC), for example metastatic CRPC) in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of **Formula (I)** or PROTAC of **Formula (Ia)**, or a pharmaceutically acceptable salt thereof, according to any one of statements 1-14 or 21-41.

CLAIMS

1. A compound of Formula (I):



5

or a pharmaceutically acceptable salt thereof,

wherein:

X^1 is C & 0, 1 or 2 of X^2 , X^3 & X^4 is/are N, and are otherwise C;

or

10

X^3 & X^4

are both C and are substituted by $-X^5=X^6-X^7=X^8-$ with X^5 attached to X^3 and with X^8 attached to X^4 , where 1 or 2 of X^1 , X^2 , X^5 , X^6 , X^7 & X^8 is/are N, and are otherwise C;

p

is 1 or 2 and X^1 is C attached to R^1 when X^3 & X^4 are not substituted by $-X^5=X^6-X^7=X^8-$; and otherwise p is 0, 1 or 2;

15

where:

each R^1

is a substituent on any C atom at X^1 , X^2 , X^3 & X^4 , (or at X^1 , X^2 , X^5 , X^6 , X^7 & X^8 when X^3 & X^4 are substituted by $-X^5=X^6-X^7=X^8-$), and is independently selected from F, Cl, C_{1-3} alkyl and C_{1-3} alkoxy, wherein said C_{1-3} alkyl and C_{1-3} alkoxy may be independently optionally substituted by one or more F;

20

n

is 0, 1 or 2;

m

is 0 or 1;

Q

is CH or N when n & m are both other than 0 and otherwise Q is CH;

25

R^{2a} and R^{2b}

are substituents on the same or different C atoms other than at Q , each independently selected from H, F and C_{1-3} alkyl, or R^{2a} & R^{2b} together form a $-(CH_2)_r-$ group where r is 1, 2 or 3;

0, 1 or 2 of Y^1 , Y^2 , Y^3 & Y^4

is/are N, and are otherwise C;

each R^3

is a substituent on any C atom at Y^1 , Y^2 , Y^3 & Y^4 , and is independently selected from F, Cl, CN, C_{1-3} alkyl and C_{1-3} alkoxy, wherein said C_{1-3} alkyl and C_{1-3} alkoxy may be independently optionally substituted by one or more F;

30

q

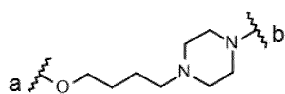
is 0, 1 or 2;

Linker

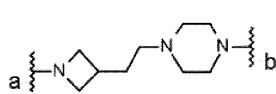
is a saturated or a partially or fully unsaturated framework comprising C and H atoms and at least one heteroatom, wherein said framework has end points of attachment 'a' and

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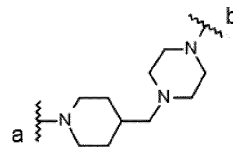
- ‘b’ and a minimum length of from 6 to 26 atoms between ‘a’ and ‘b’; wherein said framework may include one or more straight and/or branched chains and/or rings and is optionally substituted on any available C atom(s) by one or more F; and is an E3 ubiquitin ligase cereblon binder unit.
- 5 **W**
2. The compound of **Formula (I)**, or pharmaceutically acceptable salt thereof, according to claim 1 wherein the **Linker** has the **Formula**:
- ‘a’ -**Q^A**-**Q^B**-**Q^C**- ‘b’
- 10 wherein:
- ‘a’ and ‘b’ represent the end points of attachment;
- Q^A** is -**G**-**Q^H**- or -**G**-(C₁₋₅alkylene)-;
- Q^B** is a direct bond, -**Q^{B1}**-**Q^{B2}**-**Q^{B3}**- or C₁₋₃alkylene optionally substituted by one or more F (e.g. 1 or 2);
- where:
- 15 **Q^{B1}** & **Q^{B3}** each independently represent a direct bond or C₁₋₂alkylene;
- Q^{B2}** is **Q^H**, -O-CH₂CH₂-O-, -O- or -N(**R^J**)- where **R^J** is H or C₁₋₃alkyl;
- Q^C** is -**Q^H**-**G**- or -(C₁₋₅alkylene)-**G**;
- each **G** is independently a direct bond, -CH₂-, -O-, or -N(**R^G**)- where **R^G** is H or C₁₋₃alkyl;
- each **Q^H** is independently a 4-12-membered nitrogen-containing saturated or partially unsaturated
- 20 heterocyclic group;
- where the values of **Q^A**, **Q^B** and **Q^C** are selected so that the **Linker** does not contain any N-N or N-O bonds.
- 25 3. The compound of **Formula (I)**, or pharmaceutically acceptable salt thereof, according to claim 2 wherein **Q^{B2}** is **Q^H**, -O-CH₂CH₂-O- or -N(**R^J**)- where **R^J** is C₁₋₃alkyl.
4. The compound of **Formula (I)**, or pharmaceutically acceptable salt thereof, according to claim 2 or claim 3 wherein **Q^C** is -**Q^H**-**G**- or -(C₁₋₂alkylene)-**G**-.
- 30 5. The compound of **Formula (I)**, or pharmaceutically acceptable salt thereof, according to any one of claims 2 to 4, wherein each **Q^H** is independently selected from piperazin-1,4-diyl, azetidin-1,3-diyl, piperidin-1,4-diyl, 1,4-diazepan-1,4-diyl, 12-oxa-3,9-diazaspiro[5.6]dodecan-3,9-diyl, pyrrolidin-1,3-diyl, 3,9-diazaspiro[5.5]undecan-3,9-diyl, 2,5-diazabicyclo[2.2.1]heptan-2,5-diyl, 1,3,3a,4,6,6a-hexahdropyrrolo[3,4-*c*]pyrrol-2,5-diyl, 3,6-dihydro-2*H*-pyridin-1,4-diyl and 9-azaspiro[5.5]undecan-
- 35 3,9-diyl.
6. The compound of **Formula (I)**, or pharmaceutically acceptable salt thereof, according to claim 1, wherein the **Linker** is selected from any of **Linkers 1** to 46 or 1 to 48:



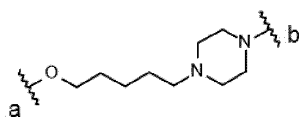
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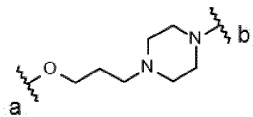
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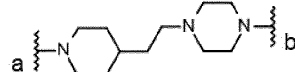
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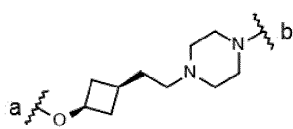
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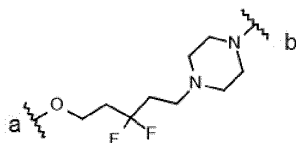
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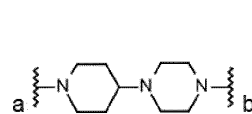
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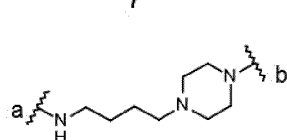
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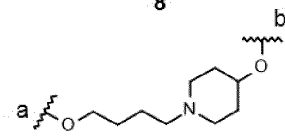
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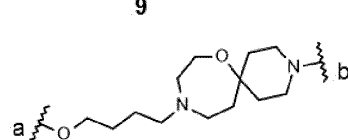
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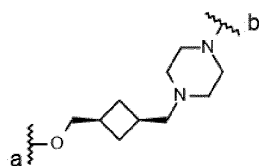
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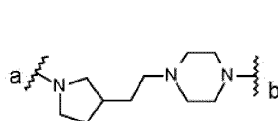
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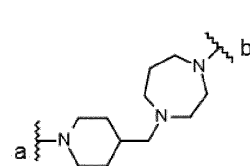
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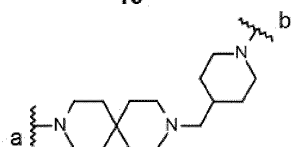
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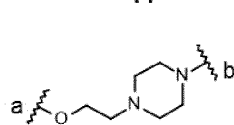
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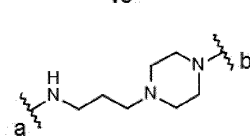
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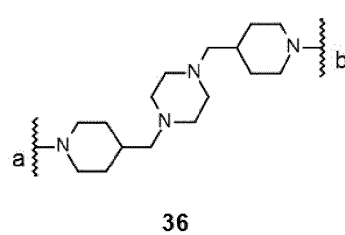
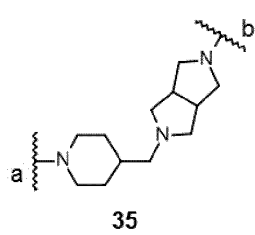
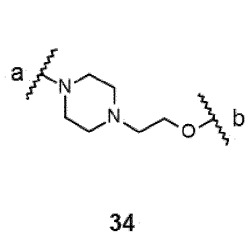
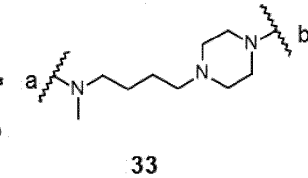
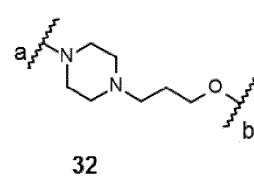
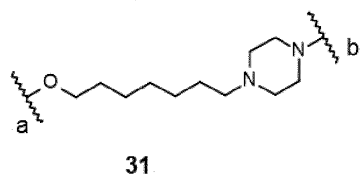
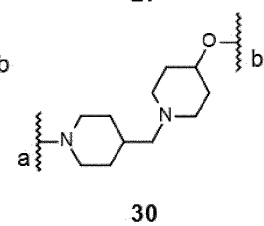
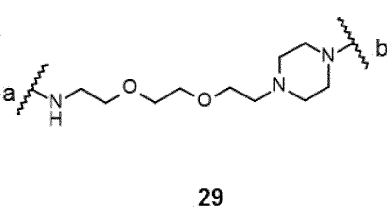
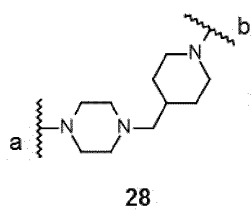
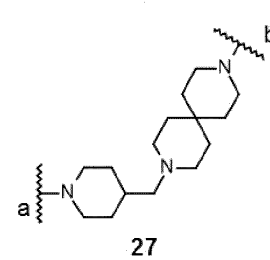
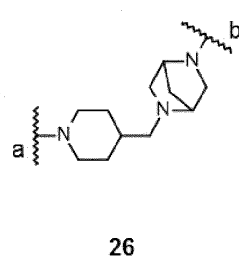
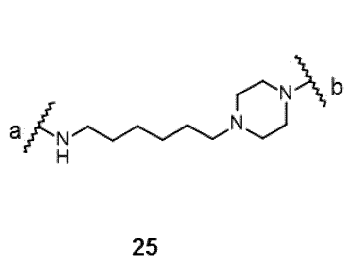
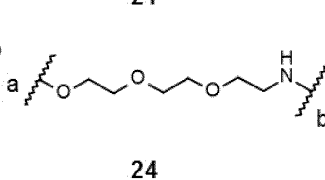
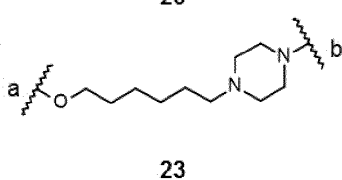
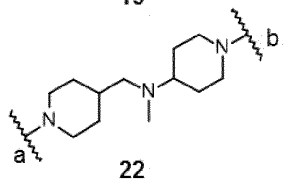
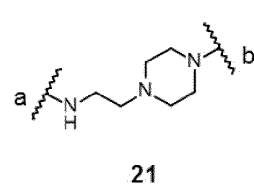
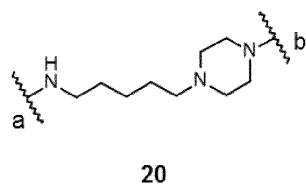
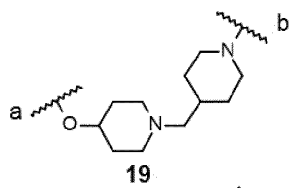
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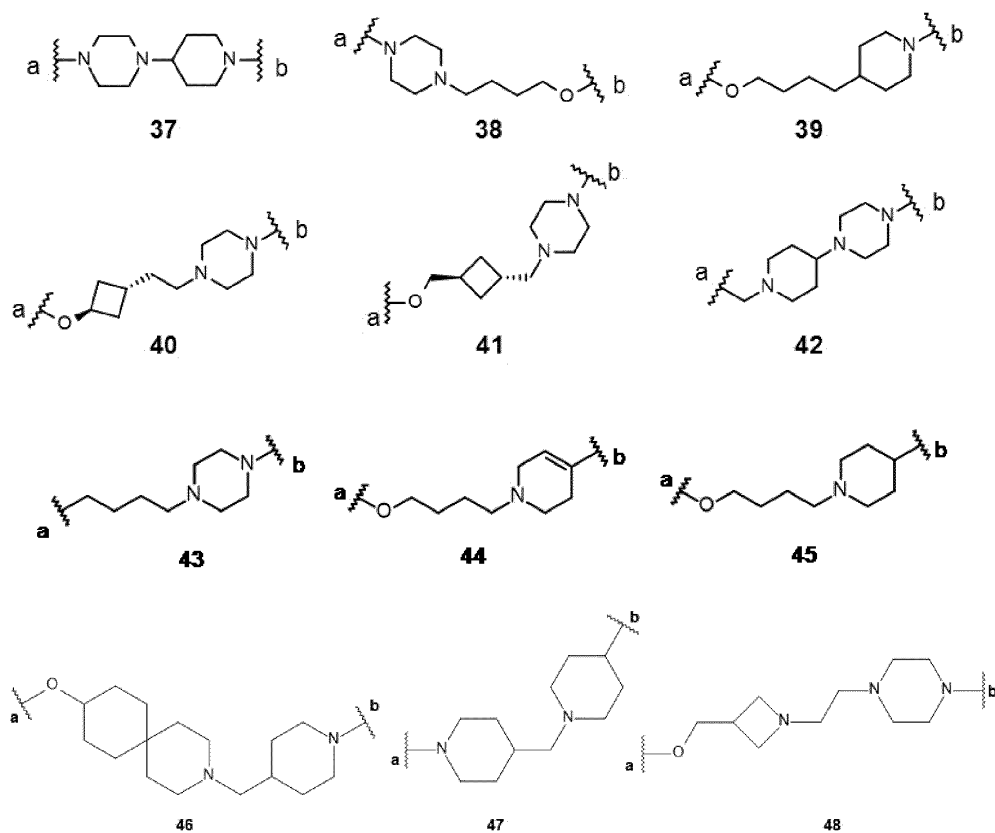


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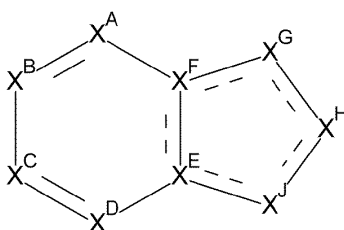




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7. The compound of **Formula (I)**, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 6, wherein **W** is **W1** which is: $-\text{Z}-(\text{R}^A)_n$

where **Z** is:



10

wherein:

represents a single covalent bond or a double covalent bond;

0, 1 or 2 of X^A , X^B , X^C , X^D , X^E & X^F

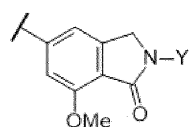
is/are N, where X^E & X^F are not both N, and are otherwise C;

15

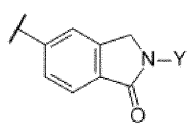
1 of X^G , X^H & X^J

is C(O);

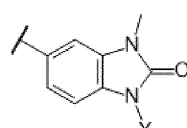
- 1 of X^G , X^H & X^J
 1 of X^G , X^H & X^J
- 5 is N-(2,6-dioxopiperidin-3-yl) (**Y**); and
 is selected from $C(R^T)_2$, $-CH_2CH_2-$, $C(O)$, $N(C_{1-3}alkyl)$,
 $-O-$ and $-N=$, wherein each R^T is selected from H, F, Me
 or together with the carbon of $C(R^T)_2$ forms a
 cycloprop-1,1-diyl group;
 where X^G , X^H & X^J are selected such that there are not
 two $C(O)$ groups present at adjacent positions, and that
 the N-(2,6-dioxopiperidin-3-yl) is not at an adjacent
 position to either $N(C_{1-3}alkyl)$ or O ;
- 10 each R^A
 is independently a substituent on any available C atom at
 X^A , X^B , X^C or X^D selected from F, Cl, $C_{1-3}alkyl$,
 $C_{1-3}alkoxy$ wherein said $C_{1-3}alkyl$ and $C_{1-3}alkoxy$ is
 independently optionally substituted by one or more F;
- 15 **h**
 wherein the **Linker**
 is 0, 1 or 2; and
 is attached to any C atom at X^A , X^B , X^C or X^D .
8. The compound of **Formula (I)**, or a pharmaceutically acceptable salt thereof, according to claim 7
 where each R^A is a substituent on any available C at X^A , X^B , X^C or X^D selected from F, Cl and
 $C_{1-3}alkoxy$ optionally substituted by one or more F.
- 20 9. The compound of **Formula (I)**, or a pharmaceutically acceptable salt thereof, according to claim 7 or
 statement 22 where $X^G-X^H-X^J$ is:
- (i) $X^G-NY-C(O)$ where X^G is $-CH_2-$, $-CH_2CH_2-$, $=N-$ or $C(O)$;
- (ii) $X^G-C(O)-NY$ where X^G is $-O-$ or $N(C_{1-3}alkyl)$; or
- 25 (iii) $C(O)-NY-CH_2$.
10. The compound of **Formula (I)**, or a pharmaceutically acceptable salt thereof, according to any one of
 claims 1 to 6 where W is any one of groups 1 to 21:



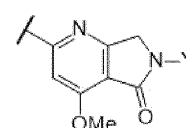
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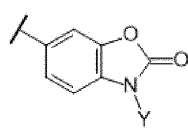
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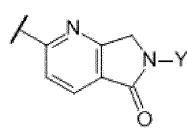
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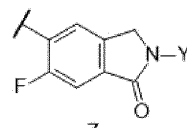
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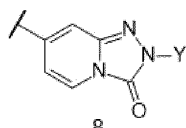
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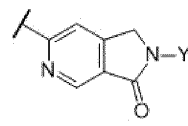
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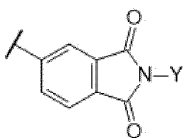
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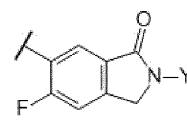
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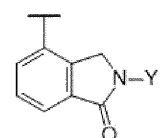
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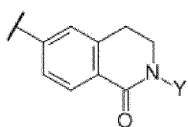
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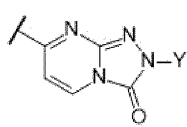
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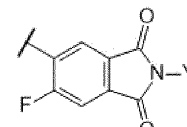
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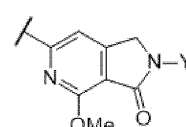
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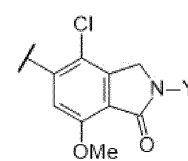
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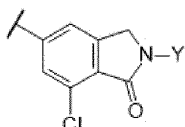
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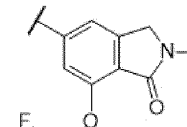
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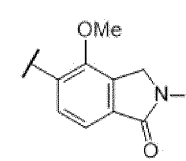
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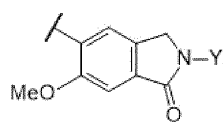
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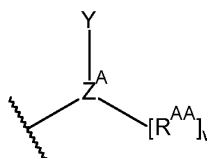


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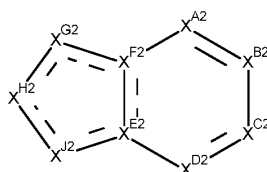
21

11. The compound of **Formula (I)**, or a pharmaceutically acceptable salt thereof, according to any one of



claims 1 to 6, wherein **W** is **W2** which is

5 **Z^A** is:



wherein:

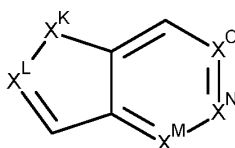
- 10 ----- represents a single covalent bond or a double covalent bond;
 1 of X^{A2} , X^{B2} , X^{C2} & X^{D2} is C and covalently bound to **Y**;
 0, 1 or 2 of X^{A2} , X^{B2} , X^{C2} , X^{D2} , X^{E2} & X^{F2} is/are N (where X^{E2} & X^{F2} are not both N) and are otherwise C;
 1 or 2 of X^{G2} , X^{H2} & X^{J2} is/are N; and are otherwise C;
 each R^{AA} is a substituent on any available C or N atom of **Z** – in each case independently selected from R^{AA1} optionally substituted by one or more R^{AA2} ; where R^{AA} is further selected from R^{AA2} when R^{AA} is a substituent on an available C atom of **Z^A**;
 15 each R^{AA1} is independently C_{1-4} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{1-3} alkoxy C_{1-3} alkyl, carboxy C_{1-3} alkyl, C_{5-7} carbocyclyl or a 4-6 membered heterocyclyl;
 20 each R^{AA2} is independently selected from F, Cl, Br, CN, NH_2 , C_{1-3} alkyl, $\text{O}(\text{C}_{1-3}$ alkyl), $\text{NH}(\text{C}_{1-3}$ alkyl) and $\text{N}(\text{C}_{1-3}$ alkyl)₂; wherein said C_{1-3} alkyls are optionally substituted by one or more F;
 v is 0, 1 or 2;
 Y is N-(2,6-dioxopiperidin-3-yl).

25

12. The compound or salt thereof according to claim 11, wherein

- 1 of X^{A2} & X^{B2} is C and covalently bound to **Y** and the other of X^{A2} & X^{B2} is C;
 0 or 1 of X^{C2} & X^{D2} is N and is/are otherwise C;
 1 of X^{G2} & X^{J2} is N and the other of X^{G2} & X^{J2} is C; and
 30 X^{H2} , X^{E2} & X^{F2} are all C.

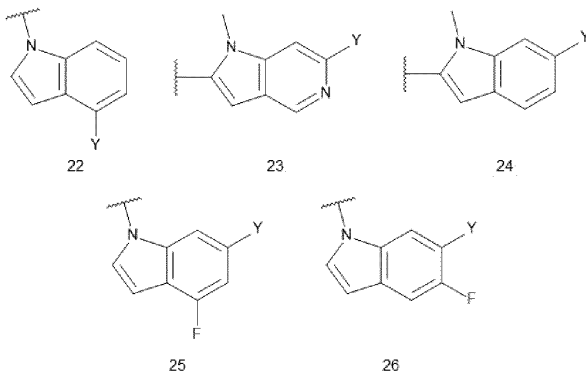
13. The compound or salt thereof according to claim 11, wherein **W** is **W2-1**



wherein:

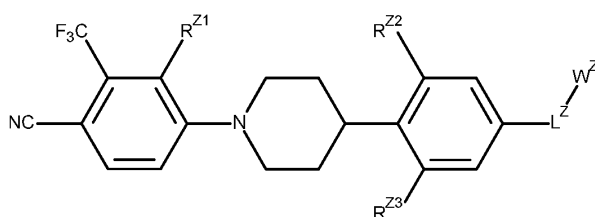
- X^K** and **X^L** are either N-linker and CH or NMe and C-linker respectively;
1 of **X^M** and **X^O** is N-(2,6-dioxopiperidin-3-yl) (**Y**);
0 or **1** of **X^M** and **X^N** is C-F;
X^N may be N if **X^M** is not C-F;
the remainder of **X^N**, **X^M** and **X^O** are CH.

- 10** 14. The compound or salt thereof according to any one of claims 1 to 6, wherein **W** represents any of the groups 22 to 26 shown below:



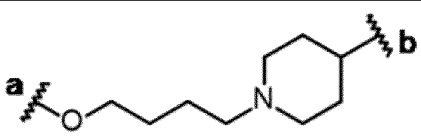
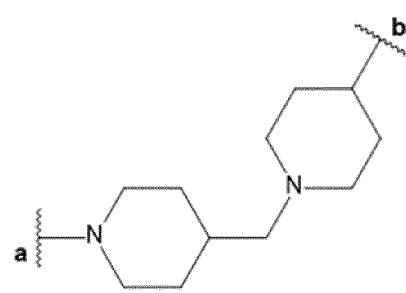
- 15** 15. The compound or salt thereof, according to any one of claims 1 to 14 wherein **R^{2a}** and **R^{2b}** are substituents on the same or different C atoms adjacent **Q**.
16. The compound or salt thereof according to any one of claims 1 to 15 wherein **R^{2a}** and **R^{2b}** are substituents on the same or different C atoms, each independently selected from H and C₁₋₃alkyl.
- 20** 17. The compound or salt thereof according to any one of claims 1 to 16 wherein **p** is 1; **X³** & **X⁴** are not substituted by **-X⁵=X⁶-X⁷=X⁸-**; **X¹**, **X²**, **X³** & **X⁴** are all C and **R¹** is a substituent on **X¹** and is CF₃.
- 25** 18. The compound or salt thereof according to any one of claims 1 to 16 wherein **p** is 2; **X³** & **X⁴** are not substituted by **-X⁵=X⁶-X⁷=X⁸-**; **X¹**, **X²**, **X³** & **X⁴** are all C; one **R¹** substituent is on **X¹** and is CF₃, and the other **R¹** substituent is on **X²** and is F or ethyl.

19. The compound of salt thereof according to any one of claims 1 to 18 wherein **n** is 1, **m** is 1, **Q** is CH, **R^{2a}** is H and **R^{2b}** is H.
20. The compound of salt thereof according to any one of claims 1 to 19 wherein **Y¹**, **Y²**, **Y³** & **Y⁴** are all C.
21. The compound of salt thereof according to any one of claims 1 to 20 wherein **q** is 0.
22. The compound of salt thereof according to any one of claims 1 to 20, wherein **q** is 1 and **R³** is attached to C at **Y¹**, and **R³** is selected from F, CN and Me.
23. The compound of salt thereof according to any one of claims 1 to 21, wherein **q** is 2 and each **R³** group is F, which are attached to C at **Y¹** and **Y³**.
24. The compound or salt thereof according to claim 1 which is of Formula (VI):

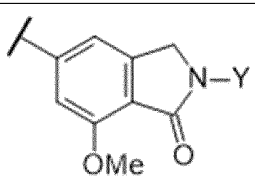
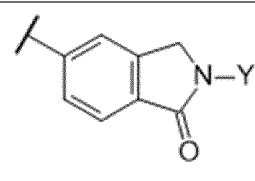
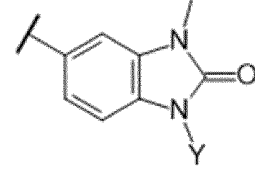
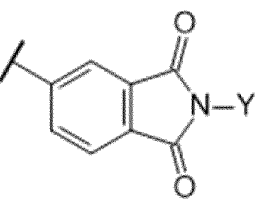


- or a pharmaceutically acceptable salt thereof,
wherein:
- R^{Z1}** is H or F;
R^{Z2} is H or F;
R^{Z3} is H or F;
L^Z is a linker selected from 1, 3, 45 and 47:

1	Chemical structure 1: A linker consisting of a piperidine ring connected to a piperazine ring. The piperidine ring is connected to a group 'a' at position 1, and the piperazine ring is connected to a group 'b' at position 1.
3	Chemical structure 3: A linker consisting of a piperidine ring connected to a piperazine ring. The piperidine ring is connected to a group 'a' at position 1, and the piperazine ring is connected to a group 'b' at position 1.

45	
47	

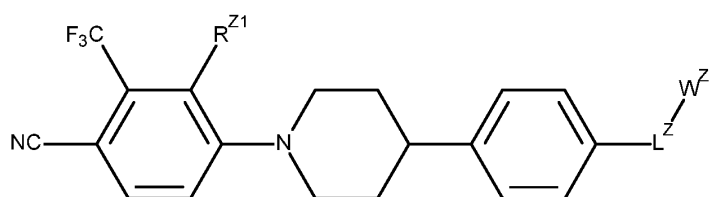
and W^Z is selected from 1, 2, 3, 10, 16, 22, 23, 24 and 26:

1	
2	
3	
10	

16	
22	
23	
24	
26	

where Y is N-(2,6-dioxopiperidin-3-yl).

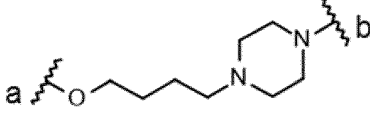
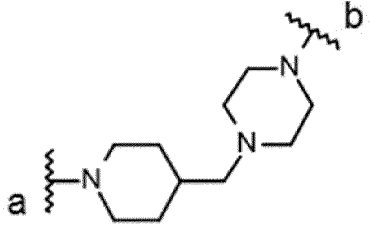
25. The compound or salt thereof according to claim 1 which is of Formula (VI-1):



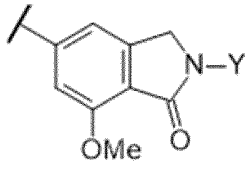
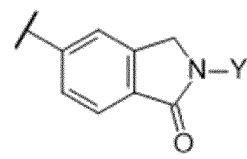
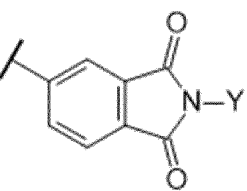
5 or a pharmaceutically acceptable salt thereof,
wherein:

R^{Z1} is H or F;

L^Z is a linker selected from 1 and 3:

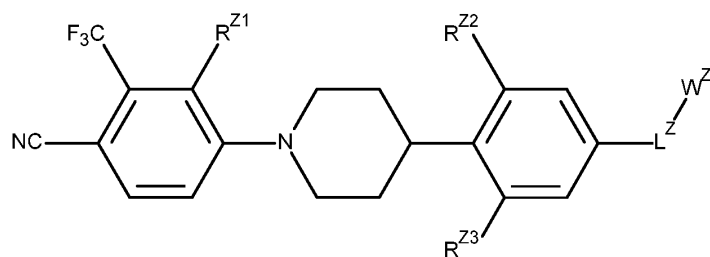
1	
3	

and W^Z is selected from 1, 2 and 10:

1	
2	
10	

where Y is N-(2,6-dioxopiperidin-3-yl).

26. The compound or salt thereof according to claim 1 which is of Formula (VI-2):



5

or a pharmaceutically acceptable salt thereof,

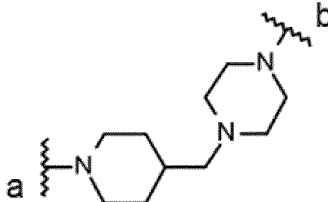
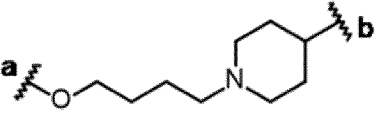
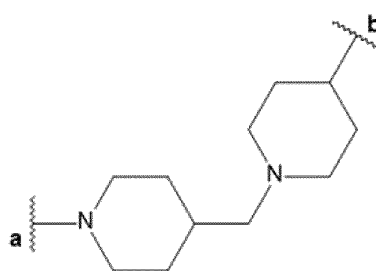
wherein:

R^{Z1} is H or F;

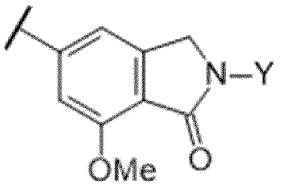
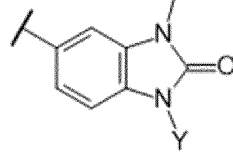
R^{Z2} is H or F;

R^{Z3} is H or F;

5 L^Z is a linker selected from 3, 45 and 47:

3	
45	
47	

and W^Z is selected from 1, 3, 16, 22, 23, 24 and 26:

1	
3	

16	
22	
23	
24	
26	

where Y is N-(2,6-dioxopiperidin-3-yl).

27. A pharmaceutical composition, which comprises a compound of **Formula (I)** or a pharmaceutically acceptable salt thereof according to one of claims 1 to 26, in association with a pharmaceutically acceptable excipient.
28. A compound of **Formula (I)** or a pharmaceutically acceptable salt thereof according to one of claims 1 to 26 or a pharmaceutical composition according to claim 24, for use in the prevention or treatment of tumour types that are sensitive to degradation of androgen receptors or for use in the treatment of prostate cancer (for example castrate-resistant prostate cancer (CRPC), for example metastatic CRPC)).