

PYRIDINE DERIVATIVES AS TMEM16A MODULATORS FOR USE IN THE
TREATMENT OF RESPIRATORY CONDITIONS

The present invention relates to novel compounds which have activity as positive modulators of the calcium-activated chloride channel (CaCC), TMEM16A. The invention
5 also relates to methods of preparing the compounds and pharmaceutical compositions containing them as well as to the use of these compounds in treating diseases and conditions modulated by TMEM16A, particularly respiratory diseases and conditions.

Background

10 Humans can inhale up to 12,000 L of air each day and with it comes the potential for airborne pathogens (such as bacteria, viruses and fungal spores) to enter the airways. To protect against these airborne pathogens, the lung has evolved innate defence mechanisms to minimise the potential for infection and colonisation of the airways. One such mechanism is the mucus clearance system, whereby secreted mucus is propelled
15 up and out of the airways by the coordinated beating of cilia together with cough clearance. This ongoing 'cleansing' of the lung constantly removes inhaled particles and microbes thereby reducing the risk of infection.

In recent years it has become clear that the hydration of the mucus gel is critical to enable
20 mucus clearance (Boucher 2007; Matsui *et al*, 1998). In a normal, healthy airway, the mucus gel is typically 97% water and 3% w/v solids under which conditions the mucus is cleared by mucociliary action. The hydration of the airway mucosa is regulated by the coordinated activity of a number of ion channels and transporters. The balance of anion (Cl^- / HCO_3^-) secretion mediated *via* the Cystic Fibrosis Transmembrane Conductance
25 Regulator (CFTR) and the Calcium Activated Chloride Conductance (CaCC; TMEM16A) and Na^+ absorption through the epithelial Na^+ channel (ENaC) determine the hydration status of the airway mucosa. As ions are transported across the epithelium, water is osmotically obliged to follow and thus fluid is either secreted or absorbed.

30 In respiratory diseases such as chronic bronchitis and cystic fibrosis, the % solids of the mucus gel is increased as the hydration is reduced and mucus clearance is reduced (Boucher, 2007). In cystic fibrosis, where loss of function mutations in CFTR attenuates the ability of the airway to secrete fluid, the % solids can be increased to 15% which is believed to contribute towards the plugging of small airways and failure of mucus
35 clearance. Strategies to increase the hydration of the airway mucus include either the stimulation of anions and thereby fluid secretion or the inhibition of Na^+ absorption. To this

end, stimulating the activity of TMEM16A channels will increase anion secretion and therefore increase fluid accumulation in the airway mucosa, hydrate mucus and enhance mucus clearance mechanisms.

5 TMEM16A, also referred to as Anoctamin-1 (Ano1), is the molecular identity of calcium-activated chloride channels (Caputo *et al*, 2008; Yang *et al*, 2008). TMEM16A channels open in response to elevation of intracellular calcium levels and allow the bidirectional flux of chloride, bicarbonate and other anions across the cell membrane. Functionally
10 TMEM16A channels have been proposed to modulate transepithelial ion transport, gastrointestinal peristalsis, nociception and cell migration/proliferation (Pedemonte & Galletta, 2014).

TMEM16A channels are expressed by the epithelial cells of different organs including the lungs, liver, kidney, pancreas and salivary glands. In the airway epithelium TMEM16A
15 is expressed at high levels in mucus producing goblet cells, ciliated cells and in submucosal glands. Physiologically TMEM16A is activated by stimuli which mobilise intracellular calcium, particularly purinergic agonists (ATP, UTP), which are released by the respiratory epithelium in response to cyclical shear stress caused by breathing and other mechanical stimuli such as cough. In addition to increasing anion secretion leading to enhanced
20 hydration of the airways, activation of TMEM16A plays an important role in bicarbonate secretion. Bicarbonate secretion is reported to be an important regulator of mucus properties and in controlling airway lumen pH and hence the activity of native antimicrobials such as defensins (Pezzulo *et al*, 2012).

25 Indirect modulation of TMEM16A, via elevation of intracellular calcium, has been clinically explored eg. denufosol (Kunzelmann & Mall, 2003). Although encouraging initial results were observed in small patient cohorts this approach did not deliver clinical benefit in larger patient cohorts (Accurso *et al* 2011; Kellerman *et al* 2008). This lack of clinical effect was ascribed to only a transient elevation in anion secretion, the result of a short half-life of
30 denufosol on the surface of the epithelium and receptor/pathway desensitisation, and unwanted effects of elevating intracellular calcium such as increased release of mucus from goblet cells (Moss, 2013). Compounds which act directly upon TMEM16A to enhance channel opening at low levels of calcium elevation are expected to durably enhance anion secretion and mucociliary clearance in patients and improve innate defence. As TMEM16A
35 activity is independent of CFTR function, TMEM16A positive modulators have the potential to deliver clinical benefit to all CF patients and non-CF respiratory diseases characterised

by mucus congestion including chronic bronchitis and severe asthma.

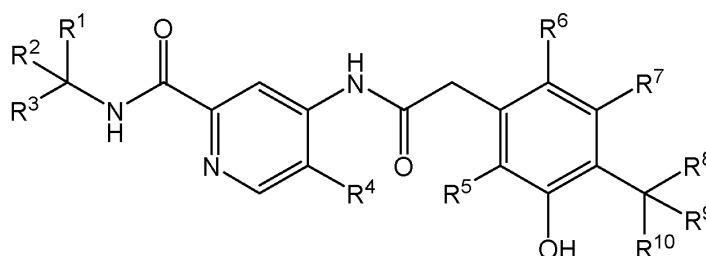
TMEM16A modulation has been implicated as a therapy for dry mouth (xerostomia), resultant from salivary gland dysfunction in Sjorgen's syndrome and radiation therapy, dry eye, cholestasis and gastrointestinal motility disorders.

Our application, WO2019/145726 relates to compounds which are positive modulators of TMEM16A and which are therefore of use in the treatment of diseases and conditions in which modulation of TMEM16A plays a role, particularly respiratory diseases and conditions.

The present inventors have developed further compounds which are positive modulators of TMEM16A. Many of the compounds of the present invention have advantages over related compounds exemplified in WO2019/145726. These advantages include reduced lipophilicity (as represented by reduced log D values) and lower metabolic clearance, properties which lead to improved pharmacokinetics (PK) when the compounds are administered systemically, including orally. In particular, reduced lipophilicity leads to increased solubility in water. Several of the compounds of the present invention have either or both improved solubility and lower metabolic clearance than the compounds exemplified in WO2019/145726. This leads to advantages such as lower efficacious dose, longer half-life following administration or, in the case of oral administration, higher bioavailability.

Summary of the Invention

In a first aspect of the present invention there is provided a compound of general formula (I) including all tautomeric forms, all enantiomers, isotopic variants, and salts and solvates thereof:



(I)

wherein:

R¹ is selected from methyl, fluoromethyl, difluoromethyl, trifluoromethyl, chlorodifluoromethyl, dichlorofluoromethyl, ethynyl and CN; or

when R² and R³ together with the carbon atom to which they are attached form a 4- to 6-
5 membered carbocyclic ring substituted in addition to the R¹ group, with OH, halo, methyl
or CH₂OH, R¹ may also be H; or

when R² and R³ together with the carbon atom to which they are attached form a 4- to 6-
membered carbocyclic ring, which is unsubstituted apart from the R¹ group; R¹ may also
10 be CH₂OH;

R² is selected from methyl and CH₂OH;

R³ is selected from H and methyl; or

15 R² and R³ together with the carbon atom to which they are attached form a 3- to 10-
membered carbocyclic or oxygen-containing heterocyclic ring system either of which is
optionally substituted, in addition to the R¹ group, with one or more substituents selected
from OH, halo, C₁₋₄ alkyl, C₁₋₄ alkyl substituted with one or more OH substituents, and
20 C₁₋₄ haloalkyl; or

R¹, R² and R³ together with the carbon atom to which they are attached combine to form
a 5- to 8-membered bridged carbocyclic or heterocyclic ring system optionally substituted
with one or more substituents selected from OH, halo, C₁₋₄ alkyl and C₁₋₄ haloalkyl;

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R⁴ is H or halo;

each of R⁵ and R⁷ is independently selected from H, halo, C₁₋₃ alkyl and C₁₋₃ haloalkyl;

30 R⁶ is selected from H, halo, CN and C₁₋₄ alkyl optionally substituted with one or more
substituents selected from halo and OH;

R⁸ is methyl or ethyl, either of which is optionally substituted with one or more halogen
substituents;

35 R⁹ is OH, CH₂OH or methyl or ethyl, either of which is optionally substituted with one or
more halogen substituents; or

R⁸ and R⁹ together with the carbon atom to which they are attached form either a 3- to 6-membered cycloalkyl or oxygen-containing heterocyclic ring optionally substituted, in addition to the R¹⁰ group, with one or more substituents selected from OH, F and CH₂OH; or an ethenyl group optionally substituted with one or two halogen substituents;

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R¹⁰ is selected from H, CN, OH, cycloalkyl optionally substituted with OH, and C₁₋₄ alkyl optionally substituted with one or more substituents selected from halo, OH and a 3- to 6-membered cycloalkyl or heterocyclic group, either of which is optionally substituted with OH; or

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R⁸, R⁹ and R¹⁰ together with the carbon atom to which they are attached form a 5- to 8-membered fused or bridged carbocyclic ring system optionally substituted with one or more substituents selected from OH, F and CH₂OH;

15 provided that:

i. when R⁵ and R⁷ are H and R⁶ is H or F, R¹, R², R³, R⁸, R⁹ and R¹⁰ are not all methyl; and

ii. when R², R³, R⁸, R⁹ and R¹⁰ are all methyl, R⁵, R⁶ and R⁷ are not all H; and

iii. when R¹ is CN and R² and R³ together with the carbon atom to which they are attached form a 3- to 10-membered oxygen-containing heterocyclic ring, R⁸, R⁹ and R¹⁰ are not all methyl; and

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iv. R⁹ and R¹⁰ are not both OH.

Suitably there is provided a compound of general formula (I). There is also provided salts, such as pharmaceutically acceptable salts, of a compound of formula (I). There is also provided solvates, such as hydrates, or a compound of formula (I).

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Since the compounds of general formula (I) are positive modulators of TMEM16A, they are useful for treating diseases and conditions in which modulation of TMEM16A plays a role, especially respiratory diseases and conditions.

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Detailed Description of the Invention

In the present specification, except where the context requires otherwise due to express language or necessary implication, the word “comprises”, or variations such as “comprising” or “comprising” is used in an inclusive sense i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in

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various embodiments of the invention.

All literature and patent documents referred to herein are incorporated by reference to the fullest extent possible.

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In the present specification, references to “pharmaceutical use” refer to use for administration to a human or an animal, in particular a human or a mammal, for example a domesticated or livestock mammal, for the treatment or prophylaxis of a disease or medical condition. The term “pharmaceutical composition” refers to a composition which
10 is suitable for pharmaceutical use and “pharmaceutically acceptable” refers to an agent which is suitable for use in a pharmaceutical composition. Other similar terms should be construed accordingly.

Salts and solvates (such as hydrates) of the compounds of general formula (I) are suitably
15 pharmaceutically acceptable. Suitable pharmaceutically acceptable salts are well known to those of skill in the art and are described, for example by Gupta *et al* (2018). Some particularly suitable salts of the compounds of general formula (I) include basic addition salts such as sodium, potassium, calcium, aluminium, zinc, magnesium and other metal salts as well as choline, diethanolamine, ethanolamine, ethyl diamine and meglumine
20 salts. Alternatively, acid addition salts may be formed, for example hydrochloride, mesylate, hydrobromide, sulphate, and fumarate salts. Salts of synthetic intermediates need not be pharmaceutically acceptable.

In the present specification, the term “C₁₋₄ alkyl” refers to a straight or branched fully
25 saturated hydrocarbon group having from 1 to 4 carbon atoms. The term encompasses methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl and t-butyl. Other alkyl groups, for example C₁₋₆ alkyl and C₁₋₃ alkyl are as defined above but contain the stated number of carbon atoms.

The term “3- to 10-membered carbocyclic” refers to a non-aromatic hydrocarbon ring
30 system containing from 3 to 10 ring carbon atoms. The carbocyclic ring system may contain one or more carbon-carbon double bonds but preferably is a cycloalkyl group. The carbocyclic ring system may be a single ring or may contain two rings which may be fused or in a spiro arrangement or bridged, where carbon atoms in a bridge are included in the number of ring carbon atoms. Carbocyclic ring systems may contain other numbers of
35 ring atoms as specified, for example 5 to 8 ring atoms or 3 to 6 ring atoms.

In the context of the present specification, the term “cycloalkyl” refers to a fully saturated carbocyclic ring system as defined above. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, as well as bridged cycloalkyl systems such as bicyclo[1.1.1]pentyl.

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In the context of the present specification, the terms “3- to 10-membered heterocyclic” and “3- to 10-membered heterocyclyl” refer to a non-aromatic ring system containing 3 to 10 ring atoms, including at least one heteroatom selected from N, O and S. A heterocyclic ring system may contain one or more carbon-carbon double bonds but preferably is fully saturated. The heterocyclic ring system may be a single ring or may contain two or three rings which may be fused or in a spiro arrangement or bridged, where bridge atoms are included in the number of ring atoms. An oxygen-containing heterocyclic ring contains at least one oxygen as a ring atom and optionally one or two further heteroatoms selected from O, N and S. Examples of 3- to 6-membered heterocyclic ring systems include oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl and 2-oxaspiro[3.3]heptan-6-yl. Heterocyclic ring systems may contain other numbers of ring atoms as specified, for example 5 to 8 ring atoms or 3 to 6 ring atoms.

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The term “halogen” refers to fluorine, chlorine, bromine or iodine and the term “halo” to fluoro, chloro, bromo or iodo groups. Similarly, “halide” refers to fluoride, chloride, bromide or iodide.

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The term “C₁₋₄ haloalkyl” as used herein refers to a C₁₋₄ alkyl group as defined above in which one or more of the hydrogen atoms is replaced by a halo group. Any number of hydrogen atoms may be replaced, up to perhalo substitution. Examples include trifluoromethyl, chloroethyl and 1,1-difluoroethyl. A fluoroalkyl group is a haloalkyl group in which halo is fluoro. Other haloalkyl groups, for example C₁₋₃ haloalkyl, are as defined above but contain the stated number of carbon atoms.

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The term “isotopic variant” refers to isotopically-labelled compounds which are identical to those recited in formula (I) but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number most commonly found in nature, or in which the proportion of an atom having an atomic mass or mass number found less commonly in nature has been increased (the latter concept being referred to as “isotopic enrichment”). Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon,

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nitrogen, oxygen, fluorine, iodine and chlorine such as 2H (deuterium), 3H , ^{11}C , ^{13}C , ^{14}C , ^{18}F , ^{123}I or ^{125}I (e.g. 3H , ^{11}C , ^{14}C , ^{18}F , ^{123}I or ^{125}I), which may be naturally occurring or non-naturally occurring isotopes.

- 5 In particularly suitable isotopic variants of the compounds of general formula (I), some or all methyl groups are replaced by CD_3 . For example, one of, two of or all of R^8 , R^9 and R^{10} may be CD_3 .

In some suitable compounds of general formula (I):

- 10 R^1 is selected from methyl, fluoromethyl, difluoromethyl, trifluoromethyl, chlorodifluoromethyl, dichlorofluoromethyl, ethynyl, and CN ;

R^2 is selected from methyl and CH_2OH ;

- 15 R^3 is selected from H and methyl; or

- R^2 and R^3 together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic or oxygen-containing heterocyclic ring system either of which is optionally substituted, in addition to the R^1 group, with one or more substituents selected from OH , halo, C_{1-4} alkyl and C_{1-4} haloalkyl; or
- 20

R^1 , R^2 and R^3 together with the carbon atom to which they are attached combine to form a 5- to 8-membered bridged carbocyclic or heterocyclic ring system optionally substituted with one or more substituents selected from OH , halo, C_{1-4} alkyl and C_{1-4} haloalkyl;

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R^4 is H or halo;

each of R^5 and R^7 is independently selected from H , halo, C_{1-3} alkyl and C_{1-3} haloalkyl;

- R^6 is selected from H , halo, CN and C_{1-4} alkyl optionally substituted with one or more substituents selected from halo and OH ;
- 30

R^8 is methyl or ethyl, either of which is optionally substituted with one or more halogen substituents;

- R^9 is OH , CH_2OH or methyl or ethyl, either of which is optionally substituted with one or more halogen substituents; or
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R⁸ and R⁹ together with the carbon atom to which they are attached form either a 3- to 6-membered cycloalkyl or oxygen-containing heterocyclic ring optionally substituted, in addition to the R¹⁰ group, with one or more substituents selected from OH, F and CH₂OH; or an ethenyl group optionally substituted with one or two halogen substituents;

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R¹⁰ is selected from H, CN, OH, cycloalkyl optionally substituted with OH, and C₁₋₄ alkyl optionally substituted with one or more substituents selected from halo, OH and a 3- to 6-membered cycloalkyl or heterocyclic group, either of which is optionally substituted with OH; or

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R⁸, R⁹ and R¹⁰ together with the carbon atom to which they are attached form a 5- to 8-membered fused or bridged carbocyclic ring system optionally substituted with one or more substituents selected from OH, F and CH₂OH;

15 provided that:

i. when R⁵ and R⁷ are H and R⁶ is H or F, R¹, R², R³, R⁸, R⁹ and R¹⁰ are not all methyl; and

ii. when R², R³, R⁸, R⁹ and R¹⁰ are all methyl, R⁵, R⁶ and R⁷ are not all H; and

iii. when R¹ is CN and R² and R³ together with the carbon atom to which they are attached form a 3- to 10-membered oxygen-containing heterocyclic ring, R⁸, R⁹ and R¹⁰ are not all methyl; and

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iv. R⁹ and R¹⁰ are not both OH.

In other suitable compounds of general formula (I):

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R¹ is selected from methyl, fluoromethyl, difluoromethyl, trifluoromethyl, chlorodifluoromethyl, dichlorofluoromethyl, ethynyl and CN; or

when R² and R³ together with the carbon atom to which they are attached form a 4- to 6-membered carbocyclic ring substituted with OH, halo, methyl or CH₂OH, R¹ may also be

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H;

R² is selected from methyl and CH₂OH;

R³ is selected from H and methyl; or

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R² and R³ together with the carbon atom to which they are attached form a 3- to 10-

membered carbocyclic or oxygen-containing heterocyclic ring system either of which is optionally substituted, in addition to the R¹ group, with one or more substituents selected from OH, halo, C₁₋₄ alkyl, C₁₋₄ alkyl substituted with one or more OH substituents, and C₁₋₄ haloalkyl; or

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R¹, R² and R³ together with the carbon atom to which they are attached combine to form a 5- to 8-membered bridged carbocyclic or heterocyclic ring system optionally substituted with one or more substituents selected from OH, halo, C₁₋₄ alkyl and C₁₋₄ haloalkyl;

10 R⁴ is H or halo;

each of R⁵ and R⁷ is independently selected from H, halo, C₁₋₃ alkyl and C₁₋₃ haloalkyl;

15 R⁶ is selected from H, halo, CN and C₁₋₄ alkyl optionally substituted with one or more substituents selected from halo and OH;

R⁸ is methyl or ethyl, either of which is optionally substituted with one or more halogen substituents;

20 R⁹ is OH, CH₂OH or methyl or ethyl, either of which is optionally substituted with one or more halogen substituents; or25 R⁸ and R⁹ together with the carbon atom to which they are attached form either a 3- to 6-membered cycloalkyl or oxygen-containing heterocyclic ring optionally substituted, in addition to the R¹⁰ group, with one or more substituents selected from OH, F and CH₂OH; or an ethenyl group optionally substituted with one or two halogen substituents;30 R¹⁰ is selected from H, CN, OH, cycloalkyl optionally substituted with OH, and C₁₋₄ alkyl optionally substituted with one or more substituents selected from halo, OH and a 3- to 6-membered cycloalkyl or heterocyclic group, either of which is optionally substituted with OH; or

R⁸, R⁹ and R¹⁰ together with the carbon atom to which they are attached form a 5- to 8-membered fused or bridged carbocyclic ring system optionally substituted with one or more substituents selected from OH, F and CH₂OH;

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provided that:

- i. when R^5 and R^7 are H and R^6 is H or F, R^1 , R^2 , R^3 , R^8 , R^9 and R^{10} are not all methyl; and
- ii. when R^2 , R^3 , R^8 , R^9 and R^{10} are all methyl, R^5 , R^6 and R^7 are not all H; and
- iii. when R^1 is CN and R^2 and R^3 together with the carbon atom to which they are attached form a 3- to 10-membered oxygen-containing heterocyclic ring, R^8 , R^9 and R^{10} are not all methyl; and
- iv. R^9 and R^{10} are not both OH.

In some compounds of general formula (I) either:

- 10 R^8 and R^9 together with the carbon atom to which they are attached form a 3- to 6-membered cycloalkyl or oxygen-containing heterocyclic ring substituted, in addition to the R^{10} group, with one or more CH_2OH substituents and optionally with one or more further substituents selected from OH and F; or
- 15 R^8 and R^9 together with the carbon atom to which they are attached form a 3- to 6-membered cycloalkyl or oxygen-containing heterocyclic ring optionally substituted, in addition to the R^{10} group, with one or more substituents selected from OH and F; and R^{10} is CN or C_{1-4} alkyl substituted with one or more substituents selected from OH, a 3- to 6-membered cycloalkyl group optionally substituted with OH and a 3- to 6-membered
- 20 heterocyclic group optionally substituted with OH; or

R^8 and R^9 together with the carbon atom to which they are attached form an ethenyl group optionally substituted with one or two halogen substituents; or

- 25 R^8 , R^9 and R^{10} together with the carbon atom to which they are attached form a 5- to 8-membered fused or bridged carbocyclic ring system substituted with one or more CH_2OH substituents and optionally with one or more further substituents selected from OH and F.

In these compounds, more suitably either:

- 30 R^8 and R^9 together with the carbon atom to which they are attached form a 3- to 6-membered cycloalkyl or oxygen-containing heterocyclic ring system which is unsubstituted except for the R^{10} group; and R^{10} is selected from CN and CH_2OH ; or

- 35 R^8 , R^9 and R^{10} together with the carbon atom to which they are attached form a 5- to 8-membered fused or bridged carbocyclic ring system substituted with CH_2OH .

In some compounds of general formula (I):

R⁸ is methyl or ethyl, either of which is optionally substituted with one or more halogen substituents; and

R⁹ is OH, CH₂OH or methyl or ethyl, either of which is optionally substituted with one or
5 more halogen substituents; or

R⁸ and R⁹ together with the carbon atom to which they are attached form a 3- to 6-
membered cycloalkyl or oxygen-containing heterocyclic ring optionally substituted, in
addition to the R¹⁰ group, with one or more substituents selected from OH and F, and R¹⁰
10 is H, OH or C₁₋₄ alkyl optionally substituted with one or more halo substituents; or

R⁸, R⁹ and R¹⁰ together with the carbon atom to which they are attached form a 5- to 8-
membered fused or bridged carbocyclic ring system optionally substituted with one or
more substituents selected from OH and F.

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In some more suitable compounds of this type:

R⁸ is methyl or ethyl, R⁹ is OH or CH₂OH and R¹⁰ is methyl or ethyl. More suitably, R⁸ is
methyl, R⁹ OH or CH₂OH and R¹⁰ is methyl or ethyl. Still more suitably either R⁸ is methyl,
R⁹ is OH, and R¹⁰ is methyl or ethyl; or R⁸ is methyl, R⁹ is CH₂OH and R¹⁰ is methyl.

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Alternatively, R⁸ is methyl or ethyl, R⁹ is methyl or ethyl and R¹⁰ is OH or C₁₋₄ alkyl
substituted with OH. More suitably, R⁸ is methyl, R⁹ is methyl or ethyl and R¹⁰ is OH or
CH₂CH₂OH. Still more suitably either R⁸ is methyl, R⁹ is methyl or ethyl, and R¹⁰ is OH; or
R⁸ is methyl, R⁹ is methyl and R¹⁰ is CH₂OH.

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In other more suitable compounds of this type, R⁸ and R⁹ together with the carbon atom to
which they are attached form a 3- to 6-membered cycloalkyl ring, which is unsubstituted
except for the R¹⁰ substituent; and R¹⁰ is OH or CH₂OH. Still more suitably, R⁸ and R⁹
together with the carbon atom to which they are attached form a cyclopropyl or cyclobutyl
30 ring, which is unsubstituted except for the R¹⁰ substituent; and R¹⁰ is CH₂OH.

In other more suitable compounds of this type, R⁸, R⁹ and R¹⁰ are all methyl.

In some compounds of general formula (I), R¹, R² and R³ are not all methyl.

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In some compounds of general formula (I), R⁸, R⁹ and R¹⁰ are not all methyl.

In some compounds of general formula (I), R^1 , R^2 , R^3 , R^8 , R^9 and R^{10} are not all methyl

Suitably, in the compounds of general formula (I), R^1 is methyl, difluoromethyl, trifluoromethyl, ethynyl or CN.

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In some compounds of general formula (I), R^1 is methyl.

In other compounds of general formula (I), R^1 is ethynyl.

10 In some more suitable compounds of general formula (I), R^1 is difluoromethyl or trifluoromethyl, especially trifluoromethyl.

In other more suitable compounds of general formula (I), R^1 is CN.

15 In some suitable compounds of general formula (I), R^2 is methyl.

In other compounds of general formula (I), R^2 is CH_2OH .

In compounds of general formula (I) where R^2 is methyl or CH_2OH , R^3 is H or methyl.

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In some such compounds, R^3 is H. However, more suitably, R^3 is methyl.

In some suitable compounds of general formula (I), R^2 is methyl and R^3 is H. In some suitable compounds of general formula (I), R^2 is methyl and R^3 is methyl.

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Alternatively, as described above, R^2 and R^3 together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic or oxygen-containing heterocyclic ring system, optionally substituted as described above. In some suitable compounds of general formula (I), the ring system is a 3- to 6-membered cycloalkyl or oxygen-containing heterocyclic ring. In this case, the ring may be a cycloalkyl ring, for example cyclopropyl, cyclobutyl or cyclopentyl and especially cyclopropyl. Alternatively, the ring may be a fully saturated 3- to 6-membered oxygen-containing heterocyclic ring, for example a tetrahydropyran, tetrahydrofuran or oxetane ring. The 3- to 6-membered cycloalkyl or oxygen-containing heterocyclic ring may be substituted, in addition to R^1 , with one or more substituents selected from OH, halo, C_{1-4} alkyl and C_{1-4} haloalkyl, more suitably OH, halo, methyl, difluoromethyl or trifluoromethyl, still more suitably OH and halo, for example OH

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and fluoro.

Suitably, when R^2 and R^3 form a ring system of this type, R^1 is H, methyl, trifluoromethyl, difluoromethyl or CN, more suitably methyl, difluoromethyl, trifluoromethyl or CN, still more
5 suitably trifluoromethyl or CN, and especially trifluoromethyl. The ring system formed by R^2 and R^3 together with the carbon atom to which they are attached is suitably unsubstituted apart from the group R^1 .

In compounds of general formula (I) in which R^1 is H and R^2 and R^3 together with the
10 carbon atom to which they are attached form a 4- to 6-membered carbocyclic ring substituted with OH, halo, methyl or CH_2OH , a preferred substituent for the 4- to 6-membered carbocyclic ring is OH. Suitably, the ring is a cyclopentyl ring.

In some suitable compounds, R^2 and R^3 together with the carbon atom to which they are
15 attached form a 4- to 6-membered carbocyclic ring, which is unsubstituted apart from the R^1 group.

In some suitable compounds of this type, R^1 is CH_2OH . In this case, R^2 and R^3 together
20 with the carbon atom to which they are attached suitably form a cyclobutyl or cyclopentyl ring, most suitably a cyclobutyl ring which is unsubstituted apart from the R^1 group.

In some particularly suitable compounds, R^1 is trifluoromethyl; and R^2 and R^3 together with
the carbon atom to which they are attached form a cyclopropyl ring which is unsubstituted
except for R^1 .

25 In some suitable compounds of general formula (I), R^1 , R^2 and R^3 together with the carbon atom to which they are attached combine to form a 5- to 8-membered bridged carbocyclic or heterocyclic ring system optionally substituted with one or more substituents selected from OH, halo, C_{1-4} alkyl and C_{1-4} haloalkyl.

30 In some suitable compounds R^4 is H or halo such as F. In particularly suitable compounds, R^4 is H.

In some suitable compounds, each of R^5 and R^7 is H.

35 In suitable compounds of general formula (I), R^6 is selected from H, halo, CN and methyl

optionally substituted with one or more substituents selected from halo and OH. More suitably, R⁶ is H, halo, CN, CH₃, CF₃, CHF₂, CH₂F or CH₂OH, still more suitably halo or methyl and particularly halo such as fluoro or chloro.

5 In suitable compounds of general formula (I), R⁴ is H; and/or each of R⁵ and R⁷ is H; and/or R⁶ is H, halo, CN, CH₃, CF₃, CHF₂, CH₂F or CH₂OH. Suitably, R⁴ is H and each of R⁵ and R⁷ is H. Suitably, R⁴ is H and R⁶ is H, halo, CN, CH₃, CF₃, CHF₂, CH₂F or CH₂OH. Suitably, each of R⁵ and R⁷ is H and R⁶ is H, halo, CN, CH₃, CF₃, CHF₂, CH₂F or CH₂OH. Suitably, R⁴ is H, each of R⁵ and R⁷ is H, and R⁶ is H, halo, CN, CH₃, CF₃, CHF₂, CH₂F or CH₂OH.

10

In some suitable compounds of general formula (I), R⁸ is methyl or ethyl, especially methyl. In some suitable compounds of the present invention, R⁸ is methyl or ethyl, especially methyl, and R⁹ is methyl, CH₂OH or OH. In particular, R⁸ is methyl and R⁹ is OH. In other suitable compounds of the invention R⁸ and R⁹ are each independently methyl or ethyl. More suitably, one of R⁸ and R⁹ is methyl and the other of R⁸ and R⁹ is methyl or ethyl.

15

Alternatively, when R⁸ and R⁹ together with the carbon atom to which they are attached form a 3- to 6-membered cycloalkyl or oxygen-containing heterocyclic ring, the ring is suitably unsubstituted except for the R¹⁰ moiety. The ring formed by R⁸ and R⁹ together with the carbon atom to which they are attached is suitably selected from cycloalkyl rings and heterocyclic rings having a single ring oxygen atom, for example cyclopropyl, cyclobutyl, tetrahydropyranyl, tetrahydrofuranyl and oxetanyl.

20

25 R¹⁰ is suitably selected from H, CN, cyclopropyl, cyclobutyl and methyl or ethyl, wherein the methyl or ethyl is unsubstituted or is substituted with one or more substituents selected from fluoro, OH and a 3- to 6-membered cycloalkyl or heterocyclyl group.

More suitably, R¹⁰ is CN, cyclopropyl, cyclobutyl, unsubstituted methyl or methyl substituted with one or more substituents selected from fluoro, OH and a 3- to 6-membered cycloalkyl or heterocyclyl group.

30

When R¹⁰ is methyl or ethyl substituted with a heterocyclic group, it is suitably a 5- or 6-membered nitrogen containing heterocycle optionally containing one or more additional heteroatom and bound to the carbon atom in the methyl or ethyl group via a ring nitrogen atom. Examples of such heterocyclic groups include morpholinyl, pyrrolidinyl, piperidinyl

35

and piperazinyl.

In particularly suitable compounds of general formula (I), R¹⁰ is CN, methyl, CF₃, CH₂OH, cyclopropylmethyl or morpholinylmethyl, for example morpholin-4-ylmethyl, and especially
5 CH₂OH.

When R⁸ is methyl or ethyl and R⁹ is OH or CH₂OH, R¹⁰ is suitably methyl or ethyl.

When R⁸ is methyl or ethyl, R⁹ is methyl or ethyl, R¹⁰ is suitably OH or C₁₋₄ alkyl substituted
10 with OH; more suitably OH or CH₂OH.

When R⁸ and R⁹ together with the carbon atom to which they are attached form a 3- to 6-
membered cycloalkyl or oxygen-containing heterocyclic ring, R¹⁰ is more suitably methyl,
ethyl, CH₂OH, CH₂CH₂OH, trifluoromethyl or CN.
15

In some particularly suitable compounds, R¹⁰ is CH₂OH

In some compounds of general formula (I), R⁸ and R⁹ together with the carbon atom to
which they are attached form a cyclopropyl, cyclobutyl, cyclopentyl or oxetanyl ring,
20 especially a cyclopropyl, cyclobutyl or oxetanyl ring, which may be unsubstituted except
for the R¹⁰ group or may have a single CH₂OH substituent in addition to the R¹⁰ group; and
R¹⁰ is methyl, CH₂OH, trifluoromethyl or cyano.

In some such compounds, R¹⁰ is CH₂OH or cyano.
25

In some such compounds, the ring is unsubstituted except for the R¹⁰ group and R¹⁰ is
CH₂OH or cyano, especially CH₂OH.

In other such compounds, the ring is unsubstituted except for the R¹⁰ group and R¹⁰ is
30 methyl or trifluoromethyl.

When R⁸, R⁹ and R¹⁰ together with the carbon atom to which they are attached form an
unsubstituted 5- to 8-membered fused or bridged carbocyclic ring system, it is suitably a
bridged ring system such as bicyclo[1.1.1]pentane, bicyclo[2.1.1]hexane or
35 bicyclo[2.2.1]heptane. Suitably, the ring is unsubstituted or is substituted with a single
CH₂OH substituent.

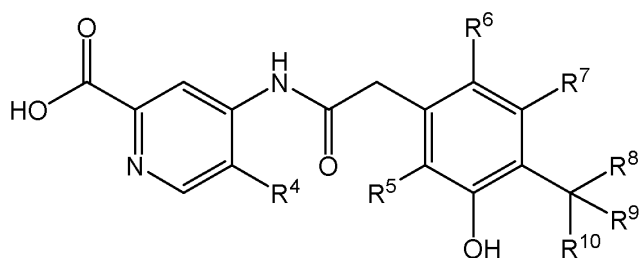
Specific examples of compounds of general formula (I) include the following:

- 4-[[2-(4-*tert*-Butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-(1-methylcyclopropyl)pyridine-2-carboxamide (Compound 1);
- 4-[[2-(4-*tert*-Butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 1.1);
- 4-[[2-(4-*tert*-Butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-(1-ethynylcyclopentyl)pyridine-2-carboxamide (Compound 1.2);
- 4-[[2-(4-*tert*-Butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-(1-cyanoethyl)pyridine-2-carboxamide (Compound 1.3);
- 4-[[2-(4-*tert*-Butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-[(1R)-1-cyanoethyl]pyridine-2-carboxamide (Compound 1.3a/b);
- 4-[[2-(4-*tert*-butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-[(1S)-1-cyanoethyl]pyridine-2-carboxamide (Compound 1.3 a/b);
- 4-[[2-(4-*tert*-Butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide (Compound 1.4);
- 4-[[2-(4-*tert*-Butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-(1-cyanocyclopropyl)pyridine-2-carboxamide (Compound 1.5);
- 4-[[2-(4-*tert*-Butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-2-hydroxy-1-methyl-ethyl)pyridine-2-carboxamide (Compound 1.6);
- 4-[[2-(4-*tert*-Butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-[(1R)-1-cyano-2-hydroxy-1-methyl-ethyl]pyridine-2-carboxamide (Compound 1.6 a/b);
- 4-[[2-(4-*tert*-butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-[(1S)-1-cyano-2-hydroxy-1-methyl-ethyl]pyridine-2-carboxamide (Compound 1.6 a/b);
- 4-[[2-(4-*tert*-Butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Compound 1.7);
- 4-[[2-[2-Fluoro-5-hydroxy-4-(1-hydroxy-1-methyl-ethyl)phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Compound 2);
- N-(1-Cyano-1-methyl-ethyl)-4-[[2-[2-fluoro-5-hydroxy-4-(1-hydroxy-1-methyl-ethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 2.1);
- N-*tert*-Butyl-4-[[2-[4-(1-cyano-1-methyl-ethyl)-2-fluoro-5-hydroxy-phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 2.2);
- 4-[[2-[4-(1-Cyano-1-methyl-ethyl)-2-fluoro-5-hydroxy-phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Compound 2.3);
- N-*tert*-Butyl-4-[[2-[4-(1-cyanocyclopropyl)-2-fluoro-5-hydroxy-phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 2.4);
- N-(1-Cyano-1-methyl-ethyl)-4-[[2-[4-(1,1-dimethyl-2-morpholino-ethyl)-2-fluoro-5-

- hydroxy-phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 2.5);
4-[[2-[2-fluoro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetyl] amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Compound 2.6);
N-(1-Cyano-1-methyl-ethyl)-4-[[2-[2-fluoro-5-hydroxy-4-(2,2,2-trifluoro-1-hydroxy-1-methyl-ethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 2.7);
5 4-[[2-[4-(1-Cyclopropyl-1-hydroxy-ethyl)-2-fluoro-5-hydroxy-phenyl]acetyl] amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Compound 2.8);
4-[[2-[4-(4-Cyanotetrahydropyran-4-yl)-2-fluoro-5-hydroxy-phenyl]acetyl] amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Compound 2.9);
10 4-[[2-[2-Fluoro-5-hydroxy-4-[2-(trifluoromethyl)oxetan-2-yl]phenyl] acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Compound 2.10);
4-[[2-[2-Fluoro-5-hydroxy-4-(1-hydroxy-1-methyl-propyl)phenyl] acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Compound 2.11);
4-[[2-[2-Fluoro-5-hydroxy-4-[(1S)-1-hydroxy-1-methyl-propyl]phenyl]acetyl] amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Compound 2.11 a/b);
15 4-[[2-[2-fluoro-5-hydroxy-4-[(1R)-1-hydroxy-1-methyl-propyl]phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl] pyridine-2-carboxamide (Compound 2.11 a/b);
4-[[2-[5-Hydroxy-4-(1-hydroxy-1-methyl-ethyl)-2-methyl-phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Compound 2.12);
20 4-[[2-[2-Fluoro-5-hydroxy-4-[1-(hydroxymethyl)cyclobutyl]phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Compound 2.13);
N-(1-Cyano-1-methyl-ethyl)-4-[[2-[2-fluoro-5-hydroxy-4-[2-(trifluoromethyl)oxetan-2-yl]phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 2.14);
4-[[2-[2-Fluoro-5-hydroxy-4-[4-(hydroxymethyl)tetrahydropyran-4-yl]phenyl]acetyl]
25 amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Compound 2.15);
4-[[2-[2-Fluoro-5-hydroxy-4-[1-(hydroxymethyl)cyclopropyl]phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Compound 2.16);
4-[[2-(4-*tert*-Butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-1-methyl-ethyl)-5-fluoro-pyridine-2-carboxamide (Compound 3);
30 N-(1-Cyanocyclopropyl)-4-[[2-[2-deuterio-6-fluoro-3-hydroxy-4-[2,2,2-trideuterio-1,1-bis(trideuteriomethyl)ethyl]phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 4);
N-(1-Cyano-1-methyl-ethyl)-4-[[2-[2-fluoro-5-hydroxy-4-(1-methylcyclobutyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 5);
N-*tert*-Butyl-4-[[2-(4-*tert*-butyl-5-hydroxy-2-isopropyl-phenyl)acetyl]amino] pyridine-2-
35 carboxamide (Compound 6);
N-*tert*-Butyl-4-[[2-[2-fluoro-5-hydroxy-4-(1-hydroxy-1-methyl-ethyl)phenyl]

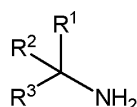
- acetyl]amino]pyridine-2-carboxamide (Compound 7);
4-[[2-(2-Fluoro-5-hydroxy-4-isopropenyl-phenyl)acetyl]amino]-N-[1-(trifluoromethyl)
cyclopropyl]pyridine-2-carboxamide (Compound 7.1);
N-*tert*-Butyl-4-[[2-[2-fluoro-5-hydroxy-4-(1-methylcyclopropyl)phenyl]
5 acetyl]amino]pyridine-2-carboxamide (Compound 8);
N-(1-Cyanocyclopropyl)-4-[[2-[2-fluoro-5-hydroxy-4-[1-(trifluoromethyl)
cyclopropyl]phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 9);
4-[[2-(4-*tert*-Butyl-2-chloro-5-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-1-methyl-
ethyl)pyridine-2-carboxamide (Compound 10);
10 4-[[2-(4-*tert*-Butyl-2-chloro-5-hydroxy-phenyl)acetyl]amino]-N-[1-(trifluoromethyl)
cyclopropyl]pyridine-2-carboxamide (Compound 10.1);
4-[[2-(4-*tert*-Butyl-2-chloro-5-hydroxy-phenyl)acetyl]amino]-N-(1-cyanocyclopropyl)
pyridine-2-carboxamide (Compound 10.2);
4-[[2-[2-Fluoro-5-hydroxy-4-(3-hydroxy-1,1-dimethyl-propyl)phenyl]acetyl]amino]-N-[1-
15 (trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Compound 11);
N-(4-Cyanotetrahydropyran-4-yl)-4-[[2-[2-fluoro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-
ethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 12);
4-[[2-[2-Fluoro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetyl]amino]-N-[3-
(trifluoromethyl)oxetan-3-yl]pyridine-2-carboxamide (Compound 12.1);
20 4-[[2-[2-Fluoro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetyl]amino]-N-
[(1S,2S)-2-hydroxycyclopentyl]pyridine-2-carboxamide (Compound 12.2);
4-[[2-[2-Fluoro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetyl]amino]-N-(2-
hydroxy-1,1-dimethyl-ethyl)pyridine-2-carboxamide (Compound 12.3);
4-[[2-[2-Fluoro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetyl]amino]-N-[1-
25 (hydroxymethyl)cyclobutyl]pyridine-2-carboxamide (Compound 12.4);
4-[[2-[2-Fluoro-5-hydroxy-4-(4-hydroxytetrahydropyran-4-yl)phenyl]acetyl]amino]-N-[1-
(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Compound 13);
4-[[2-[2-Chloro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetyl]amino]-N-[1-
(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Compound 14);
30 4-[[2-[5-Hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)-2-methyl-phenyl]acetyl]amino]-N-[1-
(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Compound 14.1);
N-(3,3-Difluoro-1-methyl-cyclobutyl)-4-[[2-[2-fluoro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-
ethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 15);
4-[[2-[2-Chloro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetyl]amino]-N-(1,1-
35 dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 15.1);
4-[[2-[2-Chloro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetyl]amino]-N-(3,3-

- difluoro-1-methyl-cyclobutyl)pyridine-2-carboxamide (Compound 15.2);
4-[[2-[2-Chloro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetyl]amino]-N-[1-(difluoromethyl)cyclopropyl]pyridine-2-carboxamide (Compound 15.3);
N-[1-(Difluoromethyl)cyclopropyl]-4-[[2-[2-fluoro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 15.4);
5 N-(1,1-Dimethylprop-2-ynyl)-4-[[2-[2-fluoro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 16);
4-[[2-[2-Fluoro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetyl]amino]-N-(4-methyltetrahydropyran-4-yl)pyridine-2-carboxamide (Compound 16.1);
10 N-(1-Cyano-1-methyl-ethyl)-4-[[2-[2-fluoro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 16.2);
4-[[2-[2-Fluoro-5-hydroxy-4-(2-hydroxy-1-methyl-ethyl)phenyl]acetyl]amino]-N-(4-methyltetrahydropyran-4-yl)pyridine-2-carboxamide (Compound 16.3);
4-[[2-[2,6-Difluoro-3-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Compound 16.4);
15 4-[[2-[2-Fluoro-5-hydroxy-4-[2,2,2-trifluoro-1-(hydroxymethyl)ethyl]phenyl]acetyl] amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Compound 17);
4-[[2-[2-Chloro-6-fluoro-3-hydroxy-4-(1-hydroxy-1-methyl-ethyl)phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Compound 18);
20 4-[[2-[2-Chloro-5-hydroxy-4-(1-hydroxy-1-methyl-ethyl)phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Compound 19);
4-[[2-[2-Fluoro-5-hydroxy-4-(2-hydroxy-1-methyl-ethyl)phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Compound 20);
4-[[2-[2-Fluoro-5-hydroxy-4-[(1S)-2-hydroxy-1-methyl-ethyl]phenyl]acetyl] amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Compound 20a/b);
25 4-[[2-[2-fluoro-5-hydroxy-4-[(1R)-2-hydroxy-1-methyl-ethyl]phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl] pyridine-2-carboxamide (Compound 20a/b);
and salts and solvates of the above.
- 30 Compounds of general formula (I) may be prepared by reacting a compound of general formula (II):



(II)

wherein R^4 , R^5 , R^6 , R^7 , R^8 , R^9 and R^{10} are as defined for general formula (I);
with a compound of general formula (III):



(III)

wherein R^1 , R^2 and R^3 are as defined in general formula (I).

Suitably, the reaction is conducted in the presence of a coupling reagent and under basic conditions, for example in the presence of an amine such as diisopropylethylamine (DIPEA) and in an organic solvent such as DMF.

Suitable coupling reagents include known peptide coupling agents such as O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU), O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TATU), (Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP), (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) carbodiimides such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) and triazoles such as 1-hydroxy-7-azabenzotriazole (HOAt) or hydroxybenzotriazole (HOBt).

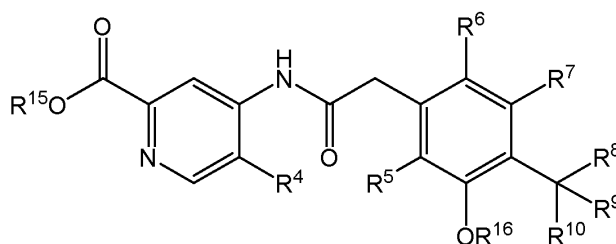
Suitably, when these coupling agents are used, the reaction is conducted under basic conditions, for example in the presence of an amine such as diisopropylethylamine (DIPEA) and in an organic solvent such as DMF.

Alternatively, the coupling reagent may be propylphosphonic anhydride (T3P®). When T3P is used as the coupling reagent, the reaction may be conducted under basic conditions, for example in the presence of an amine such as diisopropylethylamine (DIPEA) or triethylamine (TEA) and in an organic solvent such as dioxane.

Coupling agents such as HATU, HBTU, TBTU and TATU are particularly suitable for this reaction.

Compounds of general formula (III) are readily available or may be synthesised by known methods.

A compound of general formula (II) may be prepared by deprotecting a compound of general formula (IV):



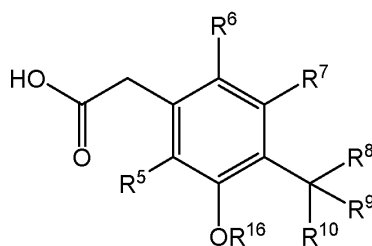
(IV)

wherein R^4 , R^5 , R^6 , R^7 , R^8 , R^9 and R^{10} are as defined for general formula (I) and each of R^{15} and R^{16} is independently C_{1-6} alkyl.

Suitably, deprotection is carried out by reaction with boron tribromide, which is particularly useful when both R^{15} and R^{16} are methyl.

Boron tribromide deprotection may be carried out in a polar organic solvent such as dichloromethane. Cooling may be required initially, for example to about -5 to 5 $^{\circ}\text{C}$, and the reaction may subsequently be allowed to warm to a temperature of about 15 to 25 $^{\circ}\text{C}$, typically room temperature.

A compound of general formula (IV) may be prepared by reacting a compound of general formula (V):

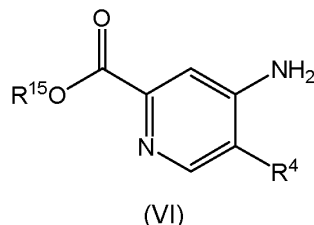


(V)

wherein R^5 , R^6 , R^7 , R^8 , R^9 and R^{10} are as defined for general formula (I) and R^{16} is as

defined for general formula (IV);

with a compound of general formula (VI):



- 5 wherein R^4 is as defined for general formula (I) and R^{15} is as defined for general formula (IV).

Suitably, the reaction takes place in the presence of a coupling agent as described above, with T3P® being particularly suitable.

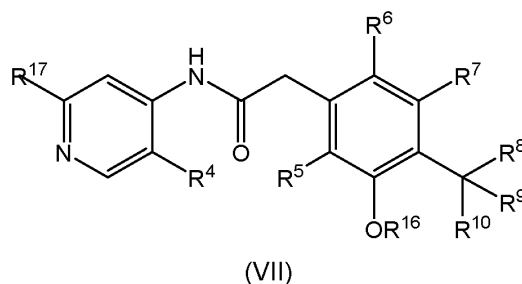
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Compounds of general formula (VI) are known and are readily available or may be synthesised by known methods.

The synthesis of compounds of general formula (V) will be discussed in greater detail below.

15

An alternative method for the synthesis of a compound of general formula (IV) is by carbonylation of a compound of general formula (VII):



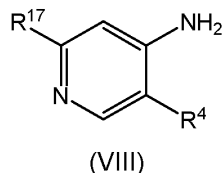
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wherein R^4 , R^5 , R^6 , R^7 , R^8 , R^9 and R^{10} are as defined for general formula (I), R^{16} is as defined for general formula (IV) and R^{17} is halo, for example bromo.

Carbonylation may be carried out by reaction with carbon monoxide in the presence of a palladium catalyst such as Pd(dppf)Cl_2 ([1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium(II)) and a base such as trimethylamine and in an alcoholic solvent such as methanol. Carbon monoxide may be generated *in situ* by reaction with formic acid and methane sulfonyl chloride with triethylamine.

25

A compound of general formula (VII) may be prepared by reacting a compound of general formula (V) as defined above with a compound of general formula (VIII):



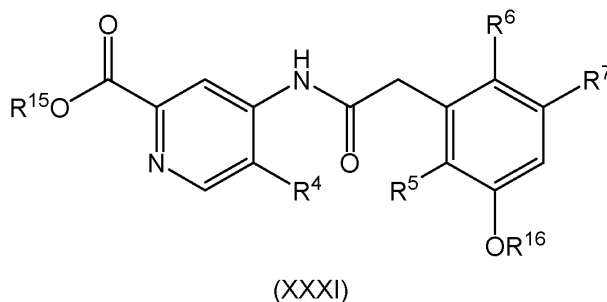
- 5 wherein R^4 is as defined for general formula (I) and R^{17} is as defined for general formula (VII).

Suitably, the reaction is carried out in the presence of a coupling reagent as defined above, with T3P® being particularly suitable.

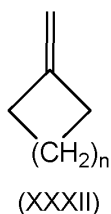
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Compounds of general formula (VIII) are known and are readily available or may be prepared by known methods.

- 15 A compound of general formula (IV) in which R^8 and R^9 together with the carbon atom to which they are attached form a cycloalkyl group and R^{10} is methyl may be prepared by reacting a compound of general formula (XXXI):



- 20 wherein R^4 , R^5 , R^6 and R^7 are as defined for general formula (I) and R^{15} and R^{16} are as defined for general formula (IV);
with a compound of general formula (XXXII):



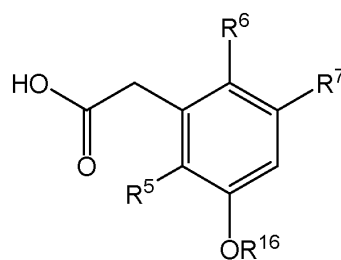
- 25 wherein n is 0 to 3.

Suitably, the reaction takes place in the presence of concentrated sulfuric acid.

Compounds of general formula (XXXII) are known and are readily available or may be synthesised by those of skill in the art.

5

A compound of general formula (XXXI) may be prepared by reacting a compound of general formula (IX):



(IX)

- 10 wherein R⁵, R⁶ and R⁷ are as defined for general formula (I) and R¹⁶ is as defined for general formula (IV);
with a compound of general formula (VI) as defined above.

- Suitably, the reaction takes place in the presence of a coupling agent as described above,
15 with T3P® being particularly suitable.

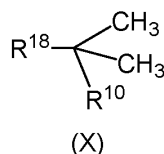
Compounds of general formulae (VI) and (IX) are known and are readily available or may be synthesised by known methods.

- 20 There are a number of methods for preparing compounds of general formula (V) depending on the nature of the substituents.

- For example, a compound of general formula (V) in which R⁸ and R⁹ are methyl and R¹⁰ is methyl or halomethyl can be prepared by the alkylation of a compound of general formula
25 (IX) as defined above.

Suitable alkylation reactions include Friedel-Crafts alkylation, with a compound of general formula (X):

26



wherein R^{10} is methyl optionally substituted with halo and R^{18} is halo, for example chloro or bromo;

- 5 in the presence of a Lewis acid catalyst, for example FeCl_3 . This method is particularly suitable for compounds in which R^6 is F.

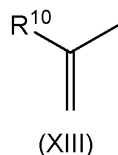
Alternatively, for a compound of general formula (IX) in which R^6 is halo, alkylation may be carried out by reaction of the with a compound of general formula (XI):



wherein R^{10} is methyl optionally substituted with halo.

Suitably, the reaction is carried out in the presence of concentrated sulfuric acid.

- 15 Alternatively, the alkylation can be carried out by reaction with a compound of general formula (XIII):

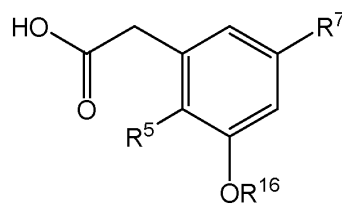


- 20 wherein R^{10} is methyl optionally substituted with halo;
in the presence of concentrated sulfuric acid.

Compounds of general formulae (X), (XI) and (XIII) are known and are readily available or may be prepared by known methods.

- 25 Compounds of general formula (IX) are also known and are readily available or may be prepared by known methods. For example, a compound of general formula (IX) in which R^6 is Cl or Br can be prepared by the chlorination or bromination of a compound of general formula (XII):

27



(XII)

wherein R^5 and R^7 are as defined for general formula (I) and R^{16} is as defined for general formula (IV).

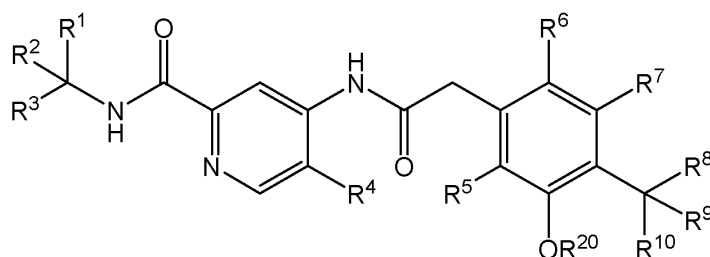
5

Suitable halogenating agents include N-chloro succinimide and N-bromosuccinimide.

Compounds of general formula (XII) are known and are readily available or may be prepared by known methods.

10

An alternative method for the preparation of compounds of general formula (I) is by the deprotection of a compound of general formula (XXI):



(XXI)

15 wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 and R^{10} are as defined for general formula (I); and R^{20} is benzyl optionally substituted with one or more methoxy groups.

Suitably, deprotection can be achieved by catalytic hydrogenation, for example using a palladium catalyst, typically palladium on carbon. The reaction may be carried out in an alcoholic solvent, for example methanol or ethanol. When R^{20} is benzyl substituted with one or more methoxy groups, deprotection can also be achieved by treatment with a strong acid such as hydrochloric acid or trifluoroacetic acid. Further deprotection methods include treatment with sodium borohydride in the presence of a Nickel (II) salt, for example under the conditions set out in Example 19 below.

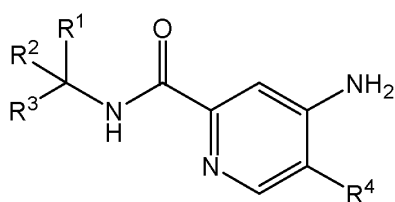
25

This method is particularly suitable for compounds of general formula (I) in which R^{10} is OH, CN, halomethyl (e.g. CF_3) or methyl substituted with OH or a heterocyclic ring,

particularly when the heterocyclic ring is bound to CH₂ via a nitrogen atom. In addition, it is suitable for compounds of general formula (I) in which R⁸ and R⁹ together with the carbon atom to which they are attached form a 3- to 6-membered cycloalkyl or oxygen-containing heterocyclic ring (either alone or in combination with the R¹⁰ groups just mentioned).

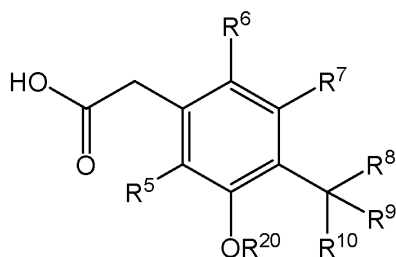
5

A compound of general formula (XXI) may be prepared by reacting a compound of general formula (XXII):



(XXII)

- 10 wherein R¹, R², R³ and R⁴ are as defined for general formula (I);
with a compound of general formula (XXV):

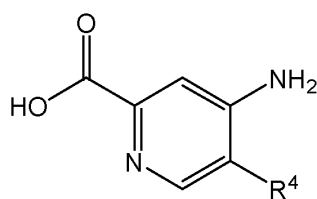


(XXV)

- 15 wherein R⁵, R⁶, R⁷, R⁸, R⁹ and R¹⁰ are as defined for general formula (I); and R²⁰ is as defined for general formula (XXI).

Suitably, the reaction is carried out in the presence of a coupling reagent as described above. Typically, T3P® may be used as the coupling reagent.

- 20 A compound of general formula (XXII) may be prepared by reacting a compound of general formula (III) as defined above with a compound of general formula (XXIII):



(XXIII)

wherein R⁴ is as defined for general formula (I).

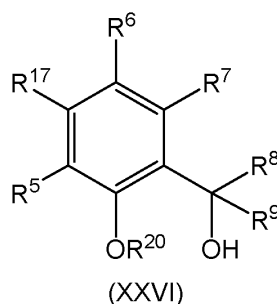
Suitably, the reaction is carried out in the presence of a coupling reagent as described above, for example a coupling reagent such as HATU.

- 5 Compounds of general formula (XXIII) are known and are readily available or may be prepared by known methods.

Some compounds of general formula (XXV) are known, while others may be synthesised by those of skill in the art.

10

For example, a compound of general formula (XXV) in which each of R⁸ and R⁹ is independently methyl or ethyl and R¹⁰ is OH can be prepared from a compound of general formula (XXVI):

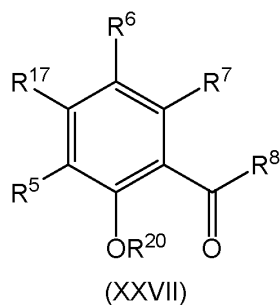


15

wherein R⁵, R⁶ and R⁷ are as defined for general formula (I); R¹⁷ is as defined for general formula (VII); each of R⁸ and R⁹ is independently methyl or ethyl; and R²⁰ is as defined for general formula (XXI);

- by reaction with the alkali metal salt of a malonic acid monoester (such as methyl
20 potassium malonate) or the alkali metal salt of cyanoacetic acid (such as potassium 2-cyanoacetate) in the presence of a Pd catalyst (such as [Pd(allyl)Cl]₂), a phosphine ligand (such as BINAP) and an organic base (such as DMAP). The resulting ester or nitrile can then be hydrolysed with aqueous base.

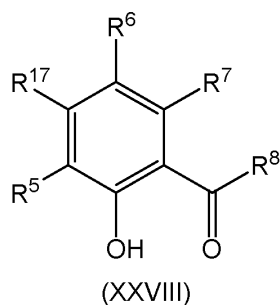
- A compound of general formula (XXVI) may be prepared from a compound of general
25 formula (XXVII):



wherein R^5 , R^6 and R^7 are as defined for general formula (I); R^{17} is as defined for general formula (VII); R^8 is methyl or ethyl and R^{20} is as defined for general formula (XXI);

- 5 by reaction with an alkyl Grignard reagent, as $R^9\text{-MgBr}$, where R^9 is methyl or ethyl, under appropriate conditions.

A compound of general formula (XXVII) may be prepared by protection of a compound of general formula (XXVIII):

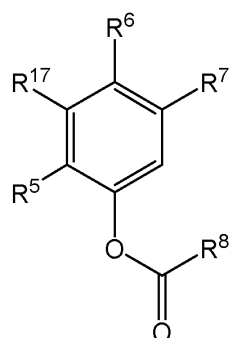


wherein R^5 , R^6 and R^7 are as defined for general formula (I); R^8 is methyl or ethyl; and R^{17} is as defined for general formula (VII);

- 10 by reaction with a compound $R^{20}\text{-Br}$, wherein R^{20} is as defined for general formula (XXI),
 15 suitably in the presence of a weak base such as potassium carbonate.

A compound of general formula (XXVIII) may be prepared from a compound of general formula (XXIX):

31

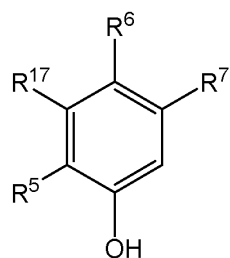


(XXIX)

wherein R⁵, R⁶ and R⁷ are as defined for general formula (I); R⁸ is methyl or ethyl; and R¹⁷ is as defined for general formula (VII);

- 5 by reaction with aluminium chloride in a solvent free reaction at elevated temperature, typically about 150 to 200 °C.

A compound of general formula (XXIX) may be prepared from a compound of general formula (XXX):



(XXX)

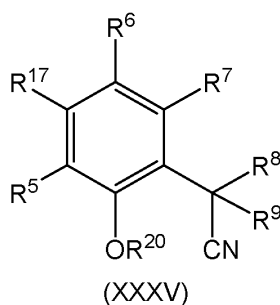
wherein R⁵, R⁶ and R⁷ are as defined for general formula (I); and R¹⁷ is as defined for general formula (VII);

- by reaction with ethanoyl chloride for compounds for compounds of general formula (XXIX)
 15 in which R⁸ is methyl or propanoyl chloride for compounds for compounds of general formula (XXIX) in which R⁸ is ethyl.

Compounds of general formula (XXX) are known and are readily available or may be prepared by known methods.

20

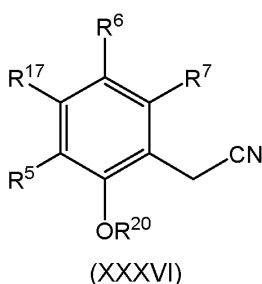
A compound of general formula (XXV) in which R⁹ is methyl or halomethyl and R¹⁰ is CN may be prepared from a compound of general formula (XXXV):



wherein R^5 , R^6 , R^7 and R^8 are as defined for general formula (I), R^9 is methyl; R^{17} is as defined for general formula (VII) and R^{20} is as defined for general formula (XXI);

- 5 by reaction with the alkali metal salt of a malonic acid monoester (such as methyl potassium malonate) in the presence of a Pd catalyst (such as $[Pd(allyl)Cl]_2$), a phosphine ligand (such as BINAP) and an organic base (such as DMAP). The resulting ester can then be hydrolysed with aqueous base.

- 10 A compound of general formula (XXXV) in which R^8 and R^9 are independently methyl or ethyl may be prepared from a compound of general formula (XXXVI):



- 15 wherein R^5 , R^6 and R^7 are as defined for general formula (I); R^{17} is as defined for general formula (VII) and R^{20} is as defined for general formula (XXI).

For compounds in which R^8 and R^9 are the same, the compound of general formula (XXXVI) may be reacted with a compound of general formula:

- 20 R^8-I ;

wherein R^8 is methyl or ethyl;

in the presence of strong base such as sodium hydride.

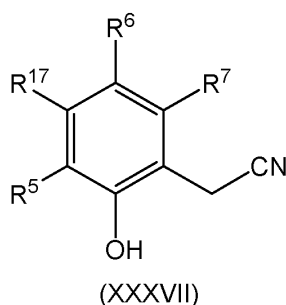
- 25 When R^8 and R^9 are not the same, sequential reactions may be carried out with compounds of general formulae:

R^8 -I and R^9 -I;

wherein one of R^8 and R^9 is methyl and the other is ethyl;
again in the presence of a strong base such as sodium hydride.

5

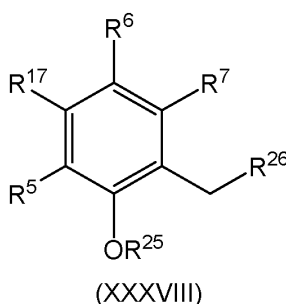
A compound of general formula (XXXVI) may be prepared by reacting a compound of general formula (XXXVII):



- 10 wherein R^5 , R^6 and R^7 are as defined for general formula (I); and R^{17} is as defined for general formula (VII);
with a compound R^{20} -Br, wherein R^{20} is as defined for general formula (XXI).

- 15 Compounds R^{20} -Br are known and are readily available or may be prepared by known methods.

Compounds of general formula (XXXVII) may be prepared by reacting a protected compound of general formula (XXXVIII):



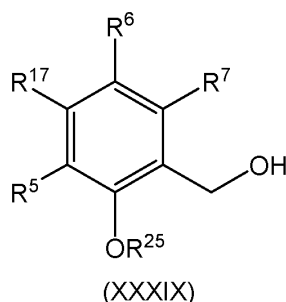
20

wherein R^5 , R^6 and R^7 are as defined for general formula (I); R^{17} is as defined for general formula (VII); R^{25} is an OH protecting group, for example tri(C_{1-6} alkyl) silyl or benzyl and R^{26} is halo, for example chloro or bromo;
with sodium cyanide followed by aqueous workup to remove the silyl protecting group.

25

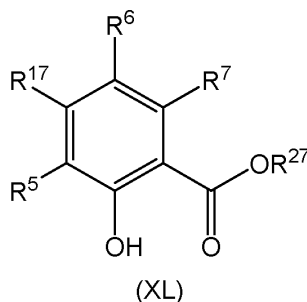
Compounds of general formula (XXXVI) can also be made directly from a compound of general formula (XXXVIII) in which R²⁵ is benzyl by reaction with sodium cyanide.

A compound of general formula (XXXVIII) can be prepared from a compound of general
5 formula (XXXIX):



wherein R⁵, R⁶ and R⁷ are as defined for general formula (I); R¹⁷ is as defined for general
10 formula (VII); and R²⁵ is as defined for general formula (XXXVIII);
by reaction with an appropriate halogenating agent. For example, when R²⁶ is chloro,
thionyl chloride may be used.

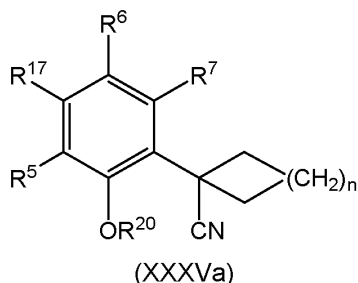
A compound of general formula (XXXIX) may be prepared from a compound of general
formula (XL):



15 wherein R⁵, R⁶ and R⁷ are as defined for general formula (I); R¹⁷ is as defined for general
formula (VII) and R²⁷ is C₁₋₆ alkyl or benzyl;
by protecting the OH group with a group R²⁵ as defined above for general formula
20 (XXXVIII) followed by reaction with a reducing agent, typically a hydride such as sodium
or lithium borohydride.
Compounds of general formula (XL) are readily available or may be synthesised by known
methods.

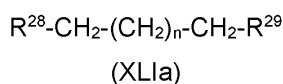
25 A compound of general formula (XXV) in which R⁸ and R⁹ together with the atom to which

they are attached form a carbocyclic ring and R¹⁰ is CN can be prepared from a compound of general formula (XXXVa):



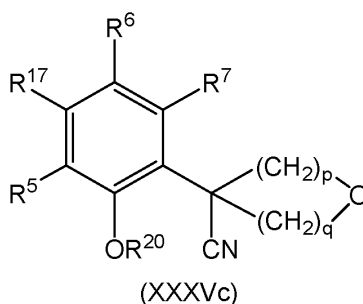
- 5 wherein R⁵, R⁶ and R⁷ are as defined for general formula (I); R¹⁷ is as defined for general formula (VII); R²⁰ is as defined for general formula (XXI); and n is 0, 1, 2 or 3;
by reaction with the alkali metal salt of a malonic acid monoester (such as methyl potassium malonate) in the presence of a Pd catalyst (such as [Pd(allyl)Cl]₂), a phosphine ligand (such as BINAP) and an organic base (such as DMAP), followed by hydrolysis with
10 aqueous base as described above for the conversion of the compound of general formula (XXXV) to the compound of general formula (XXV).

A compound of general formula (XXXVa) can be prepared from a compound of general formula (XXXVI) as defined above by reaction with a compound of general formula (XLla):



wherein n is as defined above for general formula (XXXVa) and each of R²⁸ and R²⁹ is independently halo such as chloro, bromo or iodo.

A compound of general formula (XXV) in which R⁸ and R⁹ together with the atom to which they are attached form 3- to 6-membered oxygen-containing heterocyclic ring and R¹⁰ is CN can be prepared from a compound of general formula (XXXVc):

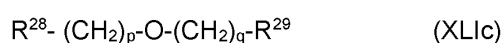


wherein R^5 , R^6 and R^7 are as defined for general formula (I); R^{17} is as defined for general formula (VII); R^{20} is as defined for general formula (XXI); and each p and q is 0, 1, 2, 3 or 4 provided that the sum of p and q is from 1 to 4.

- 5 The method is analogous to that described above for the reaction of the compounds of general formulae (XXV) and (XXXVa).

A compound of general formula (XXXVa) can be prepared from a compound of general formula (XXXVI) as defined above by reaction with a compound of general formula (XLlc):

10

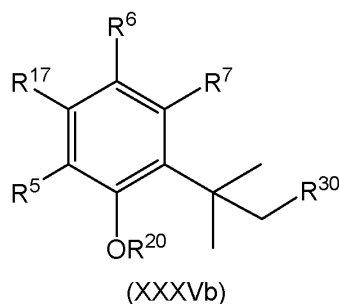


wherein p and q are as defined above for general formula (XXXVc) and each of R^{28} and R^{29} is independently as defined above for general formula (XLla)

- 15 Compounds of general formula (XLla) and (XLlc) are known and are either readily available or may be prepared by known methods.

A compound of general formula (XXV) in which R^8 and R^9 are methyl and R^{10} is methyl substituted with a heterocyclic group, especially a nitrogen-containing heterocyclic group bound to the methyl carbon via a ring nitrogen atom, may be prepared from a compound of general formula (XXXVb):

20



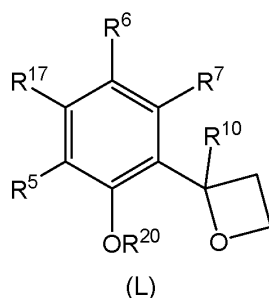
- 25 wherein R^5 , R^6 and R^7 are as defined for general formula (I); R^{17} is as defined for general formula (VII); R^{20} is as defined for general formula (XXI); and R^{30} is a heterocyclic group, especially a nitrogen-containing heterocyclic group bound to the methyl carbon via a ring nitrogen atom;

by reaction with the alkali metal salt of a malonic acid monoester (such as methyl potassium malonate) in the presence of a Pd catalyst (such as $[Pd(allyl)Cl]_2$), a phosphine ligand (such as BINAP) and an organic base (such as DMAP), followed by hydrolysis with aqueous base as described above.

30

A compound of general formula (XXXVb) may be prepared from a compound of general formula (XXXV) as defined above in two steps. Firstly, the compound of general formula (XXXV) is reduced, for example using a hydride reducing agent such as diisobutyl aluminium hydride (DIBAL) to convert the cyano group to an aldehyde. Then the aldehyde moiety is reacted with a compound of formula $R^{30}\text{-H}$, where R^{30} is as defined above for general formula (XXXVb) under acidic conditions (e.g. acetic acid) and in the presence of a reducing agent such as sodium triacetoxyborohydride (STAB).

- 10 A compound of general formula (XXV) in which R^8 and R^9 together with the carbon atom to which they are attached form an oxetane ring and R^{10} is methyl optionally substituted with halo may be prepared from a compound of general formula (L):

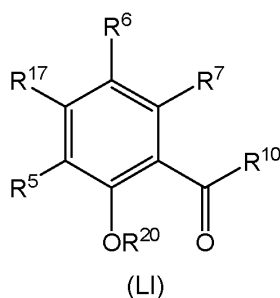


- 15 wherein R^5 , R^6 and R^7 are as defined for general formula (I), R^{10} is methyl optionally substituted with halo; R^{17} is as defined for general formula (VII); R^{20} is as defined for general formula (XXI);

by reaction with a halo-(2-alkoxy-2-oxo-ethyl)zinc (such as bromo-(2-tert-butoxy-2-oxo-ethyl)zinc) in the presence of a palladium catalyst (such as $[\text{Pd}(\text{allyl})\text{Cl}]_2$), a phosphine ligand (such as QPhos) and an organic base such as DMAP, followed by hydrolysis of the resulting ester using an aqueous base.

20

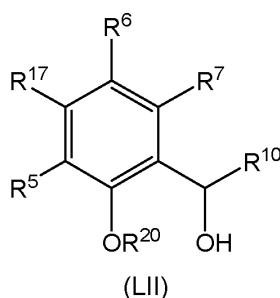
The compound of general formula (L) may be prepared from a compound of general formula (LI):



wherein R^5 , R^6 and R^7 are as defined for general formula (I), R^{10} is methyl optionally substituted with halo; R^{17} is as defined for general formula (VII); and R^{20} is as defined for general formula (XXI);

by reaction with a sulfur ylide such as trimethylsulfoxonium iodide in a Corey Chaykovsky
5 type reaction.

A compound of general formula (LI) may be obtained by oxidation of a compound of general formula (LII):

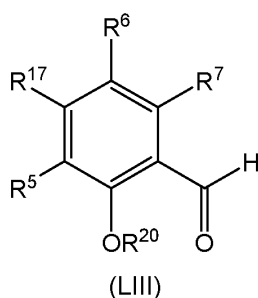


10

wherein R^5 , R^6 and R^7 are as defined for general formula (I), R^{10} is methyl optionally substituted with halo; R^{17} is as defined for general formula (VII); and R^{20} is as defined for general formula (XXI).

The oxidation may be carried out using Dess-Martin periodinane under acidic conditions,
15 for example in the presence of trifluoroacetic acid.

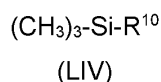
A compound of general formula (LII) in which R^{10} is CF_3 or CHF_2 may be prepared from a compound of general formula (LIII):



20

wherein R^5 , R^6 and R^7 are as defined for general formula (I); R^{17} is as defined for general formula (VII); and R^{20} is as defined for general formula (XXI);

by reaction with a compound of general formula (LIV):



25

wherein R^{10} is methyl optionally substituted with halo;

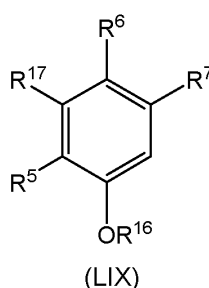
or an alternative trialkyl silane.

The reaction may be conducted at about 15 to 25°C, typically at room temperature in an organic solvent such as dichloromethane.

5

Compounds of general formula (LIV) are readily available or may be synthesised by known methods.

A compound of general formula (LIII) may be prepared from a compound of general formula (LIX):



10

wherein R⁵, R⁶ and R⁷ are as defined for general formula (I); R¹⁷ is as defined for general formula (VII) and R¹⁶ is as defined for general formula (IV);

by reaction with dichloro(methoxy)methane in the presence of a Lewis acid such as titanium tetrachloride, followed by removal of the group R¹⁶, for example using boron tribromide and reprotection with a group R²⁰, for example by reaction with a compound R²⁰-Br, wherein R²⁰ is as defined for general formula (XXI), suitably in the presence of a weak base such as potassium carbonate.

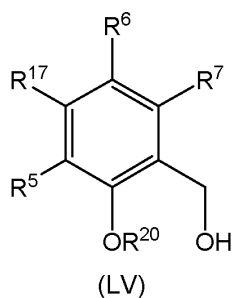
Compounds of general formula (LIX) are known and are readily available or may be synthesised by known methods.

Compounds of general formula (LIII) may be modified by treating the aldehyde in an olefination reaction, for example a Wittig type reaction and the product may be further modified to produce compounds which are similar in structure to the compounds of general formulae (XXXV), (XXXVa), (XXXVb), (XXXVc), (XXXVI), (XXXVII) and (L) but which have alternative substituents at the position between the R⁷ and OH substituents (see preparation of Intermediate R below). The syntheses of further similar compounds with alternative substituents are also given below (see preparation of Intermediates B, BA, BB, BC, BD, BE, C, CA, CB, D, E, M, N and W).

30

To obtain a compound of general formula (LII) in which R^{10} is C_{1-4} alkyl, an appropriate Grignard reagent may be reacted with the compound of general formula (LIII).

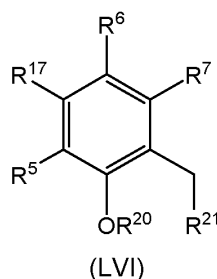
A compound of general formula (LIII) may be obtained by oxidation of a compound of general formula (LV):



wherein R^5 , R^6 and R^7 are as defined for general formula (I); R^{17} is as defined for general formula (VII); and R^{20} is as defined for general formula (XXI).

- 10 A suitable oxidising agent for this reaction is manganese dioxide and the reaction may be conducted in an organic solvent such as toluene at the reflux temperature of the solvent.

A compound of general formula (LV) may be prepared from a compound of general formula (LVI):



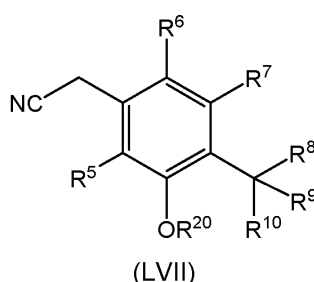
wherein R^5 , R^6 and R^7 are as defined for general formula (I); R^{17} is as defined for general formula (VII); R^{20} is as defined for general formula (XXI) and R^{21} is halo, for example chloro or bromo;

- 20 by reaction with a hydroxide, suitably an alkali metal hydroxide such as sodium or potassium hydroxide in an organic solvent such as dioxane. Suitably, the reaction is carried out at the reflux temperature of the solvent.

- 25 Compounds of general formula (LV) can also be prepared directly from a compound of general formula (XL) via protection of the phenol followed by reduction of the ester using a reducing agent such as $NaBH_4$.

A compound of general formula (LVI) may be prepared from a compound of general formula (XL) as defined above by protecting the OH group with a group R^{20} as defined above for general formula (XXI) followed by reduction of the ester then conversion of the
 5 resulting alcohol to the alkyl halide (e.g. using thionyl chloride).

A further method for preparing a compound of general formula (XXV) is by reaction of a compound of general formula (LVII):



10

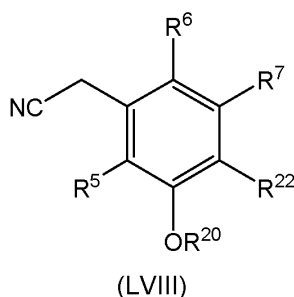
wherein R^5 , R^6 , R^7 , R^8 , R^9 and R^{10} are as defined for general formula (I); and R^{20} is as defined for general formula (XXI);

with a hydroxide, for example an aqueous base, for example an alkali metal hydroxide such as sodium or potassium hydroxide in a solvent such as THF. The reaction may be
 15 carried out in an organic solvent such as tetrahydrofuran at elevated temperature, for example at the reflux temperature of the solvent.

This method is particularly suitable for compounds in which R^8 , R^9 and R^{10} together with the carbon atom to which they are attached form a fused or bridged ring system.

20

When R^8 , R^9 and R^{10} together with the carbon atom to which they are attached form a fused or bridged ring system, the compound of general formula (LVII) may be prepared from a compound of formula (LVIII):



25

wherein R^5 , R^6 and R^7 are as defined for general formula (I); R^{20} is as defined for general

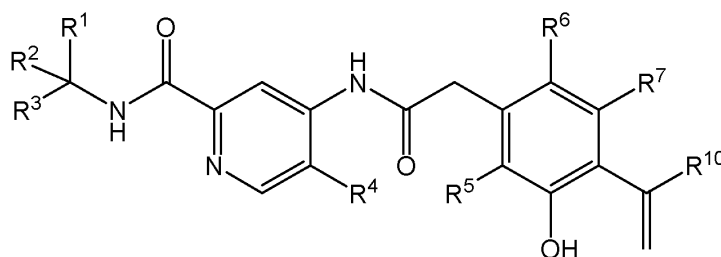
formula (XXI); and R^{22} is halo, for example bromo or chloro.

The compound of general formula (LVIII) may be reacted with a halide of a suitable bridged or fused ring and the substituents on the ring may be manipulated as required.

5

Compounds of general formula (LVIII) are readily available or may be synthesised by known methods.

10 A compound of general formula (I) in which R^9 is OH and R^{10} is methyl optionally substituted with halo may be prepared from a compound of general formula (LX), which is a compound of general formula (I) in which R^8 and R^9 combine to form an ethenyl group and R^{10} is methyl optionally substituted with halo:



15

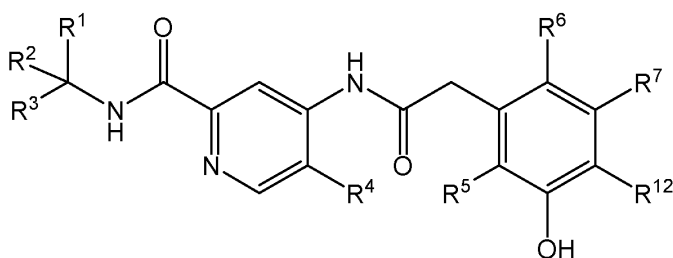
(LX)

wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 and R^7 are as defined for general formula (I); and R^{10} is methyl optionally substituted with halo;

by reaction with an aqueous acid such as methanesulfonic acid in a mixture of 1,4-dioxane and water.

20

A compound of general formula (LX) can be prepared from a compound of general formula (LXI):



25

(LXI)

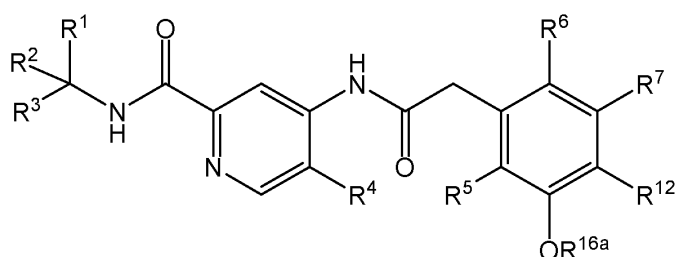
wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 and R^7 are as defined for general formula (I); and R^{12} is halo, for example chloro or bromo;

by reaction with 2-isopropenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in the presence of tripotassium phosphate, tricyclohexylphosphine and palladium acetate ($\text{Pd}(\text{OAc})_2$).

5

An analogous method may be used to prepare a compound of general formula (I) in which R^8 and R^9 combine to form a 3- to 6-membered cycloalkyl or oxygen-containing heterocyclic ring and R^{10} is OH. In this method, the compound of general formula (LXI) is reacted with an appropriate cyclic 1,3,2-dioxaborolane to give a compound similar to that of general formula (LX) but in which the moiety $-\text{C}(=\text{CH}_2)-R^{10}$ is replaced with a cyclic group containing a C=C double bond at the position at which the cyclic group is connected to the remainder of the molecule. This can be hydrated under reducing conditions, for example as described in Example 13 below, to give the required product.

15 A compound of general formula (LXI) may be prepared by deprotecting a compound of general formula (LXII):



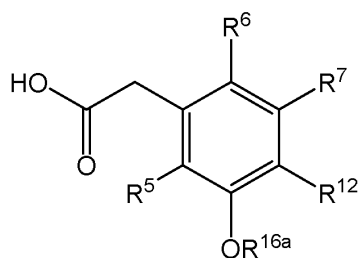
(LXII)

wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 and R^7 are as defined for general formula (I); R^{16a} is C_{1-6} alkyl or benzyl; and R^{12} is as defined for general formula (LXI).

20

Deprotection is suitably achieved by treatment with boron tribromide as described above for the deprotection of a compound of general formula (IV).

25 A compound of general formula (LXII) may be prepared by reacting a compound of general formula (XXII) as defined above with a compound of general formula (LXIII):



(LXIII)

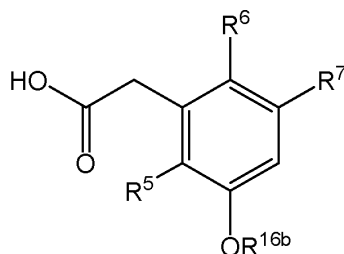
wherein R^5 , R^6 and R^7 are as defined for general formula (I); R^{16a} is as defined for general formula (LXII); and R^{12} is as defined for general formula (LXI).

5

Suitably, the reaction is carried out under similar conditions to those described above for the reaction of the compound of general formula (V) with the compound of general formula (VI).

- 10 Compounds of general formula (LXIII) are known and are readily available or may be prepared by known methods.

For example, a compound of general formula (LXIII) may be prepared by brominating or chlorinating a compound of general formula (LXIV):



(LXIV)

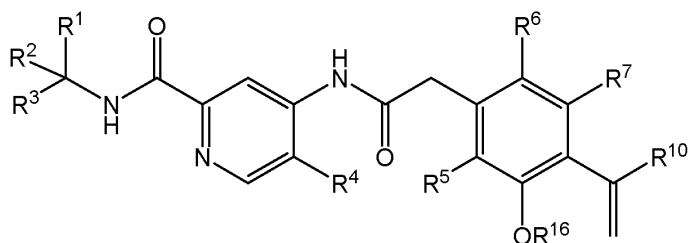
15

wherein R^5 , R^6 and R^7 are as defined for general formula (I); R^{16b} is H or C_{1-6} alkyl.

- 20 Bromination or chlorination may be carried out using any suitable agent, for example N-bromo succinimide, N-chlorosuccinimide or bromine. Where R^{16b} is H, reaction with a suitable protecting reagent may be carried out to obtain the compound of general formula (LXIII). For example, reaction with benzyl bromide gives a compound of general formula (LXIII) in which R^{16a} is benzyl.

- 25 A method for the preparation of a compound of general formula (XXI) in which R^8 and R^9

combine with the carbon atom to which they are attached to form a cyclopropyl ring and R^{10} is methyl optionally substituted with halo is by reaction of a compound of general formula (LXV):



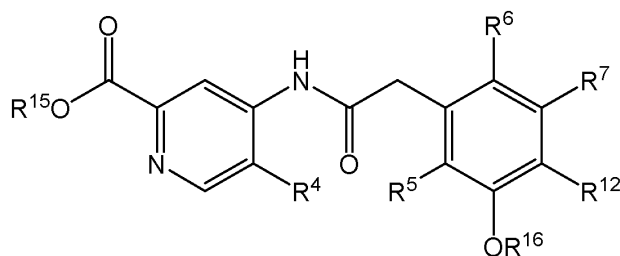
(LXV)

wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 and R^7 are as defined for general formula (I); R^{16} is as defined for general formula (IV) and R^{10} is methyl optionally substituted with halo; with 8-(iodomethyl)-8,8'-spirobi[7,9-dioxo-8-silanolidabicyclo[4.3.0]nona-1,3,5-triene]; triethylammonium in the presence of (4,4'-di-*t*-butyl-2,2'-bipyridine)bis[3,5-difluoro-2-[5-trifluoromethyl-2-pyridinyl-*k*(N)]phenyl-*k*(C)]iridium(III) hexafluorophosphate; under irradiation with blue light.

Suitably, the process is as described in Example 8 below and takes place under an inert atmosphere such as nitrogen in an anhydrous organic solvent such as dimethylsulfoxide.

A compound of general formula (LXV) in which R^{10} is methyl may be prepared from a compound of general formula (LXII) as defined above by reaction with 2-isopropenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and tripotassium phosphate followed by tricyclohexylphosphine and palladium acetate.

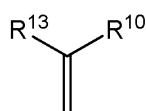
In some cases, the introduction of the cyclopropyl group may take place at an earlier stage of the process. For example, a compound of general formula (LXX):



(LXX)

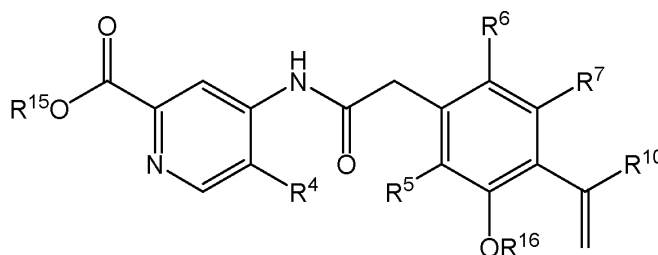
wherein R^4 , R^5 , R^6 and R^7 are as defined for general formula (I); R^{15} and R^{16} are as defined for general formula (IV) and R^{12} is halo, for example chloro or bromo;

may be treated with bis(pinacolato)diboron in the presence of a palladium catalyst such as Pd(dppf)Cl₂. The boronic ester product of this reaction may then be treated with a compound of general formula (LXXI):



(LXXI)

wherein R¹⁰ is methyl optionally substituted with halo and R¹³ is halo, for example chloro or bromo to yield a product of general formula (LXXII):



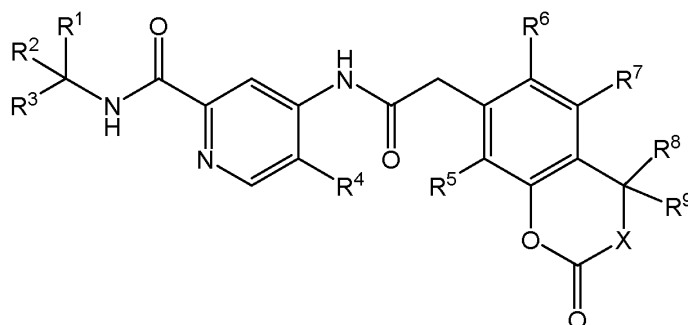
(LXXII)

wherein R⁴, R⁵, R⁶ and R⁷ are as defined for general formula (I); R¹⁵ and R¹⁶ are as defined for general formula (IV) and R¹⁰ is methyl optionally substituted with halo;

The compound of general formula (LXXII) can be converted to a compound of general formula (IV) in which R⁸ and R⁹ together with the carbon atom to which they are attached form a cyclopropyl group and R¹⁰ is methyl optionally substituted with halo by reaction with 8-(iodomethyl)-8,8'-spirobi[7,9-dioxo-8-silanuidabicyclo[4.3.0]nona-1,3,5-triene]; triethylammonium and (4,4'-di-*t*-butyl-2,2'-bipyridine)bis[3,5-difluoro-2-[5-trifluoromethyl-2-pyridinyl-*k*N]phenyl-*k*C]iridium(III) hexafluorophosphate; under irradiation with blue light as described for the reaction of the compound of general formula (LXV) above.

A compound of general formulae (LXI) can be prepared by methods analogous to those described above for compounds of general formula (I) except that the intermediates analogous to the compounds of general formulae (V) and (XXV) will have a group R¹² in place of the -C(R⁸)(R⁹)(R¹⁰) substituent.

Compounds of general formula (I) in which R⁸ and R⁹ are methyl or ethyl and R¹⁰ is CH₂OH or CH₂CH₂OH may be prepared from compounds of general formula (LXXV):



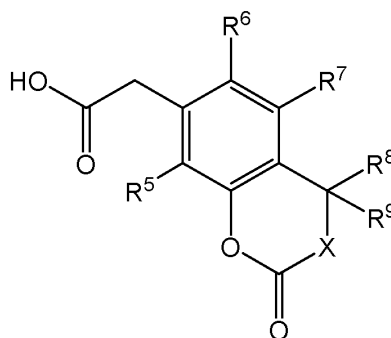
(LXXV)

wherein R^5 , R^6 and R^7 are as defined for general formula (I); each of R^8 and R^9 is independently methyl or ethyl and X is a bond or $-CH_2-$;

- 5 by reduction, for example using a hydride reducing agent such as lithium borohydride.

Suitably, the reaction is carried out in an organic solvent such as tetrahydrofuran and the reducing agent is added with cooling, for example at -78°C .

- 10 A compound of general formula (LXXV) may be prepared by reacting a compound of general formula (XXII) as defined above with a compound of general formula (LXXX):



(LXXX)

wherein R^5 , R^6 and R^7 are as defined for general formula (I); each of R^8 and R^9 is independently methyl or ethyl and X is as defined for general formula (LXXV).

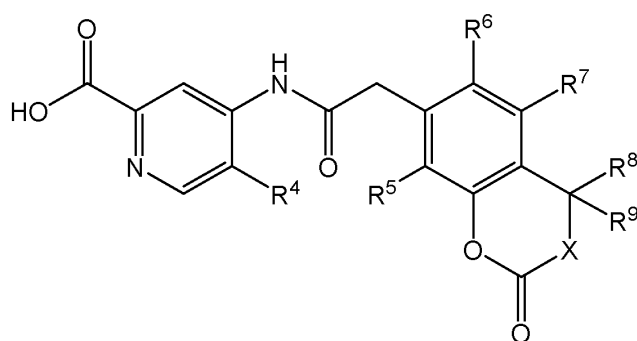
- 15

Suitably, the reaction is carried out in the presence of a coupling reagent as described above. T3P® is particularly suitable.

- 20 In some cases, the compound of general formula (LXXV) is isolated and purified before reduction to give the compound of general formula (I). In other cases, however, the compounds of general formulae (LXXX) and (XXII) react to give a compound of general

formula (LXXX), which is then reduced to give a compound of general formula (I) without further purification. This is more usually the case for 5-membered lactone intermediates (LXXX), i.e. when X is a bond.

- 5 In a variation of this method, a compound of general formula (LXXV) may be prepared by reacting a compound of general formula (III) as defined above with a compound of general formula (LXXVI):



(LXXVI)

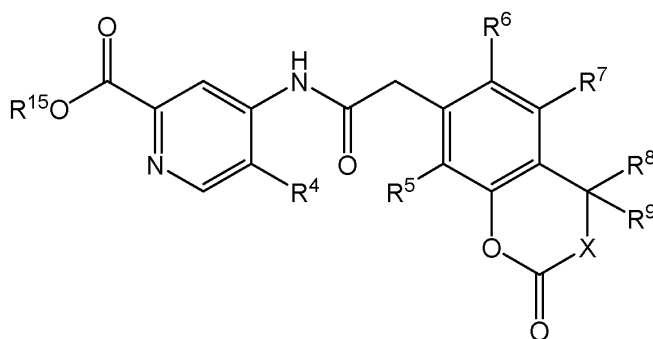
- 10 wherein R⁴, R⁵, R⁶ and R⁷ are as defined for general formula (I); each of R⁸ and R⁹ is independently methyl or ethyl and X is as defined for general formula (LXXV).

Suitably, the reaction is carried out in the presence of a coupling reagent as described above, with HATU being an example of a suitable coupling reagent.

15

The compound of general formula (LXXV) may be reduced to a compound of general formula (I) without further purification.

- 20 A compound of general formula (LXXVI) may be prepared by hydrolysis of a compound of general formula (LXXVII):



(LXXVII)

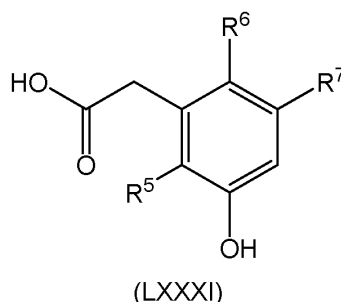
wherein R^4 , R^5 , R^6 and R^7 are as defined for general formula (I); R^{15} is as defined for general formula (IV); each of R^8 and R^9 is independently methyl or ethyl and X is as defined for general formula (LXXV).

- 5 Suitably, the hydrolysis is base hydrolysis, for example carried out using lithium hydroxide in a solvent such as tetrahydrofuran.

A compound of general formula (LXXVII) may be prepared by reacting a compound of general formula (VI) as defined above with a compound of general formula (LXXX) as
10 defined above.

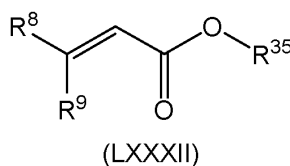
Suitably, the reaction is carried out in the presence of a coupling reagent as described above. T3P® is particularly suitable.

- 15 A compound of general formula (LXXX) in which X is $-CH_2-$ may be prepared from a compound of general formula (LXXXI):



wherein R^5 , R^6 and R^7 are as defined for general formula (I);

- 20 by reaction with a compound of general formula (LXXXII):



wherein R^8 and R^9 are as defined for general formula (I) and R^{35} is C_{1-6} alkyl.

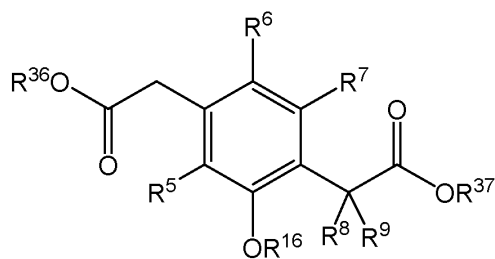
25

Suitably, the reaction is carried out in the presence of a strong acid such as methane sulfonic acid.

Compounds of general formulae (LXXXI) and (LXXXII) are known and are readily available

or may be prepared by methods known to those of skill in the art.

A compound of general formula (LXXX) in which X is a bond may be prepared from a compound of general formula (LXXXIII):

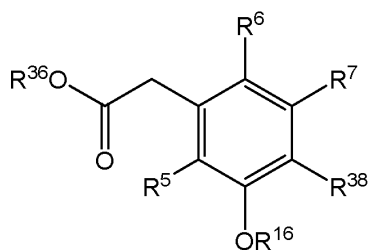


(LXXXIII)

wherein R^5 , R^6 and R^7 are as defined for general formula (I); R^{16} is as defined for general formula (IV); R^{36} is C_{1-6} alkyl or benzyl; R^{37} is C_{1-6} alkyl; and each of R^8 and R^9 is independently methyl or ethyl;

- 10 by reaction with boron tribromide. Typically, the reaction is carried out a temperature of about -5 to 5 °C in a solvent such as dichloromethane.

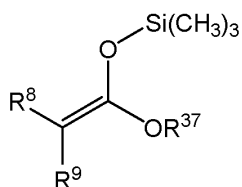
A compound of general formula (LXXXIII) can be prepared by reacting a compound of general formula (LXXXIV):



(LXXXIV)

wherein R^5 , R^6 and R^7 are as defined for general formula (I); R^{16} is as defined for general formula (IV); R^{36} is as defined for general formula (LXXXIII); and R^{38} is a halogen, especially bromine or chlorine and more especially bromine;

- 20 with a compound of general formula (LXXXV):



(LXXXV)

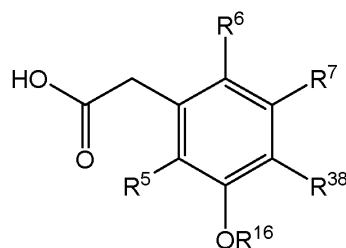
wherein R^{37} is as defined for general formula (LXXXIII) and each of R^8 and R^9 is independently methyl or ethyl.

The reaction may be carried out in the presence of zinc fluoride and a palladium/platinum catalyst such as $Pd(P^iBu_3)_2$. Suitably, the reaction is conducted under an inert atmosphere, for example under nitrogen.

Compounds of general formula (LXXXV) are known and are readily available or may be prepared by methods familiar to those of skill in the art.

10

A compound of general formula (LXXXIV) may be prepared by esterification a compound of general formula (LXXXVI):



(LXXXVI)

wherein R^5 , R^6 and R^7 are as defined for general formula (I); R^{16} is as defined for general formula (IV); and R^{38} is a halogen, especially bromine or chlorine and more especially bromine;

for example by reaction with a compound R^{36} -Hal, where Hal is bromine or chlorine, especially bromine.

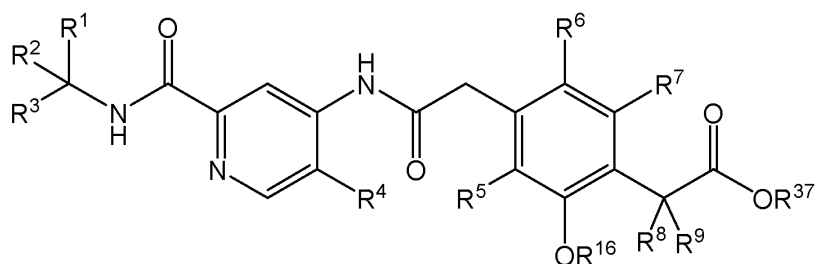
20

The reaction may be conducted under mildly basic conditions, for example in the presence of potassium carbonate, and in a solvent such as *N,N*-dimethylformamide.

A compound of general formula (LXXXVI) may be prepared by halogenation of a compound of general formula (IX) as defined above. Suitable halogenating agents include bromine in a solvent such as acetonitrile. Alternatively, *N*-chlorosuccinimide or *N*-bromosuccinimide may be used.

An alternative method for the preparation of a compound of general formula (LXXV) in which X is a bond is by the reaction of a compound of general formula (XC):

30

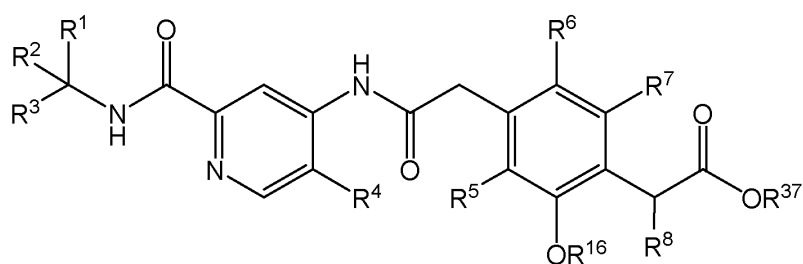


(XC)

wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 and R^7 are as defined for general formula (I); R^{16} is as defined for general formula (IV); R^{37} is as defined for general formula (LXXXIII); and each of R^8 and R^9 is independently methyl or ethyl; with boron tribromide.

Typically, the reaction is conducted in a solvent such as dichloromethane.

10 An alternative procedure for the synthesis of a compound of general formula (XXI) in which R^8 is methyl or ethyl, R^9 is CH_2OH and R^{10} is H is by the reduction of a compound of general formula (XCV):

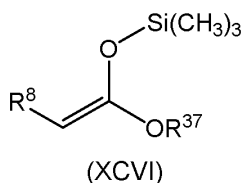


(XCV)

15 wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 and R^7 are as defined for general formula (I); R^{37} is as defined for general formula (LXXXIII); and R^8 is methyl or ethyl; typically using a hydride reducing agent such as lithium aluminium hydride. Suitably, the reaction is carried out at reduced temperature, typically -78°C in a solvent such as tetrahydrofuran.

20

A compound of general formula (XCV) may be prepared by reacting a compound of general formula (LXII) as defined above with a compound of general formula (XCVI):



wherein R^8 is methyl or ethyl and R^{37} is as defined for general formula (LXXXIII).

The reaction may be carried out in the presence of zinc fluoride and a palladium/platinum catalyst such as $Pd(P^tBu_3)_2$. Suitably, the reaction is conducted under an inert atmosphere, for example under nitrogen.

Compounds of general formula (I) may also be converted to other compounds of general formula (I). For example, a compound of general formula (I) in which R^6 is halo, especially bromo or chloro, can be converted to a compound of general formula (I) in which R^6 is alkyl in a Suzuki type reaction with an appropriate alkyl- or alkenyl-boronic acid ester, for example an alkyl- or alkenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in the presence of tricyclohexylphosphine and palladium acetate and a base (such as K_2CO_3).

A compound of general formula (I) in which R^5 is H may be converted to a compound of general formula (I) in which R^5 is halo, for example chloro or bromo, by reaction with a suitable halogenating agent such as *N*-chlorosuccinimide or *N*-bromosuccinimide, suitably at a temperature of about 15 to 25 °C, for example at room temperature, and in a solvent such as *N,N*-dimethylformamide.

The compounds of general formula (I) are positive modulators of TMEM16A and therefore, in a further aspect of the invention, there is provided a compound of general formula (I) as defined above for use in medicine, particularly in the treatment or prophylaxis of diseases and conditions affected by modulation of TMEM16A.

There is also provided the use of a compound of general formula (I) as defined above in the manufacture of a medicament for the treatment or prophylaxis of diseases and conditions affected by modulation of TMEM16A.

There is also provided a method for the treatment or prophylaxis of diseases and conditions affected by modulation of TMEM16A, the method comprising administering to a patient in need of such treatment an effective amount of a compound of general formula (I) as defined above.

The diseases and conditions affected by modulation of TMEM16A include respiratory diseases and conditions, dry mouth (xerostomia), intestinal hypermobility, cholestasis and ocular conditions.

5 There is also provided:

A compound of general formula (I) as defined above for use in the treatment or prophylaxis of respiratory diseases and conditions.

A compound of general formula (I) as defined above for use in the treatment or prophylaxis of dry mouth (xerostomia).

10 A compound of general formula (I) as defined above for use in the treatment or prophylaxis of intestinal hypermobility.

A compound of general formula (I) as defined above for use in the treatment or prophylaxis of cholestasis.

15 A compound of general formula (I) as defined above for use in the treatment or prophylaxis of ocular conditions.

The invention also provides:

The use of a compound of general formula (I) as defined above in the manufacture of a medicament for the treatment or prophylaxis of respiratory diseases and conditions.

20 The use of a compound of general formula (I) as defined above in the manufacture of a medicament for the treatment or prophylaxis of dry mouth (xerostomia).

The use of a compound of general formula (I) as defined above in the manufacture of a medicament for the treatment or prophylaxis of intestinal hypermobility.

25 The use of a compound of general formula (I) as defined above in the manufacture of a medicament for the treatment or prophylaxis of cholestasis.

The use of a compound of general formula (I) as defined above in the manufacture of a medicament for the treatment or prophylaxis of ocular conditions.

There is further provided:

30 A method for the treatment or prophylaxis of respiratory diseases and conditions, the method comprising administering to a patient in need of such treatment an effective amount of a compound of general formula (I) as defined above.

A method for the treatment or prophylaxis of dry mouth (xerostomia), the method comprising administering to a patient in need of such treatment an effective amount of a compound of general formula (I) as defined above.

35 A method for the treatment or prophylaxis of intestinal hypermobility, the method

comprising administering to a patient in need of such treatment an effective amount of a compound of general formula (I) as defined above.

A method for the treatment or prophylaxis of cholestasis, the method comprising administering to a patient in need of such treatment an effective amount of a compound of
5 general formula (I) as defined above.

A method for the treatment or prophylaxis of ocular conditions, the method comprising administering to a patient in need of such treatment an effective amount of a compound of general formula (I) as defined above.

10 Respiratory diseases and conditions which may be treated or prevented by the compounds of general formula (I) include cystic fibrosis, chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, bronchiectasis, including non-cystic fibrosis bronchiectasis, asthma and primary ciliary dyskinesia.

15 Dry mouth (xerostomia) which may be treated or prevented by the compounds of general formula (I) may result from Sjorgens syndrome, radiotherapy treatment and xerogenic drugs.

Intestinal hypermobility which may be treated or prevented by the compounds of general formula (I) may be associated with gastric dyspepsia, gastroparesis, chronic constipation
20 and irritable bowel syndrome.

Ocular conditions which may be treated or prevented by the compounds of by the compounds of general formula (I) include dry eye disease.

25 The compounds of the present invention will generally be administered as part of a pharmaceutical composition and therefore the invention further provides a pharmaceutical composition comprising a compound of general formula (I) together with a pharmaceutically acceptable excipient.

30 The pharmaceutical composition may be formulated for oral, rectal, nasal, topical (including topical administration to the lung, dermal, transdermal, eye drops, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration and may be prepared by any methods well known in the art of pharmacy.

35

The compounds of the invention are especially well adapted for oral administration.

The composition may be prepared by bringing into association the above defined active agent with the excipient. In general, the formulations are prepared by uniformly and intimately bringing into association the active agent with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product. The invention extends to
5 methods for preparing a pharmaceutical composition comprising bringing a compound of general formula (I) in conjunction or association with a pharmaceutically acceptable carrier or vehicle.

Formulations for oral administration in the present invention may be presented as: discrete
10 units such as capsules, sachets or tablets each containing a predetermined amount of the active agent; as a powder or granules; as a solution or a suspension of the active agent in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water in oil liquid emulsion; or as a bolus etc.

15 For compositions for oral administration (e.g. tablets and capsules), the term "acceptable carrier" includes vehicles such as common excipients e.g. binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, polyvinylpyrrolidone (Povidone), methylcellulose, ethylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, sucrose and starch; fillers and carriers, for example corn
20 starch, gelatin, lactose, sucrose, microcrystalline cellulose, kaolin, mannitol, dicalcium phosphate, sodium chloride and alginic acid; and lubricants such as magnesium stearate, sodium stearate and other metallic stearates, glycerol stearate, stearic acid, silicone fluid, talc waxes, oils and colloidal silica. Flavouring agents such as peppermint, oil of wintergreen, cherry flavouring and the like can also be used. It may be desirable to add a
25 colouring agent to make the dosage form readily identifiable. Tablets may also be coated by methods well known in the art.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine
30 the active agent in a free flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface-active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active
35 agent.

Other formulations suitable for oral administration include lozenges comprising the active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active agent in an inert base such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active agent in a suitable liquid carrier.

5

For topical application to the skin, compounds of general formula (I) may be made up into a cream, ointment, jelly, solution or suspension etc. Cream or ointment formulations that may be used for the drug are conventional formulations well known in the art, for example, as described in standard text books of pharmaceuticals such as the British Pharmacopoeia.

10

Topical administration to the lung may be achieved by use of an aerosol formulation. Aerosol formulations typically comprise the active ingredient suspended or dissolved in a suitable aerosol propellant, such as a chlorofluorocarbon (CFC) or a hydrofluorocarbon (HFC). Suitable CFC propellants include trichloromonofluoromethane (propellant 11), dichlorotetrafluoromethane (propellant 114), and dichlorodifluoromethane (propellant 12). Suitable HFC propellants include tetrafluoroethane (HFC-134a) and heptafluoropropane (HFC-227). The propellant typically comprises 40%-99.5% e.g. 40%-90% by weight of the total inhalation composition. The formulation may comprise excipients including co-solvents (e.g. ethanol) and surfactants (e.g. lecithin, sorbitan trioleate and the like). Other possible excipients include polyethylene glycol, polyvinylpyrrolidone, glycerine and the like. Aerosol formulations are packaged in canisters and a suitable dose is delivered by means of a metering valve (e.g. as supplied by Bepak, Valois or 3M or alternatively by Aptar, Coster or Vari).

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Topical administration to the lung may also be achieved by use of a non-pressurised formulation such as an aqueous solution or suspension. These may be administered by means of a nebuliser e.g. one that can be hand-held and portable or for home or hospital use (ie non-portable). The formulation may comprise excipients such as water, buffers, tonicity adjusting agents, pH adjusting agents, surfactants and co-solvents. Suspension liquid and aerosol formulations (whether pressurised or unpressurised) will typically contain the compound of the invention in finely divided form, for example with a D_{50} of 0.5-10 μm e.g. around 1-5 μm . Particle size distributions may be represented using D_{10} , D_{50} and D_{90} values. The D_{50} median value of particle size distributions is defined as the particle size in microns that divides the distribution in half. The measurement derived from laser diffraction is more accurately described as a volume distribution, and consequently the D_{50} value obtained using this procedure is more meaningfully referred to as a Dv_{50} value

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35

(median for a volume distribution). As used herein D_v values refer to particle size distributions measured using laser diffraction. Similarly, D_{10} and D_{90} values, used in the context of laser diffraction, are taken to mean D_{v10} and D_{v90} values and refer to the particle size whereby 10% of the distribution lies below the D_{10} value, and 90% of the distribution
5 lies below the D_{90} value, respectively.

Topical administration to the lung may also be achieved by use of a dry-powder formulation. A dry powder formulation will contain the compound of the disclosure in finely divided form, typically with a mass mean diameter (MMAD) of 1-10 μm or a D_{50} of 0.5-10
10 μm e.g. around 1-5 μm . Powders of the compound of the invention in finely divided form may be prepared by a micronization process or similar size reduction process. Micronization may be performed using a jet mill such as those manufactured by Hosokawa Alpine. The resultant particle size distribution may be measured using laser diffraction (e.g. with a Malvern Mastersizer 2000S instrument). The formulation will typically contain a
15 topically acceptable diluent such as lactose, glucose or mannitol (preferably lactose), usually of comparatively large particle size e.g. a mass mean diameter (MMAD) of 50 μm or more, e.g. 100 μm or more or a D_{50} of 40-150 μm . As used herein, the term "lactose" refers to a lactose-containing component, including α -lactose monohydrate, β -lactose monohydrate, α -lactose anhydrous, β -lactose anhydrous and amorphous lactose. Lactose
20 components may be processed by micronization, sieving, milling, compression, agglomeration or spray drying. Commercially available forms of lactose in various forms are also encompassed, for example Lactohale[®] (inhalation grade lactose; DFE Pharma), InhaLac[®]70 (sieved lactose for dry powder inhaler; Meggle), Pharmatose[®] (DFE Pharma) and Respitose[®] (sieved inhalation grade lactose; DFE Pharma) products. In one
25 embodiment, the lactose component is selected from the group consisting of α -lactose monohydrate, α -lactose anhydrous and amorphous lactose. Preferably, the lactose is α -lactose monohydrate.

Dry powder formulations may also contain other excipients. Thus in one embodiment a dry
30 powder formulation according to the present disclosure comprises magnesium or calcium stearate. Such formulations may have superior chemical and/or physical stability especially when such formulations also contain lactose.

A dry powder formulation is typically delivered using a dry powder inhaler (DPI) device.
35 Example dry powder delivery systems include SPINHALER[®], DISKHALER[®], TURBOHALER[®], DISKUS[®], SKYEHALER[®], ACCUHALER[®] and CLICKHALER[®].

Further examples of dry powder delivery systems include ECLIPSE, NEXT, ROTAHALER, HANDIHALER, AEROLISER, CYCLOHALER, BREEZHALER/NEOHALER, MONODOSE, FLOWCAPS, TWINCAPS, X-CAPS, TURBOSPIN, ELPENHALER, MIATHALER, TWISTHALER, NOVOLIZER, PRESSAIR, ELLIPTA, ORIEL dry powder
5 inhaler, MICRODOSE, PULVINAL, EASYHALER, ULTRAHALER, TAIFUN, PULMOJET, OMNIHALER, GYROHALER, TAPER, CONIX, XCELOVAIR and PROHALER.

In one embodiment a compound of general formula (I) is provided as a micronized dry powder formulation, for example comprising lactose of a suitable grade.

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Thus, as an aspect of the invention there is provided a pharmaceutical composition comprising a compound of general formula (I) in particulate form in combination with particulate lactose, said composition optionally comprising magnesium stearate.

15 In one embodiment a compound of general formula (I) is provided as a micronized dry powder formulation, comprising lactose of a suitable grade and magnesium stearate, filled into a device such as DISKUS. Suitably, such a device is a multidose device, for example the formulation is filled into blisters for use in a multi-unit dose device such as DISKUS.

20 In another embodiment a compound of general formula (I) is provided as a micronized dry powder formulation, for example comprising lactose of a suitable grade, filled into hard shell capsules for use in a single dose device such as AEROLISER.

In another embodiment a compound of general formula (I) is provided as a micronized dry
25 powder formulation, comprising lactose of a suitable grade and magnesium stearate, filled into hard shell capsules for use in a single dose device such as AEROLISER.

In another embodiment a compound of general formula (I) is provided as a fine powder for use in an inhalation dosage form wherein the powder is in fine particles with a D_{50} of 0.5-10 μm e.g. around 1-5 μm , that have been produced by a size reduction process other
30 than jet mill micronisation e.g. spray drying, spray freezing, microfluidisation, high pressure homogenisation, super critical fluid crystallisation, ultrasonic crystallisation or combinations of these methods thereof, or other suitable particle formation methods known in the art that are used to produce fine particles with an aerodynamic particle size of 0.5-10 μm . The resultant particle size distribution may be measured using laser
35 diffraction (e.g. with a Malvern Mastersizer 2000S instrument). The particles may either comprise the compound alone or in combination with suitable other excipients that may

aid the processing. The resultant fine particles may form the final formulation for delivery to humans or may optionally be further formulated with other suitable excipients to facilitate delivery in an acceptable dosage form.

5 The compound of the invention may also be administered rectally, for example in the form of suppositories or enemas, which include aqueous or oily solutions as well as suspensions and emulsions and foams. Such compositions are prepared following standard procedures, well known by those skilled in the art. For example, suppositories can be prepared by mixing the active ingredient with a conventional suppository base such
10 as cocoa butter or other glycerides. In this case, the drug is mixed with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

15 Generally, for compositions intended to be administered topically to the eye in the form of eye drops or eye ointments, the total amount of the compound of general formula (I) will be about 0.0001 to less than 4.0% (w/w).

Preferably, for topical ocular administration, the compositions administered according to
20 general formula (I) will be formulated as solutions, suspensions, emulsions and other dosage forms. Aqueous solutions are generally preferred, based on ease of formulation, as well as a patient's ability to administer such compositions easily by means of instilling one to two drops of the solutions in the affected eyes. However, the compositions may also be suspensions, viscous or semi-viscous gels, or other types of solid or semi-solid
25 compositions. Suspensions may be preferred for compounds that are sparingly soluble in water.

An alternative for administration to the eye is intravitreal injection of a solution or suspension of the compound of general formula (I). In addition, the compound of general
30 formula (I) may also be introduced by means of ocular implants or inserts.

The compositions administered according to general formula (I) may also include various other ingredients, including, but not limited to, tonicity agents, buffers, surfactants, stabilizing polymer, preservatives, co-solvents and viscosity building agents. Suitable
35 pharmaceutical compositions of general formula (I) include a compound of the invention formulated with a tonicity agent and a buffer. The pharmaceutical compositions of general

formula (I) may further optionally include a surfactant and/or a palliative agent and/or a stabilizing polymer.

Various tonicity agents may be employed to adjust the tonicity of the composition, preferably to that of natural tears for ophthalmic compositions. For example, sodium chloride, potassium chloride, magnesium chloride, calcium chloride, simple sugars such as dextrose, fructose, galactose, and/or simply polyols such as the sugar alcohols mannitol, sorbitol, xylitol, lactitol, isomaltitol, maltitol, and hydrogenated starch hydrolysates may be added to the composition to approximate physiological tonicity. Such an amount of tonicity agent will vary, depending on the particular agent to be added. In general, however, the compositions will have a tonicity agent in an amount sufficient to cause the final composition to have an ophthalmically acceptable osmolality (generally about 150-450 mOsm, preferably 250-350 mOsm and most preferably at approximately 290 mOsm). In general, the tonicity agents of the invention will be present in the range of 2 to 4% w/w. Preferred tonicity agents of the invention include the simple sugars or the sugar alcohols, such as D-mannitol.

An appropriate buffer system (e.g. sodium phosphate, sodium acetate, sodium citrate, sodium borate or boric acid) may be added to the compositions to prevent pH drift under storage conditions. The particular concentration will vary, depending on the agent employed. Preferably however, the buffer will be chosen to maintain a target pH within the range of pH 5 to 8, and more preferably to a target pH of pH 5 to 7.

Surfactants may optionally be employed to deliver higher concentrations of compound of general formula (I). The surfactants function to solubilise the compound and stabilise colloid dispersion, such as micellar solution, microemulsion, emulsion and suspension. Examples of surfactants which may optionally be used include polysorbate, poloxamer, polyosyl 40 stearate, polyoxyl castor oil, tyloxapol, Triton, and sorbitan monolaurate. Preferred surfactants to be employed in the invention have a hydrophile/lipophile/balance "HLB" in the range of 12.4 to 13.2 and are acceptable for ophthalmic use, such as TritonX114 and tyloxapol.

Additional agents that may be added to the ophthalmic compositions of compounds of general formula (I) are demulcents which function as a stabilising polymer. The stabilizing polymer should be an ionic/charged example with precedence for topical ocular use, more specifically, a polymer that carries negative charge on its surface that can exhibit a zeta-

potential of (–)10–50 mV for physical stability and capable of making a dispersion in water (i.e. water soluble). A preferred stabilising polymer of the invention would be polyelectrolyte, or polyelectrolytes if more than one, from the family of cross-linked polyacrylates, such as carbomers and Pemulen(R), specifically Carbomer 974p
5 (polyacrylic acid), at 0.1–0.5% w/w.

Other compounds may also be added to the ophthalmic compositions of the compound of general formula (I) to increase the viscosity of the carrier. Examples of viscosity enhancing agents include, but are not limited to: polysaccharides, such as hyaluronic acid and its
10 salts, chondroitin sulfate and its salts, dextrans, various polymers of the cellulose family; vinyl polymers; and acrylic acid polymers.

Topical ophthalmic products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use. Suitable preservatives
15 include: benzalkonium chloride, chlorobutanol, benzododecinium bromide, methyl paraben, propyl paraben, phenylethyl alcohol, edentate disodium, sorbic acid, polyquaternium-1, or other agents known to those skilled in the art. Such preservatives are typically employed at a level of from 0.001 to 1.0% w/v. Unit dose compositions of general formula (I) will be sterile, but typically unpreserved. Such compositions, therefore,
20 generally will not contain preservatives.

Parenteral formulations will generally be sterile.

The medical practitioner, or other skilled person, will be able to determine a suitable
25 dosage for the compound of general formula (I) and hence the amount of the compound of the invention that should be included in any particular pharmaceutical formulation (whether in unit dosage form or otherwise).

Compounds of general formula (I) may be used in combination with one or more other
30 active agents which are useful in the treatment or prophylaxis of respiratory diseases and conditions.

An additional active agent of this type may be included in the pharmaceutical composition described above but alternatively it may be administered separately, either at the same
35 time as the compound of general formula (I) or at an earlier or later time.

Therefore, in a further aspect of the present invention there is provided a product comprising a compound of general formula (I) and an additional agent useful in the treatment or prevention of respiratory conditions as a combined preparation for simultaneous, sequential or separate use in the treatment of a disease or condition
5 affected by modulation of TMEM16A and especially a respiratory disease or condition, for example one of the diseases and conditions mentioned above.

There is also provided a compound of general formula (I) in combination with an additional agent useful in the treatment or prevention of respiratory conditions as a combined
10 preparation for simultaneous, sequential or separate use in the treatment of a disease or condition affected by modulation of TMEM16A and especially a respiratory disease or condition, for example one of the diseases and conditions mentioned above.

Suitable additional active agents which may be included in a pharmaceutical composition or a combined preparation with the compounds of general formula (I), (Ix), (IA), (IB), (IC), (ID) or (IE) include:

β 2 adrenoreceptor agonists such as metaproterenol, isoproterenol, isoprenaline, albuterol, salbutamol, formoterol, salmeterol, indacaterol, terbutaline, orciprenaline, bitolterol mesylate, pirbuterol, olodaterol, vilanterol and abediterol;

20 antihistamines, for example histamine H₁ receptor antagonists such as loratadine, cetirizine, desloratadine, levocetirizine, fexofenadine, astemizole, azelastine and chlorpheniramine or H₄ receptor antagonists;

dornase alpha;

corticosteroids such as prednisone, prednisolone, flunisolide, triamcinolone acetonide,
25 beclomethasone dipropionate, budesonide, fluticasone propionate mometasone furoate and fluticasone furoate;

Leukotriene antagonists such as montelukast and zafirlukast;

anticholinergic compounds, particularly muscarinic antagonists such as ipratropium, tiotropium, glycopyrrolate, aclidinium and umeclidinium;

30 CFTR repair therapies (e.g. CFTR potentiators, correctors or amplifiers) such as Ivacaftor, QBW251, Bamacaftor (VX659), Elexacaftor (VX445), VX561/CPT-656, VX152, VX440, GLP2737, GLP2222, GLP2451, PTI438, PTI801, PTI808, FDL-169 and FDL-176 and CFTR correctors such as Lumacaftor and Tezacaftor or combinations thereof (for example a combination of Ivacaftor, Tezacaftor and Elexacaftor);

35 ENaC modulators, particularly ENaC inhibitors;

Antibiotics;

Antivirals such as ribavirin and neuraminidase inhibitors such as zanamivir;

Antifungals such as PUR1900;

Airway hydrating agents (osmoloytes) such as hypertonic saline and mannitol (Bronchitol®); and

- 5 Mucolytic agents such as. N-acetyl cysteine.

When the additional active agent is an ENaC modulator, it may be an ENaC inhibitor such as amiloride, VX-371, AZD5634, QBW276, SPX-101, BI443651, BI1265162 and ETD001. Other suitable ENaC blockers are disclosed in our applications WO 2017/221008, WO
10 2018/096325, WO 2019/077340 and WO 2019/220147 and any of the example compounds of those applications may be used in combination with the compounds of general formula (I). Particularly suitable compounds for use in combination with the compounds of general formula (I) include compounds having a cation selected from:

2-[(3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)formamido] ethyl]-6-(4-{bis[(2*S*,3*R*,4*R*,5*R*)-
15 2,3,4,5,6-pentahydroxyhexyl]amino}piperidine-1-carbonyl)-1,3-diethyl-1*H*-1,3-benzodiazol-3-ium;

2-[(3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)formamido] methyl]-6-[[2-(4-{bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino}piperidin-1-yl)ethyl]carbamoyl]-
1,3-diethyl-1*H*-1,3-benzodiazol-3-ium;

20 2-[(3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)formamido)methyl]-5-[4-({bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino)methyl]piperidine-1-carbonyl)-1,3-diethyl-1*H*-1,3-benzodiazol-3-ium;

2-[(3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)formamido)methyl]-6-[(3*R*)-3-{bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino}pyrrolidine-1-carbonyl]-1,3-
25 diethyl-1*H*-1,3-benzodiazol-3-ium;

2-[(3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)formamido)methyl]-6-[(3*S*)-3-{bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino}pyrrolidine-1-carbonyl]-1,3-
diethyl-1*H*-1,3-benzodiazol-3-ium;

2-[(3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)formamido)methyl]-1,3-diethyl-6-[[1*r*,4*r*]-4-
30 {bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino}cyclohexyl]carbamoyl]-1*H*-1,3-benzodiazol-3-ium;

2-[(3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)formamido)methyl]-1,3-diethyl-6-[[1*s*,4*s*]-4-
{bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino}cyclohexyl]carbamoyl]-1*H*-1,3-
benzodiazol-3-ium;

35 and a suitable anion, for example halide, sulfate, nitrate, phosphate, formate, acetate, trifluoroacetate, fumarate, citrate, tartrate, oxalate, succinate, mandelate, methane

sulfonate or p-toluene sulfonate.

Description of the Drawings

FIGURE 1 is an example trace from a whole-cell patch clamp (Qpatch) TMEM16A
5 potentiator assay as used in Biological Example 21 and illustrates the methodology used
in the assay.

Examples

General Conditions:

10 Mass spectra were run on LC-MS systems using electrospray ionization. These were run
using either a Waters Acquity uPLC system with Waters PDA and ELS detectors or
Shimadzu LCMS-2010EV systems. [M+H]⁺ refers to mono-isotopic molecular weights.

NMR spectra were recorded on a Bruker Avance III HD 500 MHz with a 5mm Broad Band
15 Inverse probe, a Bruker Avance III HD 250 MHz, a 400MHz Avance III HD Nanobay fitted
with a 5mm Broad Band Observed SmartProbe using the solvent as internal deuterium
lock. Spectra were recorded at room temperature unless otherwise stated and were
referenced using the solvent peak.

20 Referring to the examples that follow, compounds of the preferred embodiments were
synthesized using the methods described herein, or other methods, which are known in
the art.

The various starting materials, intermediates, and compounds of the preferred
25 embodiments may be isolated and purified, where appropriate, using conventional
techniques such as precipitation, filtration, crystallization, evaporation, distillation, and
chromatography. Unless otherwise stated, all starting materials are obtained from
commercial suppliers and used without further purification. Salts may be prepared from
compounds by known salt-forming procedures.

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Compounds were purified by flash column chromatography on normal phase silica on
Biotage® Isolera systems using the appropriate SNAP cartridge or Sfär cartridge and
gradient. Alternatively, compounds were purified on reverse phase silica using either
Biotage® Isolera or Biotage® Selekt systems with the appropriate SNAP C18 or Sfär C18
35 cartridges and reverse phase eluent or by preparative HPLC (if stated otherwise).

Preparative HPLC using acidic pH, early elution method

Purifications by were performed on a Gilson LC system using Waters Sunfire C18 columns (30 mm x 100 mm, 10 μ M; temperature: RT) and a gradient of 10-95% B (A= 0.1% formic acid in water; B= 0.1% formic acid in acetonitrile) over 14.44 min then 95% B for 2.11 min, with an injection volume of 1500 μ L and a flow rate of 40 mL/min. UV spectra were recorded at 215 nm using a Gilson detector.

Preparative HPLC using acidic pH, standard elution method

Purifications by preparative HPLC (acidic pH, standard elution method) were performed on a Gilson LC system using Waters Sunfire C18 columns (30 mm x 100 mm, 10 μ M; temperature: RT) and a gradient of 30-95% B (A= 0.1% formic acid in water; B= 0.1% formic acid in acetonitrile) over 11 min then 95% B for 2.11 min, with an injection volume of 1500 μ L and a flow rate of 40 mL/min. UV spectra were recorded at 215 nm using a Gilson detector.

Preparative HPLC using basic pH, early elution method

Purifications by preparative HPLC (basic pH, early elution method) were performed on a Gilson LC system using Waters Xbridge C18 columns (30 mm x 100 mm, 10 μ M; temperature: RT) and a gradient of 10-95% (A= 0.2% ammonium hydroxide in water; B= 0.2% ammonium hydroxide in acetonitrile) over 14.44 min then 95% B for 2.11 min, with an injection volume of 1500 μ L and a flow rate of 40 mL/min. UV spectra were recorded at 215 nm using a Gilson detector.

Preparative HPLC using basic pH, standard elution method

Purifications by preparative HPLC (basic pH, standard elution method) were performed on a Gilson LC system using Waters Xbridge C18 columns (30 mm x 100 mm, 10 μ M; temperature: RT) and a gradient of 30-95% (A= 0.2% ammonium hydroxide in water; B= 0.2% ammonium hydroxide in acetonitrile) over 11 min then 95% B for 2.11 min, with an injection volume of 1500 μ L and a flow rate of 40 mL/min. UV spectra were recorded at 215 nm using a Gilson detector.

If not indicated otherwise, the analytical HPLC conditions are as follows:

Method A

Column: Phenomenex Kinetix-XB C18 2.1 x 100 mm, 1.7 μ m
Column Temp: 40 °C

Eluents: A: H₂O + 0.1% formic acid, B: acetonitrile + 0.1% formic acid
Flow Rate: 0.6 mL/min
Gradient: 0-5.3 min 5-100% B, 5.3-5.8 min 100% B, 5.8-5.82 min 100-5% B,
5.82-7.00 min 5% B

5

Method C

Column: Waters UPLC® BEH™ C18 2.1 x 100 mm, 1.7 µm
Column Temp: 40 °C
Eluents: A: 2 mM ammonium bicarbonate, buffered to pH10, B: acetonitrile
10 Flow Rate: 0.6 mL/min
Gradient: 0-5.3 min 5-100% B, 5.3-5.8 min 100% B, 5.8-5.82 min 100-5%
B, 5.82-7.00 min 5% B

Method E

15 Column: Kinetex Core-Shell C18 2.1 x 50 mm, 5 µm
Column Temp: 40 °C
Eluents: A: H₂O + 0.1% formic acid, B: acetonitrile + 0.1% formic acid
Flow Rate: 1.2 mL/min
Gradient: 0-1.20 min 5-100% B, 1.20-1.30 min 100% B, 1.30-1.31 min
20 100-5% B, 1.31-1.7 min 5% B

Method F

Column: Phenomenex Gemini-NX C18 2.0 x 50 mm, 3 µm
Column Temp: 40 °C
25 Eluents: A: 2 mM ammonium bicarbonate, buffered to pH10, B: acetonitrile
Flow Rate: 1 mL/min
Gradient: 0-1.80 min 1-100% B, 1.80-2.10 min 100% B, 2.10-2.30 min
100-1% B, 2.30-3.50 min 1% B

Method G

30 Column: Waters UPLC® BEH™ C18, 2.1 x 50 mm, 1.7 µm
Column Temp: 40 °C
Eluents: A: H₂O + 0.1% formic acid, B: acetonitrile + 0.1% formic acid
Flow Rate: 0.9 mL/min
35 Gradient: 0-1.10 min 5-100% B, 1.10-1.35 min 100% B, 1.35-1.40 min
100-5% B, 1.40-1.50 min 5% B

Method H

Column:	Kinetex Core-Shell C18 2.1 x 50 mm, 5 µm
Column Temp:	40 °C
Eluents:	A: H ₂ O + 0.1% formic acid, B: acetonitrile + 0.1% formic acid
5 Flow Rate:	1.2 mL/min
Gradient:	0-1.83 min 5-100% B, 1.83-2.25 min 100% B, 2.25-2.26 min 100-5% B, 2.26-2.8 min 5% B

Method I

10 Column:	Waters UPLC ® BEH™ C18 2.1 x 30mm, 1.7µm
Column Temp:	40 °C
Eluents:	A: 2mM ammonium bicarbonate, buffered to pH10, B: acetonitrile
Flow Rate:	1.0 mL/min
Gradient:	0-0.75 min 5-100%B, 0.75-0.85 min 100%B, 0.85-0.9 min 100-5%B,
15	0.9-1.0 min 5%B

The following example are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees centigrade. If not mentioned otherwise, all evaporations are performed *in vacuo*, preferably between about 20 15 mm Hg and 100 mm Hg (= 20-133 mbar). The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, e.g., microanalysis and spectroscopic characteristics, e.g., MS and NMR. Abbreviations used are those conventional in the art. If not defined, the terms have their generally accepted meanings.

25 Abbreviations

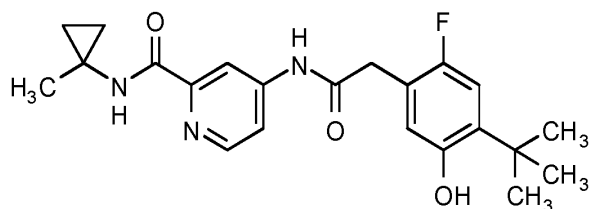
aq.	aqueous
br	broad
Cy	cyclohexyl
d	doublet
30 dd	doublet of doublets
DIBAL	diisobutylaluminium hydride
DCM	dichloromethane
DCE	1,2-dichloroethane
DIPEA	diisopropylethylamine
35 DMAP	4-dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide

	DMSO	dimethyl sulfoxide
	EtOH	ethanol
	EtOAc	ethyl acetate
	HATU	2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium
5		hexafluorophosphate
	HPLC	high pressure liquid chromatography
	IPA	isopropyl alcohol
	MeCN	acetonitrile
	MeOH	methanol
10	MS	mass spectrometry
	m	multiplet
	min	minute(s)
	mL	millilitre(s)
	m/z	mass to charge ratio
15	NMR	nuclear magnetic resonance
	Q-Phos	1,2,3,4,5-pentaphenyl-1'-(di- <i>tert</i> -butylphosphino)ferrocene
	Rt	retention time
	s	singlet
	t	triplet
20	T3P®	1-propanephosphonic anhydride solution
	TBAF	tetra-n-butylammonium fluoride
	TBTU	N,N,N',N'-tetramethyl-O-(benzotriazol-1-yl)uronium tetrafluoroborate
	TEA	TEA
	TFA	trifluoroacetic acid
25	THF	tetrahydrofuran
	μL	microlitre(s)

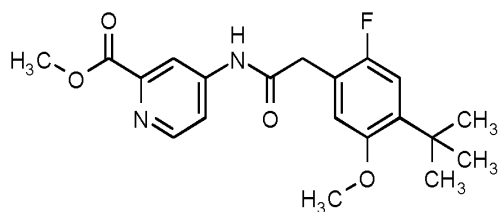
PREPARATION EXAMPLES

Example 1

4-[[2-(4-*tert*-Butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-(1-methylcyclopropyl)pyridine-2-carboxamide



Step 1: Methyl 4-[[2-(4-*tert*-butyl-2-fluoro-5-methoxy-phenyl)acetyl]amino] pyridine-2-carboxylate

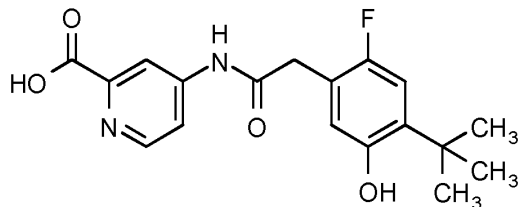


- To a stirred solution of 2-(4-*tert*-butyl-2-fluoro-5-methoxy-phenyl)acetic acid (Intermediate G) (120 mg, 0.5 mmol), methyl 4-aminopyridine-2-carboxylate (76 mg, 0.5 mmol) and DIPEA (96 μ L, 0.55 mmol) in 1,4-dioxane (1 mL) was added 50% T3P® solution in EtOAc (297 μ L, 0.5 mmol) and the mixture was stirred at room temperature for 45 min. The resulting mixture was partitioned between EtOAc (20 mL) and water (20 mL). The organic portion was separated, dried over Na₂SO₄ and concentrated *in vacuo*. The crude material was purified by chromatography on silica eluting with 0-100% EtOAc in heptanes to afford the title compound as an off-white solid.

LC-MS (Method E): Rt 1.20 min; MS m/z 375.2 = [M+H]⁺ (100% @ 215 nm)

- ¹H NMR (500 MHz, Chloroform-*d*) δ 8.61 (d, *J* = 5.5 Hz, 1H), 8.05 – 7.84 (m, 2H), 7.60 (s, 1H), 7.07 (d, *J* = 11.9 Hz, 1H), 6.77 (d, *J* = 6.6 Hz, 1H), 3.99 (s, 3H), 3.83 (s, 3H), 3.73 (d, *J* = 1.0 Hz, 2H), 1.36 (s, 9H).

Step 2: 4-[[2-(4-*tert*-Butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid



1M BBr₃ in DCM (0.21 mL, 2.24 mmol) was added dropwise to a cooled (0 °C), stirred
 5 suspension of methyl 4-[[2-(4-*tert*-butyl-2-fluoro-5-methoxy-phenyl)acetyl]amino] pyridine-2-carboxylate (step 1) (140 mg, 0.37 mmol) in DCM (4 mL). After 30 min, the ice bath was removed and the reaction mixture was stirred at room temperature for 6 h. The resulting mixture was concentrated *in vacuo* and the residue partitioned between EtOAc (10 mL) and sat. NaHCO₃ (10 mL). The aqueous portion was separated and the pH was adjusted
 10 to pH~3 using 2M aq. HCl. The mixture was extracted with EtOAc (2 x 10 mL) and the combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo* to afford the title compound as an off-white solid.

LC-MS (Method E): Rt 0.98 min; MS *m/z* 347.1 = [M+H]⁺ (94% @ 215 nm)

¹H NMR (500 MHz, DMSO-*d*₆) δ 11.26 (s, 1H), 9.33 (s, 1H), 8.62 (d, *J* = 6.1 Hz, 1H), 8.40
 15 (d, *J* = 2.1 Hz, 1H), 8.00 (dd, *J* = 6.1, 2.1 Hz, 1H), 6.88 (d, *J* = 11.9 Hz, 1H), 6.74 (d, *J* = 6.9 Hz, 1H), 3.72 (s, 2H), 1.32 (s, 9H)

Step 3: 4-[[2-(4-*tert*-Butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-(1-methylcyclopropyl)pyridine-2-carboxamide

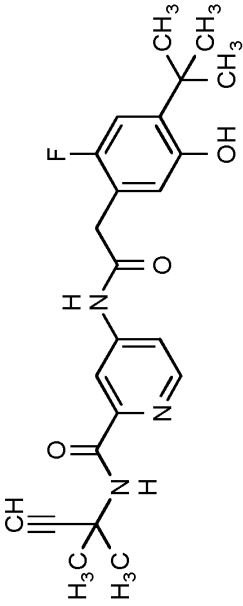
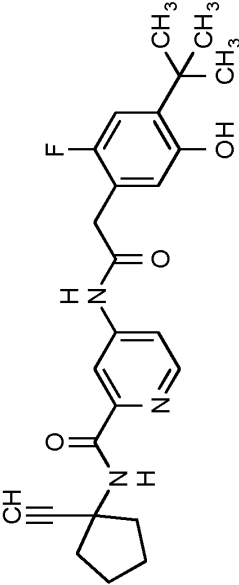
To a solution of 4-[[2-(4-*tert*-butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]pyridine-2-
 20 carboxylic acid (step 2) (80 mg, 0.21 mmol), 1-methylcyclopropanamine (15 mg, 0.21 mmol) and DIPEA (73 μL, 0.42 mmol) in DMF (1 mL) was added HATU (75 mg, 0.2 mmol) and the resulting mixture was stirred at room temperature for 1 hour. The resulting mixture was concentrated *in vacuo* and the residue was partitioned between EtOAc (5 mL) and water (5 mL). The organic layer was washed with water (2 x 5 mL), brine (5 mL), dried
 25 over Na₂SO₄ and concentrated *in vacuo*. The crude material was purified by preparative HPLC (acidic pH, early elution method) and the desired fractions were combined and lyophilised overnight to afford the title compound as an off-white powder.

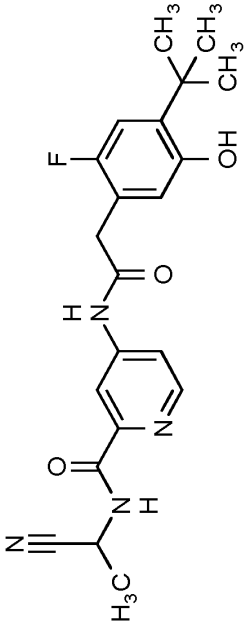
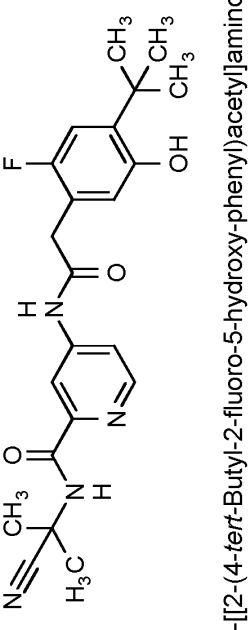
LC-MS (Method A): Rt 3.51 min; MS *m/z* 400.2 = [M+H]⁺ (96% @ 215 nm)

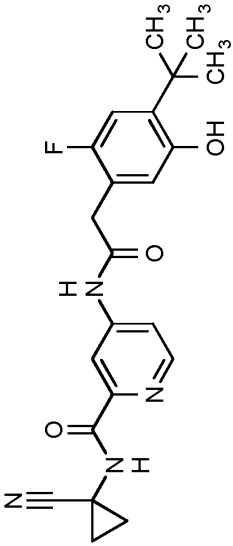
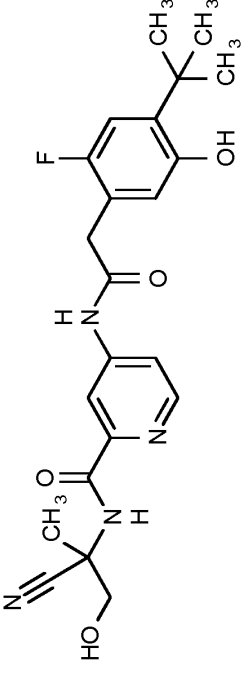
¹H NMR (500 MHz, DMSO-*d*₆) δ 10.74 (s, 1H), 9.29 (s, 1H), 8.76 (s, 1H), 8.44 (d, *J* = 5.5
 30 Hz, 1H), 8.17 (d, *J* = 2.0 Hz, 1H), 7.80 (dd, *J* = 5.5, 2.2 Hz, 1H), 6.87 (d, *J* = 11.9 Hz, 1H), 6.73 (d, *J* = 6.9 Hz, 1H), 3.64 (s, 2H), 1.35 (s, 3H), 1.31 (s, 9H), 0.82 – 0.70 (m, 2H), 0.66 – 0.55 (m, 2H).

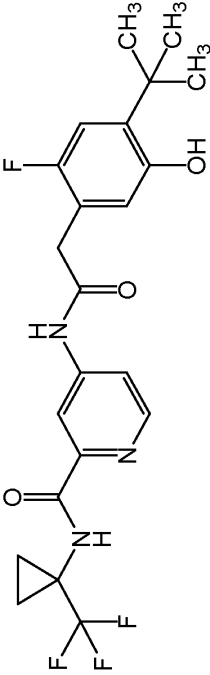
The compounds of the following tabulated Examples (Table 1) were prepared analogously to Example 1 by replacing 1-methylcyclopropanamine (step 3) with the appropriate commercially available amine.

Table 1

Ex.	Structure and Name	Retention Time, [M+H] ⁺ , 1H NMR
1.1	 4-[[2-(4-<i>tert</i>-Butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide	LC-MS (Method A): Rt 3.68 min; MS m/z 412.2 = [M+H]⁺ (100% @ 215 nm) ¹H NMR (500 MHz, DMSO-d₆) δ 10.79 (s, 1H), 9.30 (s, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.32 (s, 1H), 8.21 (d, J = 2.0 Hz, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 6.88 (d, J = 11.9 Hz, 1H), 6.74 (d, J = 6.9 Hz, 1H), 3.65 (s, 2H), 3.21 (s, 1H), 1.65 (s, 6H), 1.32 (s, 9H).
1.2	 4-[[2-(4-<i>tert</i>-Butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-(1-ethynylcyclopentyl)pyridine-2-carboxamide	LC-MS (Method A): Rt 3.89 min; MS m/z 438.3 = [M+H]⁺ (100% @ 215 nm) ¹H NMR (400 MHz, DMSO-d₆) δ 10.79 (s, 1H), 9.30 (s, 1H), 8.53 – 8.37 (m, 2H), 8.20 (d, J = 1.9 Hz, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 6.88 (d, J = 11.9 Hz, 1H), 6.74 (d, J = 7.0 Hz, 1H), 3.65 (s, 2H), 3.16 (s, 1H), 2.30 – 2.20 (m, 2H), 2.14 – 2.04 (m, 2H), 1.77 – 1.65 (m, 4H), 1.32 (s, 9H).

Ex.	Structure and Name	Retention Time, [M+H] ⁺ , ¹ H NMR
1.3	 4-[[2-(4-<i>tert</i>-Butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-(1-cyanoethyl)pyridine-2-carboxamide	LC-MS (Method A): Rt 3.30 min; MS m/z 399.2 = [M+H]⁺ (100% @ 215 nm) ¹H NMR (500 MHz, DMSO-d₆) δ 10.80 (s, 1H), 9.48 (d, J = 8.1 Hz, 1H), 9.30 (s, 1H), 8.53 (d, J = 5.5 Hz, 1H), 8.25 (d, J = 2.1 Hz, 1H), 7.85 (dd, J = 5.5, 2.2 Hz, 1H), 6.88 (d, J = 11.9 Hz, 1H), 6.74 (d, J = 7.0 Hz, 1H), 5.06 – 4.98 (m, 1H), 3.65 (s, 2H), 1.55 (d, J = 7.2 Hz, 3H), 1.32 (s, 9H).
1.4	 4-[[2-(4-<i>tert</i>-Butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide	LC-MS (Method A): Rt 3.45 min; MS m/z 413.2 = [M+H]⁺ (100% @ 215 nm) ¹H NMR (400 MHz, DMSO-d₆) δ 10.83 (s, 1H), 9.32 (s, 1H), 8.83 (s, 1H), 8.52 (d, J = 5.4 Hz, 1H), 8.24 (s, 1H), 7.85 (d, J = 4.0 Hz, 1H), 6.88 (d, J = 11.9 Hz, 1H), 6.75 (d, J = 6.8 Hz, 1H), 3.66 (s, 2H), 1.72 (s, 6H), 1.32 (s, 9H).

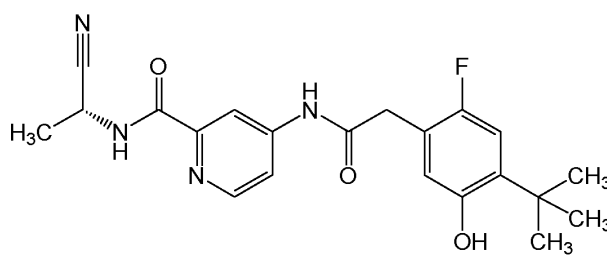
Ex.	Structure and Name	Retention Time, [M+H] ⁺ , 1H NMR
1.5	 4-[[2-(4-<i>tert</i>-Butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-(1-cyanocyclopropyl)pyridine-2-carboxamide	LC-MS (Method A): Rt 3.29 min; MS m/z 411.3 = [M+H]⁺ (100% @ 215 nm) ¹H NMR (500 MHz, DMSO-d₆) δ 10.81 (s, 1H), 9.66 (s, 1H), 9.30 (s, 1H), 8.50 (d, J = 5.5 Hz, 1H), 8.23 (d, J = 2.0 Hz, 1H), 7.85 (dd, J = 5.5, 2.2 Hz, 1H), 6.88 (d, J = 11.9 Hz, 1H), 6.74 (d, J = 7.0 Hz, 1H), 3.65 (s, 2H), 1.56 – 1.51 (m, 2H), 1.36 – 1.28 (m, 11H).
1.6	 4-[[2-(4-<i>tert</i>-Butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-2-hydroxy-1-methyl-ethyl)pyridine-2-carboxamide	LC-MS (Method A): Rt 3.16 min; MS m/z 429.2 = [M+H]⁺ (99% @ 215 nm) ¹H NMR (500 MHz, DMSO-d₆) δ 10.84 (s, 1H), 9.31 (s, 1H), 8.74 (s, 1H), 8.53 (d, J = 5.5 Hz, 1H), 8.26 (d, J = 2.1 Hz, 1H), 7.86 (dd, J = 5.5, 2.2 Hz, 1H), 6.89 (d, J = 11.9 Hz, 1H), 6.75 (d, J = 6.9 Hz, 1H), 5.94-5.86 (m, 1H), 3.88 – 3.78 (m, 1H), 3.78 – 3.70 (m, 1H), 3.67 (s, 2H), 1.67 (s, 3H), 1.33 (s, 9H).

Ex.	Structure and Name	Retention Time, [M+H] ⁺ , 1H NMR
1.7	 4-[[2-(4-<i>tert</i>-Butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide	LC-MS (Method A): Rt 3.72 min; MS m/z 454.3 = [M+H]⁺ (100% @ 215 nm) ¹H NMR (400 MHz, DMSO-d₆) δ 10.79 (s, 1H), 9.38 (s, 1H), 9.30 (s, 1H), 8.51 (d, J = 5.6 Hz, 1H), 8.22 (d, J = 1.8 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 6.88 (d, J = 11.9 Hz, 1H), 6.74 (d, J = 7.0 Hz, 1H), 3.65 (s, 2H), 1.35-1.27 (m, 11H), 1.23-1.15 (m, 2H).

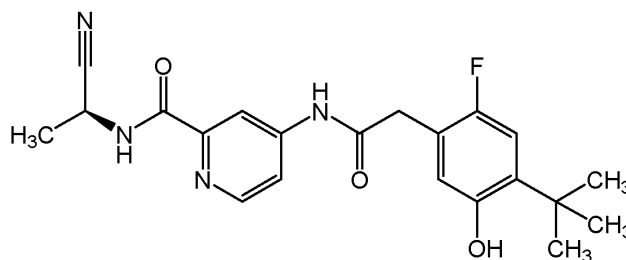
Example 1.3a and 1.3b

Chiral separation of racemic 4-[[2-(4-*tert*-Butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-(1-cyanoethyl)pyridine-2-carboxamide (Example 1.3) using Supercritical Fluid Chromatography [chiral phase column 7% MeOH : 93% CO₂ with Chiralcel OJ-H @ 15 ml/min] afforded the individual enantiomers:

Example 1.3a: 4-[[2-(4-*tert*-Butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-[(1R)-1-cyanoethyl]pyridine-2-carboxamide or 4-[[2-(4-*tert*-butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-[(1S)-1-cyanoethyl]pyridine-2-carboxamide



(R)-isomer



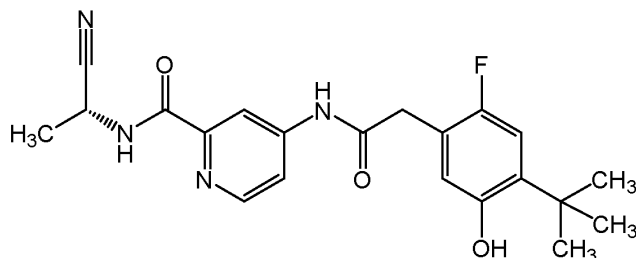
(S)-isomer

First eluted Peak: SFC retention time = 3.48 mins

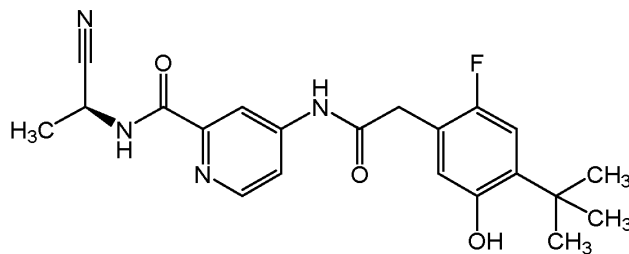
LC-MS (Method A): Rt 3.35 min; MS m/z 399.2 = [M+H]⁺ (100% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.82 (s, 1H), 9.49 (d, J = 8.1 Hz, 1H), 9.32 (s, 1H), 8.53 (d, J = 5.5 Hz, 1H), 8.25 (d, J = 2.0 Hz, 1H), 7.85 (dd, J = 5.5, 2.2 Hz, 1H), 6.88 (d, J = 11.9 Hz, 1H), 6.74 (d, J = 6.9 Hz, 1H), 5.07 – 4.99 (m, 1H), 3.65 (s, 2H), 1.55 (d, J = 7.2 Hz, 3H), 1.32 (s, 9H).

Example 1.3b: 4-[[2-(4-*tert*-Butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-[(1R)-1-cyanoethyl]pyridine-2-carboxamide or 4-[[2-(4-*tert*-butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-[(1S)-1-cyanoethyl]pyridine-2-carboxamide



(R)-isomer



(S)-isomer

Second eluted Peak: SFC retention time = 4.36 mins

LC-MS (Method A): Rt 3.35 min; MS m/z 399.2 = [M+H]⁺ (100% @ 215 nm)

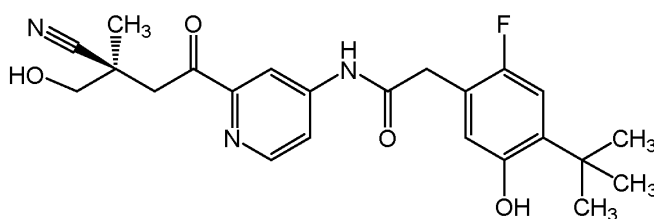
¹H NMR (500 MHz, DMSO-d₆) δ 10.83 (s, 1H), 9.49 (d, J = 8.1 Hz, 1H), 9.33 (s, 1H), 8.53 (d, J = 5.5 Hz, 1H), 8.25 (d, J = 2.0 Hz, 1H), 7.85 (dd, J = 5.5, 2.2 Hz, 1H), 6.88 (d, J = 11.9 Hz, 1H), 6.74 (d, J = 6.9 Hz, 1H), 5.07 – 4.99 (m, 1H), 3.65 (s, 2H), 1.55 (d, J = 7.2 Hz, 3H), 1.32 (s, 9H).

Example 1.6a and 1.6b

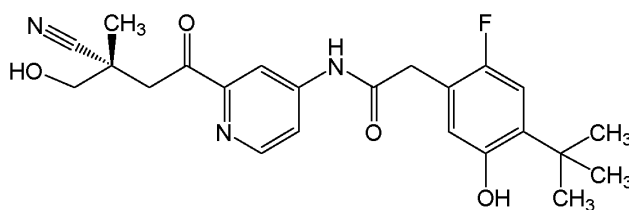
Chiral separation of racemic 4-[[2-(4-*tert*-Butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-2-hydroxy-1-methyl-ethyl)pyridine-2-carboxamide (Example 1.6) using Supercritical Fluid Chromatography [chiral phase column 25% IPA:75% CO₂ with Chiralpak IC 25 cm @ 4 ml/min] afforded the individual enantiomers:

Example 1.6a: 4-[[2-(4-*tert*-Butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-[(1R)-1-cyano-2-hydroxy-1-methyl-ethyl]pyridine-2-carboxamide or 4-[[2-(4-*tert*-butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-[(1S)-1-cyano-2-hydroxy-1-methyl-ethyl]pyridine-2-carboxamide

5



(R)-isomer



(S)-isomer

10 **First Eluted Peak:** SFC retention time = 2.33 mins

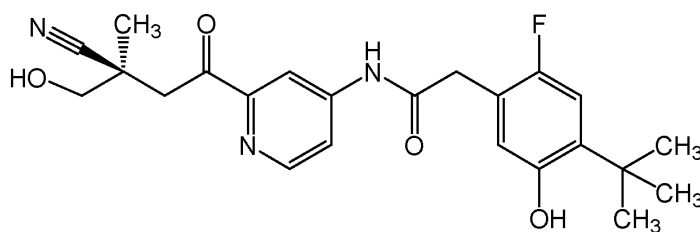
LC-MS (Method A): Rt 3.16 min; MS m/z 429.3 = [M+H]⁺ (98% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.84 (s, 1H), 9.32 (s, 1H), 8.74 (s, 1H), 8.52 (d, J = 5.5 Hz, 1H), 8.25 (d, J = 2.0 Hz, 1H), 7.86 (dd, J = 5.5, 2.1 Hz, 1H), 6.88 (d, J = 11.9 Hz, 1H), 6.75 (d, J = 6.9 Hz, 1H), 5.91 (s, 1H), 3.82 (d, J = 10.8 Hz, 1H), 3.73 (d, J = 10.9 Hz, 1H),

15 3.66 (s, 2H), 1.66 (s, 3H), 1.32 (s, 9H).

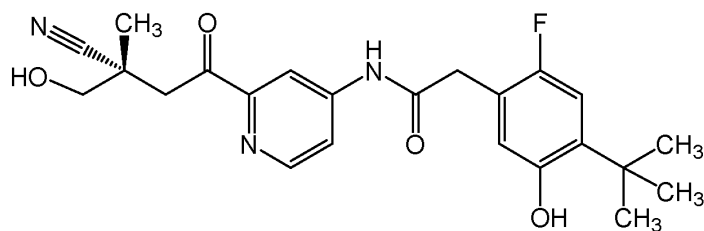
Example 1.6b: 4-[[2-(4-*tert*-Butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-[(1R)-1-cyano-2-hydroxy-1-methyl-ethyl]pyridine-2-carboxamide or 4-[[2-(4-*tert*-butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-[(1S)-1-cyano-2-hydroxy-1-methyl-ethyl]pyridine-2-carboxamide

20



(R)-isomer

80



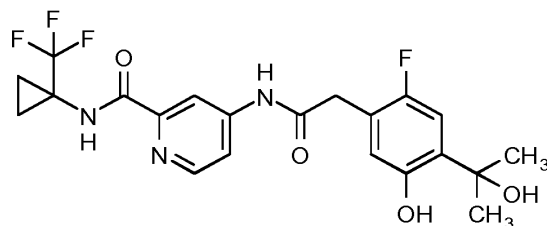
(S)-isomer

Second Eluted Peak: SFC retention time = 4.26 minsLC-MS (Method A): Rt 3.16 min; MS m/z 429.3 = [M+H]⁺ (99% @ 215 nm)

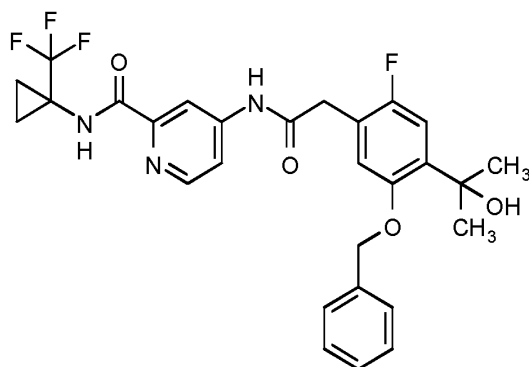
- 5 ¹H NMR (500 MHz, DMSO-d₆) δ 10.85 (s, 1H), 9.30 (s, 1H), 8.74 (s, 1H), 8.52 (d, J = 5.5 Hz, 1H), 8.25 (d, J = 2.0 Hz, 1H), 7.86 (dd, J = 5.5, 2.1 Hz, 1H), 6.88 (d, J = 11.9 Hz, 1H), 6.75 (d, J = 6.9 Hz, 1H), 5.91 (s, 1H), 3.82 (d, J = 11.0 Hz, 1H), 3.73 (d, J = 10.9 Hz, 1H), 3.66 (s, 2H), 1.66 (s, 3H), 1.32 (s, 9H).

10 **Example 2**

4-[[2-[2-Fluoro-5-hydroxy-4-(1-hydroxy-1-methyl-ethyl)phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide

Step 1: 4-[[2-[5-Benzyloxy-2-fluoro-4-(1-hydroxy-1-methyl-ethyl)phenyl]acetyl] amino]-N-

- 15 [1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide



To a stirred solution of 2-[5-benzyloxy-2-fluoro-4-(1-hydroxy-1-methyl-ethyl)phenyl]acetic acid (Intermediate B) (38 mg, 0.12 mmol), 4-amino-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Intermediate A) (29 mg, 0.12 mmol)

and DIPEA (23 μ L, 0.13 mmol) in 1,4-dioxane (0.5 mL) was added 50% T3P® solution in EtOAc (71 μ L, 0.12 mmol) and the reaction mixture was stirred at room temperature for 1.5 h. The resulting mixture was partitioned between EtOAc (5 mL) and water (5 mL). The organic layer was separated, dried over Na₂SO₄ and concentrated *in vacuo* to afford the title compound as an off-white solid.

LC-MS (Method E): Rt 1.24 mins; MS m/z 546.3 = [M+H]⁺ (93% @ 215 nm)

¹H NMR (500 MHz, MeOD) δ 8.49 (d, J = 5.3 Hz, 1H), 8.19 (s, 1H), 7.90 (d, J = 4.8 Hz, 1H), 7.46-7.42 (m, 2H), 7.37-7.26 (m, 4H), 7.02 (d, J = 6.0 Hz, 1H), 5.12 (s, 2H), 3.77 (s, 2H), 1.57 (s, 6H), 1.42 – 1.18 (m, 4H).

Step 2: 4-[[2-[2-Fluoro-5-hydroxy-4-(1-hydroxy-1-methyl-ethyl)phenyl]acetyl] amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide

To a solution of 4-[[2-[5-benzyloxy-2-fluoro-4-(1-hydroxy-1-methyl-ethyl)phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (step 1) (45 mg, 0.08 mmol) in EtOH (2 mL) was added 10 % Pd-C (9 mg, 0.01 mmol). The mixture was placed under a hydrogen atmosphere and stirred for 2 h. The resulting mixture was filtered through Celite® (filter material), rinsing with EtOH (10 mL). The filtrate was concentrated *in vacuo* and the crude material was purified by preparative HPLC (acidic pH, early elution method) to afford the title compound as an off-white solid.

LC-MS (Method A): Rt 2.95 mins; MS m/z 456.2 = [M+H]⁺ (98% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.82 (s, 1H), 9.58 (br s, 1H), 9.40 (s, 1H), 8.51 (d, J = 5.5 Hz, 1H), 8.22 (d, J = 2.0 Hz, 1H), 7.85 (dd, J = 5.5, 2.2 Hz, 1H), 7.11 (d, J = 11.4 Hz, 1H), 6.73 (d, J = 6.6 Hz, 1H), 5.63 (br s, 1H), 3.68 (s, 2H), 1.49 (s, 6H), 1.35 – 1.27 (m, 2H), 1.24 – 1.14 (m, 2H).

The title compound was also prepared according to the following method:

A cooled (0 °C) solution of 4-[[2-(2-fluoro-5-hydroxy-4-isopropenyl-phenyl)acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Example 7.1) (1.0 g, 2.29 mmol) in IPA (20 mL) and DCM (4 mL) purged with an atmosphere of air was treated with tris(2,2,6,6-tetramethyl-3,5-heptanedionato)manganese(III) (0.14 g, 0.23 mmol) followed by dropwise addition of phenylsilane (0.56 mL, 4.57 mmol). The reaction mixture was stirred at room temperature for 2 h with continuous air purging. The reaction was quenched with 20% aqueous sodium thiosulfate (100 mL) and stirred at room temperature for 30 min. The resulting mixture was extracted with EtOAc (3 x 100 mL) and the combined organic extracts were washed with brine (100 mL), dried over MgSO₄ and concentrated *in vacuo*.

Purification by chromatography on silica eluting with 0 to 100% EtOAc in heptane followed

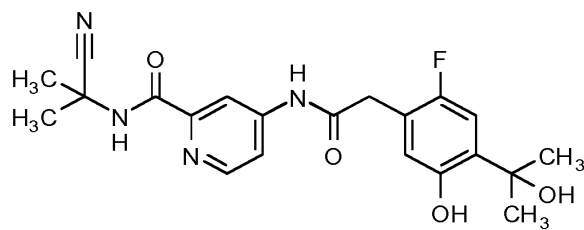
by 0 to 100% MeOH in EtOAc afforded a yellow solid. The solid was further purified by C18 reverse phase chromatography eluting with 10-100% MeCN in water (+0.1% formic acid) to yield a white solid. The solid was recrystallised from MeCN (12 mL) to afford the title compound as a white solid.

- 5 LCMS (Method A - MSQ2, 7min) Rt 2.92 mins; MS m/z 456.2 = [M+H]⁺ (100% @ 215 nm)
1H NMR (500 MHz, DMSO-d₆) δ 10.79 (s, 1H), 9.56 (bs, 1H), 9.39 (s, 1H), 8.50 (d, J = 5.5 Hz, 1H), 8.21 (d, J = 1.9 Hz, 1H), 7.84 (dd, J = 5.5, 2.1 Hz, 1H), 7.10 (d, J = 11.4 Hz, 1H), 6.72 (d, J = 6.6 Hz, 1H), 5.63 (bs, 1H), 3.67 (s, 2H), 1.48 (s, 6H), 1.35 – 1.23 (m, 2H), 1.25 – 1.10 (m, 2H).

10

Example 2.1

N-(1-Cyano-1-methyl-ethyl)-4-[[2-[2-fluoro-5-hydroxy-4-(1-hydroxy-1-methyl-ethyl)]phenyl]acetyl]amino]pyridine-2-carboxamide



- 15 The title compound was prepared from 2-[5-benzyloxy-2-fluoro-4-(1-hydroxy-1-methyl-ethyl)]phenyl]acetic acid (Intermediate B) and 4-amino-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide (Intermediate AB) analogously to Example 2 steps 1 and 2.

LC-MS (Method A): Rt 2.57 mins; MS m/z 415.3 = [M+H]⁺ (95% @ 215 nm)

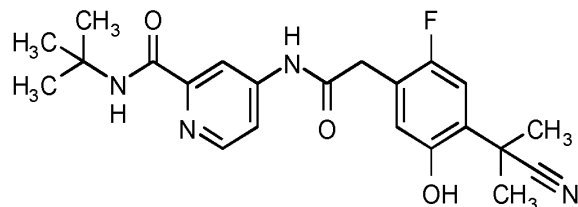
- (500 MHz, DMSO-d₆) δ 10.83 (s, 1H), 9.57 (br s, 1H), 8.84 (s, 1H), 8.53 (d, J = 5.5 Hz, 1H), 8.24 (d, J = 2.1 Hz, 1H), 7.86 (dd, J = 5.5, 2.2 Hz, 1H), 7.11 (d, J = 11.4 Hz, 1H), 6.73 (d, J = 6.7 Hz, 1H), 5.63 (s, 1H), 3.69 (s, 2H), 1.73 (s, 6H), 1.50 (s, 6H).

20

Example 2.2

N-tert-Butyl-4-[[2-[4-(1-cyano-1-methyl-ethyl)-2-fluoro-5-hydroxy-phenyl]acetyl]amino]pyridine-2-carboxamide

25



The title compound was prepared from 2-[5-benzyloxy-4-(1-cyano-1-methyl-ethyl)-2-

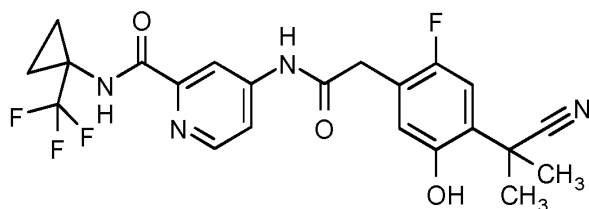
fluoro-phenyl]acetic acid (Intermediate C) and 4-amino-N-*tert*-butyl-pyridine-2-carboxamide analogously to Example 2 steps 1 and 2.

LC-MS (Method C): Rt 3.27 mins; MS m/z 411.5 = [M-H]⁻ (99% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.82 (s, 1H), 10.10 (s, 1H), 8.46 (d, J = 5.5 Hz, 1H),
5 8.18 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 7.04 (d, J = 11.0 Hz, 1H), 6.87 (d, J = 6.7 Hz, 1H), 3.72 (s, 2H), 1.69 (s, 6H), 1.40 (s, 9H).

Example 2.3

4-[[2-[4-(1-Cyano-1-methyl-ethyl)-2-fluoro-5-hydroxy-phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide



The title compound was prepared from 2-[5-benzyloxy-4-(1-cyano-1-methyl-ethyl)-2-fluoro-phenyl]acetic acid (Intermediate C) and 4-amino-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Intermediate A) analogously to
15 Example 2 steps 1 and 2.

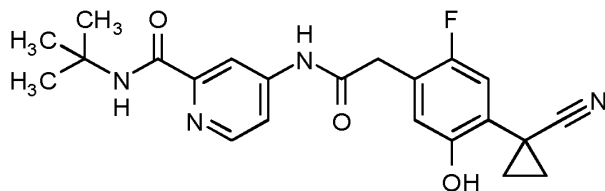
LC-MS (Method C): Rt 3.20 mins; MS m/z 465.3 = [M+H]⁺ (96% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.82 (s, 1H), 10.05 (br. s, 1H), 9.39 (s, 1H), 8.51 (d, J = 5.4 Hz, 1H), 8.21 (s, 1H), 7.87 – 7.78 (m, 1H), 7.04 (d, J = 10.9 Hz, 1H), 6.87 (d, J = 6.5 Hz, 1H), 3.72 (s, 2H), 1.69 (s, 6H), 1.33-1.26 (m, 2H), 1.20-1.12 (m, 2H).

20

Example 2.4

N-*tert*-Butyl-4-[[2-[4-(1-cyanocyclopropyl)-2-fluoro-5-hydroxy-phenyl]acetyl]amino]pyridine-2-carboxamide



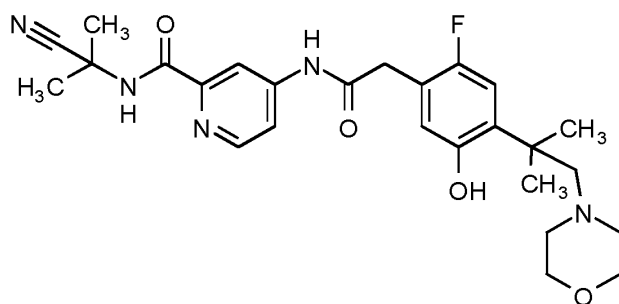
25 The title compound was prepared from 2-[5-benzyloxy-4-(1-cyanocyclopropyl)-2-fluoro-phenyl]acetic acid (Intermediate D) and 4-amino-N-*tert*-butyl-pyridine-2-carboxamide analogously to Example 2 steps 1 and 2.

LC-MS (Method A): Rt 3.05 mins; MS m/z 411.3 = [M+H]⁺ (96% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.80 (s, 1H), 9.96 (br s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 7.08 (d, J = 10.1 Hz, 1H), 6.85 (d, J = 6.5 Hz, 1H), 3.71 (s, 2H), 1.59 – 1.52 (m, 2H), 1.40 (s, 9H), 1.33 – 1.26 (m, 2H).

Example 2.5

N-(1-Cyano-1-methyl-ethyl)-4-[[2-[4-(1,1-dimethyl-2-morpholino-ethyl)-2-fluoro-5-hydroxy-phenyl]acetyl]amino]pyridine-2-carboxamide

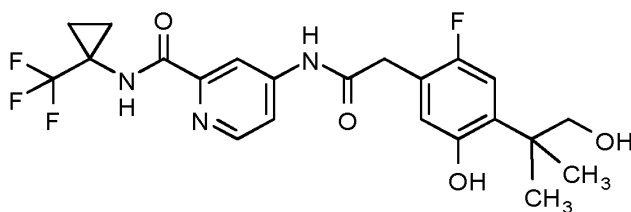


The title compound was prepared from 2-[5-benzyloxy-4-(1,1-dimethyl-2-morpholino-ethyl)-2-fluoro-phenyl]acetic acid (Intermediate E) and 4-amino-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide (Intermediate AB) analogously to Example 2 steps 1 and 2. LC-MS (Method A): Rt 1.70 mins; MS m/z 498.3 = [M+H]⁺ (99% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 11.56 (s, 1H), 10.82 (s, 1H), 8.84 (s, 1H), 8.52 (d, J = 5.5 Hz, 1H), 8.23 (d, J = 2.0 Hz, 1H), 7.85 (dd, J = 5.5, 2.2 Hz, 1H), 6.86 (d, J = 12.1 Hz, 1H), 6.71 (d, J = 7.1 Hz, 1H), 3.66 (s, 2H), 3.57 – 3.49 (m, 4H), 2.64 (s, 2H), 2.48 – 2.41 (m, 4H), 1.72 (s, 6H), 1.31 (s, 6H).

Example 2.6

4-[[2-[2-Fluoro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetyl] amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide



The title compound was prepared from 4-amino-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Intermediate A) and 2-[5-benzyloxy-2-fluoro-4-(2-hydroxy-1,1-dimethyl-ethyl)-

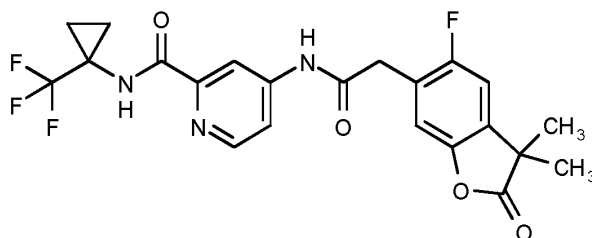
ethyl)phenyl]acetic acid (Intermediate L) analogously to Example 2 steps 1 and 2.

LC-MS (Method A): Rt 2.99 mins; MS m/z 470.2 = [M+H]⁺ (99% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.79 (s, 1H), 9.39 (s, 1H), 9.38 (s, 1H), 8.50 (d, J = 5.5 Hz, 1H), 8.21 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 6.90 (d, J = 12.1 Hz, 1H),
 5 6.72 (d, J = 7.0 Hz, 1H), 4.75 (t, J = 5.3 Hz, 1H), 3.64 (s, 2H), 3.60 (d, J = 5.0 Hz, 2H),
 1.32 – 1.28 (m, 2H), 1.25 (s, 6H), 1.21 – 1.16 (m, 2H).

The title compound was also prepared according to the following method:

Step 1: 4-[[2-(5-Fluoro-3,3-dimethyl-2-oxo-benzofuran-6-yl)acetyl]amino]-N-[1-(trifluoro
 10 methyl)cyclopropyl]pyridine-2-carboxamide



To a solution of 2-(5-fluoro-3,3-dimethyl-2-oxo-benzofuran-6-yl)acetic acid (Intermediate U) (98%, 1.82 g, 7.5 mmol) and 4-amino-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Intermediate A) (96%, 2.11 g, 8.25 mmol) in DMF (40 mL) was
 15 added DIPEA (3.93 mL, 22.49 mmol) followed by 50% T3P® solution in EtOAc (8.93 mL, 14.99 mmol) and the reaction mixture was stirred at room temperature for 2 h. The resulting mixture was diluted with EtOAc (150 mL) and washed with brine (3 x 150 mL). The combined aqueous washes were extracted with EtOAc (80 mL) and the organic extract washed with brine (3 x 80 mL). The organic extracts were combined, dried over
 20 Na₂SO₄ and concentrated *in vacuo* to afford the title compound as a pale yellow solid.

LC-MS (Method E): Rt 1.24 min; MS m/z 466.2 = [M+H]⁺ (92% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.84 (s, 1H), 9.39 (s, 1H), 8.51 (d, J = 5.5 Hz, 1H), 8.19 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.45 (d, J = 8.9 Hz, 1H), 7.31 (d, J = 5.8 Hz, 1H), 3.83 (s, 2H), 1.45 (s, 6H), 1.32 – 1.28 (m, 2H), 1.21 – 1.16 (m, 2H).

Step 2: 4-[[2-[2-Fluoro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide

To a cooled (-78 °C) solution of 4-[[2-(5-fluoro-3,3-dimethyl-2-oxo-benzofuran-6-yl)acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (step 1) (92%, 3.46 g, 6.84 mmol) in THF (65 mL) was added 4M LiBH₄ in THF (1.88 mL, 7.53 mmol).
 30 The mixture was stirred for 30 min then allowed to gradually warm to room temperature and stirred for 4 h. The resulting mixture was poured onto ice cold 1M HCl (150 mL),

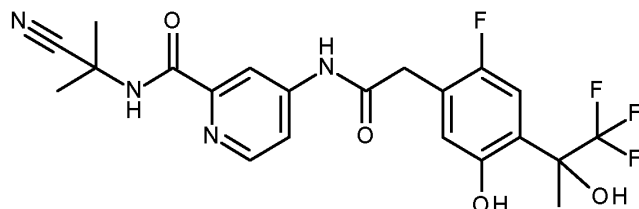
allowed to stand for 20 min and then partitioned between EtOAc (200 mL) and water (100 mL). The phases were separated and the aqueous portion was further extracted with EtOAc (200 mL). The combined organic extracts were washed with saturated NaHCO₃ solution (2 x 150 mL), brine (150 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The crude residue was suspended in EtOAc (~19mL) and filtered, washing the solids with EtOAc (3 x 10 mL). The solids were dried under vacuum for 1 h and then azeotroped with MeCN (2 x 100 mL) to give a white solid. The filtrate from the EtOAc filtration was concentrated *in vacuo* to give a yellow solid which was purified by C18 reverse phase chromatography eluting with MeCN/water 10-100% (0.1% formic acid) to afford an off-white solid. The solids from the EtOAc filtration and from the reverse phase purification were combined and recrystallised from MeCN to afford the title compound as colourless crystalline solid.

LC-MS (Method A): Rt 2.96 min; MS m/z 470.2 = [M+H]⁺ (99% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.80 (s, 1H), 9.57 – 9.20 (m, 2H), 8.50 (d, J = 5.5 Hz, 1H), 8.21 (d, J = 1.9 Hz, 1H), 7.84 (dd, J = 5.5, 2.1 Hz, 1H), 6.90 (d, J = 12.1 Hz, 1H), 6.72 (d, J = 7.0 Hz, 1H), 4.76 (s, 1H), 3.65 (s, 2H), 3.60 (s, 2H), 1.32 – 1.28 (m, 2H), 1.25 (s, 6H), 1.21 – 1.16 (m, 2H).

Example 2.7

N-(1-Cyano-1-methyl-ethyl)-4-[[2-[2-fluoro-5-hydroxy-4-(2,2,2-trifluoro-1-hydroxy-1-methyl-ethyl)phenyl]acetyl]amino]pyridine-2-carboxamide



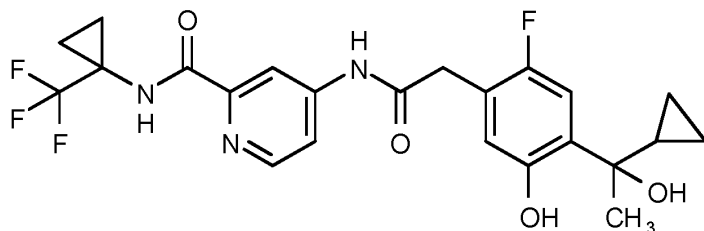
The title compound was prepared from 2-[5-benzyloxy-2-fluoro-4-(2,2,2-trifluoro-1-hydroxy-1-methyl-ethyl)phenyl]acetic acid (Intermediate BA) and 4-amino-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide (Intermediate AB) analogously to Example 2 steps 1 and 2.

LC-MS (Method A): Rt 2.91 mins; MS m/z 469.2 = [M+H]⁺ (97% @ 215 nm)

¹H NMR (400 MHz, DMSO-d₆) δ 10.86 (s, 1H), 8.84 (s, 1H), 8.52 (d, J = 5.5 Hz, 1H), 8.23 (d, J = 1.9 Hz, 1H), 7.85 (dd, J = 5.5, 2.2 Hz, 1H), 7.24 (d, J = 11.4 Hz, 1H), 6.80 (d, J = 6.6 Hz, 1H), 3.72 (s, 2H), 1.79 (s, 3H), 1.72 (s, 6H).

Example 2.8

4-[[2-[4-(1-Cyclopropyl-1-hydroxy-ethyl)-2-fluoro-5-hydroxy-phenyl]acetyl] amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide



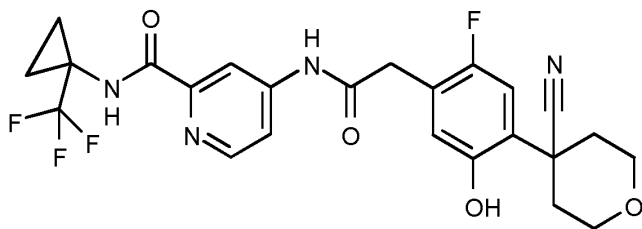
- 5 The title compound was prepared from 2-[5-benzyloxy-4-(1-cyclopropyl-1-hydroxy-ethyl)-2-fluoro-phenyl]acetic acid (Intermediate BB) and 4-amino-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Intermediate A) analogously to Example 2 steps 1 and 2.

LC-MS (Method A): Rt 3.23 mins; MS m/z 482.3 = [M+H]⁺ (98% @ 215 nm)

- 10 ¹H NMR (500 MHz, DMSO-d₆) δ 10.80 (s, 1H), 9.61 (s, 1H), 9.39 (s, 1H), 8.50 (d, J = 5.5 Hz, 1H), 8.21 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.08 (d, J = 11.4 Hz, 1H), 6.72 (d, J = 6.7 Hz, 1H), 5.36 (s, 1H), 3.67 (s, 2H), 1.55 – 1.48 (m, 4H), 1.32 – 1.27 (m, 2H), 1.21 – 1.16 (m, 2H), 0.48 – 0.41 (m, 1H), 0.36 – 0.23 (m, 2H), 0.19 – 0.13 (m, 1H).

Example 2.9

4-[[2-[4-(4-Cyanotetrahydropyran-4-yl)-2-fluoro-5-hydroxy-phenyl]acetyl] amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide



- 20 The title compound was prepared from 2-[5-benzyloxy-4-(4-cyanotetrahydropyran-4-yl)-2-fluoro-phenyl]acetic acid (Intermediate M) and 4-amino-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Intermediate A) analogously to Example 2 steps 1 and 2.

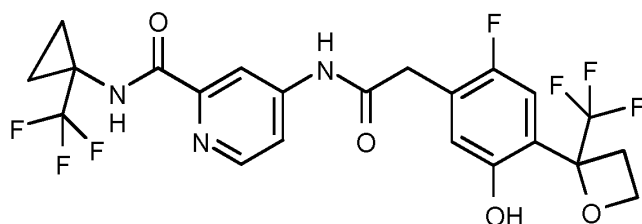
LC-MS (Method A): Rt 2.92 mins; MS m/z 507.2 = [M+H]⁺ (100% @ 215 nm)

- 25 ¹H NMR (500 MHz, DMSO-d₆) δ 10.84 (s, 1H), 10.16 (s, 1H), 9.40 (s, 1H), 8.51 (d, J = 5.5 Hz, 1H), 8.21 (d, J = 2.1 Hz, 1H), 7.84 (dd, J = 5.5, 2.1 Hz, 1H), 7.06 (d, J = 11.0 Hz, 1H), 6.90 (d, J = 6.7 Hz, 1H), 4.01 – 3.93 (m, 2H), 3.73 (s, 2H), 3.68 (m, 2H), 2.32-2.27 (m, 2H),

2.00 (td, J = 13.2, 4.2 Hz, 2H), 1.32-1.28 (m, 2H), 1.21-1.16 (m, 2H).

Example 2.10

4-[[2-[2-Fluoro-5-hydroxy-4-[2-(trifluoromethyl)oxetan-2-yl]phenyl] acetyl]amino]-N-
5 [1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide



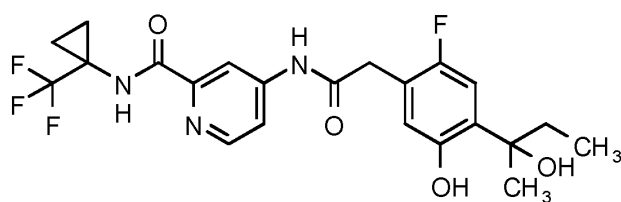
The title compound was prepared from 2-[5-benzyloxy-2-fluoro-4-[2-(trifluoromethyl)oxetan-2-yl]phenyl]acetic acid (Intermediate N) and 4-amino-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Intermediate A) analogously to
10 Example 2 steps 1 and 2.

LC-MS (Method A): Rt 3.41 mins; MS m/z 522.4 = [M+H]⁺ (95% @ 215 nm)

¹H NMR (400 MHz, DMSO-*d*₆) δ 10.86 (s, 1H), 9.88 (br. s, 1H), 9.38 (s, 1H), 8.51 (d, J = 5.5 Hz, 1H), 8.22 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 6.96 (d, J = 10.2 Hz, 1H), 6.88 (d, J = 6.3 Hz, 1H), 4.75 – 4.65 (m, 1H), 4.55-4.46 (m, 1H), 3.74 (s, 2H), 3.19 –
15 3.05 (m, 2H), 1.34-1.27 (m, 2H), 1.22-1.16 (m, 2H).

Example 2.11

4-[[2-[2-Fluoro-5-hydroxy-4-(1-hydroxy-1-methyl-propyl)phenyl] acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide



20 The title compound was prepared from 2-[5-benzyloxy-2-fluoro-4-(1-hydroxy-1-methyl-propyl)phenyl]acetic acid (Intermediate BC) and 4-amino-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Intermediate A) analogously to Example 2 steps 1 and 2.

25 LC-MS (Method A): Rt 3.12 mins; MS m/z 470.2 = [M+H]⁺ (100% @ 215 nm)

¹H NMR (500 MHz, DMSO-*d*₆) δ 10.80 (s, 1H), 9.58 (s, 1H), 9.39 (s, 1H), 8.50 (d, J = 5.5 Hz, 1H), 8.21 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.06 (d, J = 11.5 Hz, 1H),

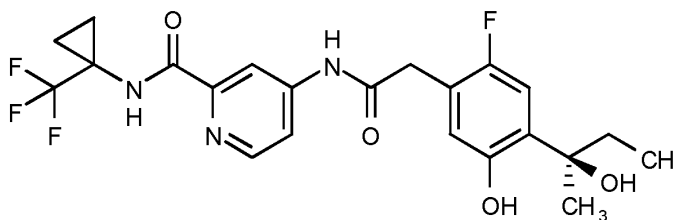
6.70 (d, $J = 6.7$ Hz, 1H), 5.43 (s, 1H), 3.67 (s, 2H), 1.95 (dq, $J = 14.8, 7.4$ Hz, 1H), 1.70 (dq, $J = 14.5, 7.2$ Hz, 1H), 1.46 (s, 3H), 1.33 – 1.27 (m, 2H), 1.22 – 1.16 (m, 2H), 0.69 (t, $J = 7.4$ Hz, 3H).

5 Example 2.11a and 2.11b

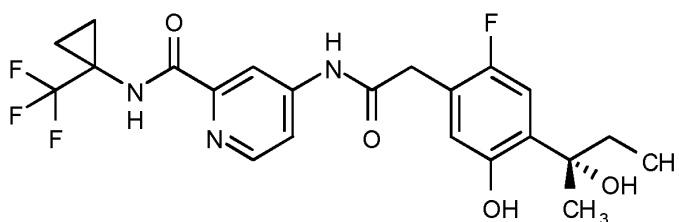
Chiral separation of racemic 4-[[2-[2-fluoro-5-hydroxy-4-(1-hydroxy-1-methyl-propyl)phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Example 2.11) using Chiral HPLC [chiral phase column 95% heptanes : 5% EtOH with Chiralcel OD-H, 4.6 x 250 mm, 5 μ L, @ 0.5 mL/min] afforded the individual enantiomers:

10

Example 2.11a: 4-[[2-[2-Fluoro-5-hydroxy-4-[(1S)-1-hydroxy-1-methyl-propyl]phenyl]acetyl] amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide or 4-[[2-[2-fluoro-5-hydroxy-4-[(1R)-1-hydroxy-1-methyl-propyl]phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl] pyridine-2-carboxamide



(*R*)-isomer



(*S*)-isomer

15

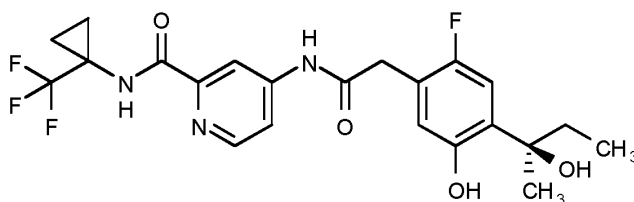
First Eluted Peak: Chiral HPLC Retention Time = 44.37 min

LC-MS (Method A): Rt 3.15 min; MS m/z 470.4 = [M+H]⁺ (98% @ 215 nm)

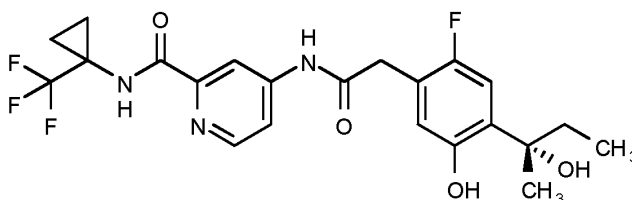
¹H NMR (500 MHz, DMSO-d₆) δ 10.80 (s, 1H), 9.58 (br. s, 1H), 9.39 (s, 1H), 8.50 (d, J = 5.5 Hz, 1H), 8.21 (d, J = 2.1 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.06 (d, J = 11.5 Hz, 1H), 6.70 (d, J = 6.7 Hz, 1H), 5.45 (br. s, 1H), 3.66 (s, 2H), 1.95 (dq, J = 14.8, 7.4 Hz, 1H),
 5 1.70 (dq, J = 14.4, 7.2 Hz, 1H), 1.46 (s, 3H), 1.36 – 1.25 (m, 2H), 1.25 – 1.16 (m, 2H), 0.69 (t, J = 7.4 Hz, 3H).

Example 2.11b:

4-[[2-[2-Fluoro-5-hydroxy-4-[(1S)-1-hydroxy-1-methyl-propyl]phenyl]acetyl] amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide or
 10 4-[[2-[2-fluoro-5-hydroxy-4-[(1R)-1-hydroxy-1-methyl-propyl]phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl] pyridine-2-carboxamide



(*R*)-isomer

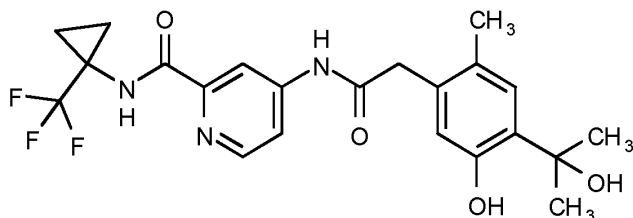


(*S*)-isomer

Second Eluted Peak: Chiral HPLC Retention Time = 50.81 min

LC-MS (Method A): Rt 3.15 min; MS m/z 470.4 = [M+H]⁺ (98% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.80 (s, 1H), 9.60 (br. s, 1H), 9.39 (s, 1H), 8.50 (d, J = 5.5 Hz, 1H), 8.21 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.06 (d, J = 11.5 Hz, 1H), 6.70 (d, J = 6.7 Hz, 1H), 5.44 (br. s, 1H), 3.67 (s, 2H), 1.95 (dq, J = 14.7, 7.4 Hz, 1H),
 15 1.70 (dq, J = 14.6, 7.3 Hz, 1H), 1.46 (s, 3H), 1.32 – 1.26 (m, 2H), 1.23 – 1.15 (m, 2H), 0.69 (t, J = 7.4 Hz, 3H).

Example 2.12**4-[[2-[5-Hydroxy-4-(1-hydroxy-1-methyl-ethyl)-2-methyl-phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide**

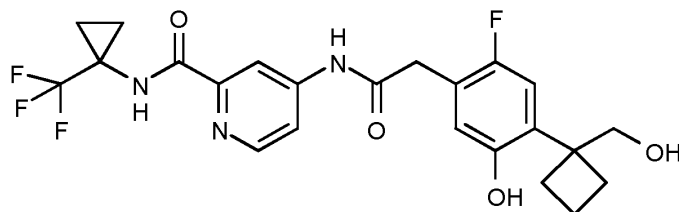
- 5 The title compound was prepared from 2-[5-benzyloxy-4-(1-hydroxy-1-methyl-ethyl)-2-methyl-phenyl]acetic acid (Intermediate BD) and 4-amino-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Intermediate A) analogously to Example 2 steps 1 and 2.

LC-MS (Method A): Rt 3.00 min; MS m/z 452.2 = [M+H]⁺ (100% @ 215 nm)

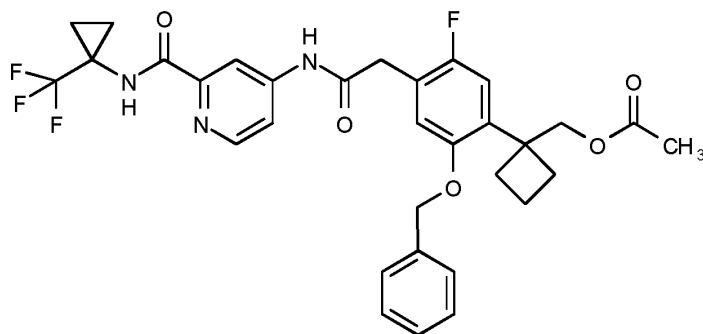
- 10 ¹H NMR (400 MHz, DMSO-d₆) δ 10.72 (s, 1H), 9.50 (s, 1H), 9.37 (s, 1H), 8.49 (d, J = 5.5 Hz, 1H), 8.21 (d, J = 1.9 Hz, 1H), 7.85 (dd, J = 5.5, 2.2 Hz, 1H), 7.04 (s, 1H), 6.63 (s, 1H), 5.76 (s, 1H), 3.61 (s, 2H), 2.16 (s, 3H), 1.48 (s, 6H), 1.33-1.27 (m, 2H), 1.22-1.15 (m, 2H).

Example 2.13

- 15 **4-[[2-[2-Fluoro-5-hydroxy-4-[1-(hydroxymethyl)cyclobutyl]phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide**



Step 1: [1-[2-Benzyloxy-5-fluoro-4-[2-oxo-2-[[2-[[1-(trifluoromethyl)cyclopropyl]carbamoyl]-4-pyridyl]amino]ethyl]phenyl]cyclobutyl]methyl acetate



To a solution of 2-[4-[1-(acetoxymethyl)cyclobutyl]-5-benzyloxy-2-fluoro-phenyl]acetic acid (Intermediate CA)(94%, 142 mg, 0.35 mmol) and 4-amino-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Intermediate A) (93 mg, 0.38 mmol) in 1,4-dioxane (2 mL) was added DIPEA (91 μ L, 0.52 mmol) followed by 50% T3P® solution in EtOAc (0.31 mL, 0.52 mmol) and the mixture was stirred at room temperature overnight. The resulting mixture was diluted with EtOAc (10 mL) and washed sequentially with 1M HCl (10 mL), sat. NaHCO₃ (10 mL) solution and brine (10 mL). The organic portion was dried over Na₂SO₄ and concentrated *in vacuo*. The crude material was purified by chromatography on silica eluting with 0-50% EtOAc in heptanes to afford the title compound as a pale yellow powder.

LC-MS (Method E): Rt 1.44 min; MS m/z 614.4 = [M+H]⁺ (99% @ 215 nm)

¹H NMR (400 MHz, DMSO-d₆) δ 10.81 (s, 1H), 9.38 (s, 1H), 8.51 (d, J = 5.5 Hz, 1H), 8.21 (d, J = 2.1 Hz, 1H), 7.85 (dd, J = 5.5, 2.2 Hz, 1H), 7.46 – 7.41 (m, 2H), 7.40 – 7.35 (m, 2H), 7.34 – 7.29 (m, 1H), 7.09 (d, J = 6.3 Hz, 1H), 6.82 (d, J = 10.4 Hz, 1H), 5.04 (s, 2H), 4.31 (s, 2H), 3.76 (s, 2H), 2.35 – 2.27 (m, 2H), 2.18 – 2.11 (m, 2H), 2.07 – 1.97 (m, 1H), 1.90 (s, 3H), 1.78 – 1.70 (m, 1H), 1.31 – 1.17 (m, 4H).

Step 2: 4-[[2-[2-Fluoro-5-hydroxy-4-[1-(hydroxymethyl)cyclobutyl]phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide

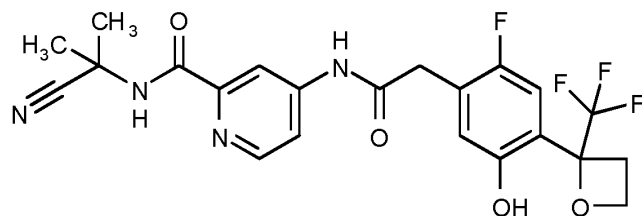
To a solution of [1-[2-benzyloxy-5-fluoro-4-[2-oxo-2-[[2-[[1-(trifluoromethyl)cyclopropyl]carbamoyl]-4-pyridyl]amino]ethyl]phenyl]cyclobutyl]methyl acetate (step 1)(99%, 135 mg, 0.22 mmol) in MeOH (1 mL) was added K₂CO₃ (33 mg, 0.24 mmol) and the mixture stirred at room temperature for 2 h. The resulting mixture was filtered through Celite® and washed through with MeOH (1 mL). To the filtrate was added 10% Pd/C (14 mg, 0.01 mmol) and the mixture placed under an atmosphere of H₂ and stirred for 2 h. The resulting mixture was filtered through Celite® and washed through with MeOH. The filtrate was concentrated *in vacuo* and purification of the crude material by chromatography on silica eluting with 50-100% EtOAc in heptanes afforded the title compound as a colourless powder.

LC-MS (Method A): Rt 3.10 min; MS m/z 482.3 = [M+H]⁺ (94% @ 215 nm)

¹H NMR (400 MHz, DMSO-d₆) δ 10.79 (s, 1H), 9.38 (s, 1H), 9.01 (s, 1H), 8.50 (d, J = 5.5 Hz, 1H), 8.22 (d, J = 1.9 Hz, 1H), 7.84 (dd, J = 5.5, 2.1 Hz, 1H), 6.69 (d, J = 6.7 Hz, 1H), 6.65 (d, J = 10.8 Hz, 1H), 4.84 (t, J = 5.4 Hz, 1H), 3.65 (s, 2H), 3.62 (d, J = 5.6 Hz, 2H), 2.21 – 2.16 (m, 4H), 2.00 – 1.90 (m, 1H), 1.74 – 1.67 (m, 1H), 1.32 – 1.27 (m, 2H), 1.21 – 1.17 (m, 2H).

Example 2.14

N-(1-Cyano-1-methyl-ethyl)-4-[[2-[2-fluoro-5-hydroxy-4-[2-(trifluoromethyl)oxetan-2-yl]]phenyl]acetyl]amino]pyridine-2-carboxamide



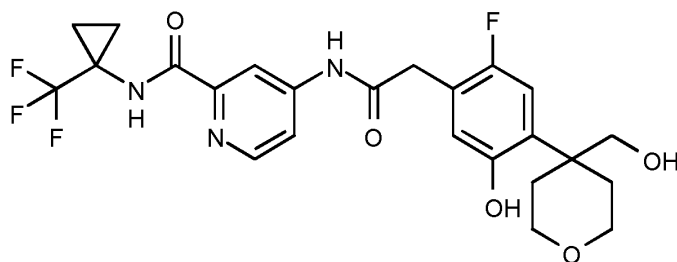
- 5 The title compound was prepared from 2-[5-benzyloxy-2-fluoro-4-[2-(trifluoromethyl)oxetan-2-yl]]phenyl]acetic acid (Intermediate N) and 4-amino-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide (Intermediate AB) analogously to Example 2 steps 1 and 2.

LC-MS (Method A): Rt 3.11 min; MS m/z 481.4 = [M+H]⁺ (100% @ 215 nm)

- 10 ¹H NMR (500 MHz, DMSO-d₆) δ 10.89 (s, 1H), 9.83 (s, 1H), 8.85 (s, 1H), 8.53 (d, J = 5.5 Hz, 1H), 8.24 (d, J = 2.0 Hz, 1H), 7.86 (dd, J = 5.5, 2.2 Hz, 1H), 6.97 (d, J = 10.1 Hz, 1H), 6.88 (d, J = 6.3 Hz, 1H), 4.73 – 4.66 (m, 1H), 4.55 – 4.48 (m, 1H), 3.76 (s, 2H), 3.18 – 3.06 (m, 2H), 1.72 (s, 6H).

15 **Example 2.15**

4-[[2-[2-Fluoro-5-hydroxy-4-[4-(hydroxymethyl)tetrahydropyran-4-yl]]phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide



- 20 The title compound was prepared from 2-[4-[4-(acetoxymethyl)tetrahydropyran-4-yl]-5-benzyloxy-2-fluoro-phenyl]acetic acid (Intermediate CB) and 4-amino-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Intermediate A) analogously to Example 2 steps 1 and 2.

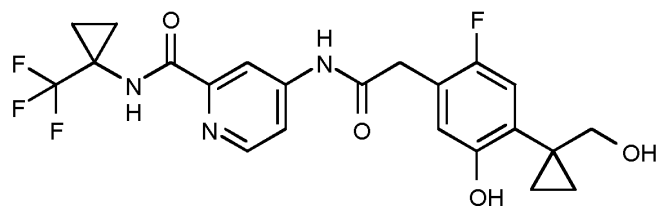
LC-MS (Method A): Rt 2.56 min; MS m/z 512.1 = [M+H]⁺ (100% @ 215 nm)

- 25 ¹H NMR (500 MHz, DMSO-d₆) δ 10.82 (s, 1H), 9.40 (d, J = 6.9 Hz, 2H), 8.51 (d, J = 5.5 Hz, 1H), 8.22 (d, J = 1.9 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 6.88 (d, J = 12.2 Hz, 1H), 6.76 (d, J = 7.0 Hz, 1H), 4.61 (t, J = 5.2 Hz, 1H), 3.70 – 3.61 (m, 6H), 3.43 – 3.37 (m, 2H),

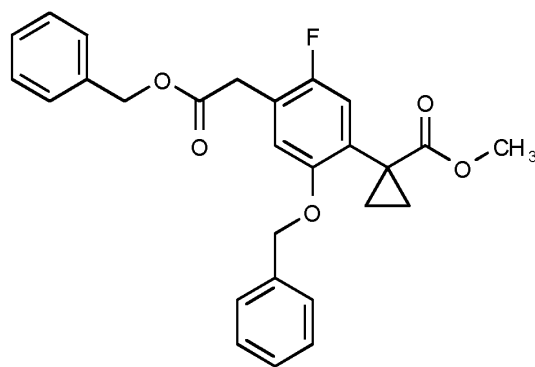
2.26 – 2.17 (m, 2H), 1.83 (ddd, J = 13.3, 9.3, 3.6 Hz, 2H), 1.33 – 1.27 (m, 2H), 1.22 – 1.15 (m, 2H).

Example 2.16

5 4-[[2-[2-Fluoro-5-hydroxy-4-[1-(hydroxymethyl)cyclopropyl]phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide



Step 1: Methyl 1-[2-benzyloxy-4-(2-benzyloxy-2-oxo-ethyl)-5-fluoro-phenyl]cyclopropanecarboxylate



10

Activated zinc (1.066 g, 16.31 mmol) in THF (54.35 mL) was heated at 65 °C and treated with bromine (70 μ L, 1.22 mmol) and stirred until the red colour had dissipated. Methyl 1-bromocyclopropanecarboxylate (21.89 g, 12.23 mmol) was added and the mixture was heated at 70 °C for 2 h. The mixture was then cooled to room temperature and allowed to settle to help remove any remaining Zn dust.

15

A separate vessel was charged with Pd(dba)₂ (234 mg, 0.41 mmol), Q-Phos (290 mg, 0.41 mmol) and benzyl 2-(5-benzyloxy-4-bromo-2-fluoro-phenyl)acetate (Intermediate S, step 2) (3.5 g, 8.15 mmol) and placed under a nitrogen atmosphere. To this mixture, transferred by syringe, was added the freshly prepared Negishi reagent and the reaction mixture was stirred at 65 °C for 3 h. The resulting mixture was concentrated *in vacuo* and purification by chromatography on silica eluting with 0-30% EtOAc in heptanes (repeated twice) afforded the title compound as a pale pink solid.

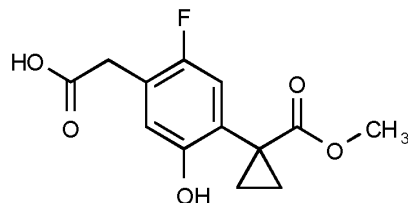
20

LC-MS (Method I): Rt 0.77 min; MS m/z 466.3 = [M+NH₄]⁺ (97% @ 215 nm)

¹H NMR (400 MHz, DMSO-d₆) δ 7.40 – 7.31 (m, 10H), 7.11 – 7.06 (m, 2H), 5.14 (s, 2H),

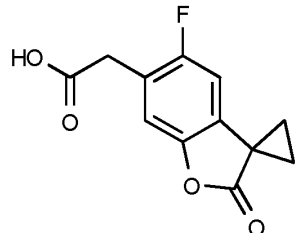
5.06 (s, 2H), 3.76 (s, 2H), 3.48 (s, 3H), 1.47 – 1.41 (m, 2H), 1.18 – 1.13 (m, 2H).

Step 2: 2-[2-Fluoro-5-hydroxy-4-(1-methoxycarbonylcyclopropyl)phenyl]acetic acid



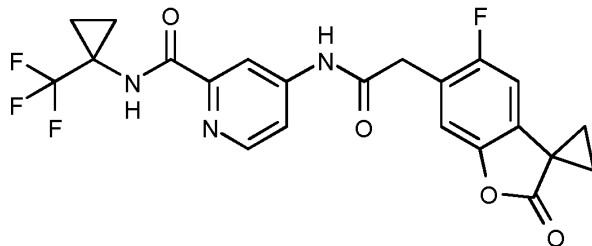
- A mixture of methyl 1-[2-benzyloxy-4-(2-benzyloxy-2-oxo-ethyl)-5-fluoro-phenyl]cyclopropanecarboxylate (step 1) (97%, 3.64 g, 7.88 mmol) in EtOH (60 mL) was treated with 10% Pd/C (50% in water) (15.38 g, 0.72 mmol), placed under a hydrogen atmosphere and stirred at room temperature for 4 h. The resulting mixture was filtered through Celite®, washing with EtOAc, and concentrated *in vacuo* to afford the title compound as a pale yellow soft glass.
- LC-MS (Method G): Rt 0.69 min; MS m/z 269.1 = $[M+H]^+$ (94% @ 215 nm)
- ^1H NMR (400 MHz, DMSO- d_6) δ 12.42 (br. s, 1H), 9.36 (s, 1H), 6.91 (d, J = 10.3 Hz, 1H), 6.69 (d, J = 6.7 Hz, 1H), 3.52 (s, 3H), 3.49 (s, 2H), 1.44 – 1.39 (m, 2H), 1.12 – 1.06 (m, 2H).

Step 3: 2-(5-Fluoro-2-oxo-spiro[benzofuran-3,1'-cyclopropane]-6-yl)acetic acid



- 2-[2-Fluoro-5-hydroxy-4-(1-methoxycarbonylcyclopropyl)phenyl]acetic acid (step 2) (94%, 2.8 g, 9.81 mmol) in THF (10 mL) was treated with 1M KOH (29.44 mL, 29.44 mmol) at room temperature and stirred for 2 h. The resulting mixture was treated with 1M aq. HCl (39.25 mL, 39.25 mmol) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in THF (20 mL), treated with 4M HCl in dioxane (3.46 mL, 98.12 mmol) and heated at 80 °C for 1 h. Additional 4 M HCl in dioxane (10 mL) was added and stirring continued at 80 °C for 1 h. After cooling to room temperature, the mixture was concentrated *in vacuo* to afford the title compound as an off-white solid.
- LC-MS (Method E): Rt 0.98 min; (83% @ 215 nm)
- ^1H NMR (400 MHz, DMSO- d_6) δ 12.46 (br. s, 1H), 7.27 (d, J = 5.8 Hz, 1H), 7.12 – 7.08 (m, 1H), 3.64 (d, J = 1.6 Hz, 2H), 1.89 – 1.84 (m, 2H), 1.76 – 1.71 (m, 2H).

Step 4: 4-[[2-(5-Fluoro-2-oxo-spiro[benzofuran-3,1'-cyclopropane]-6-yl)acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide



2-(5-Fluoro-2-oxo-spiro[benzofuran-3,1'-cyclopropane]-6-yl)acetic acid (step 3) (83%,
 5 1.860 g, 6.54 mmol) and 4-amino-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Intermediate A) (1.76 g, 7.19 mmol) in 1,4-dioxane (40 mL) were treated with DIPEA (3.42 mL, 19.61 mmol) and 50% T3P® solution in EtOAc (7.78 mL, 13.07 mmol) and the mixture was stirred at room temperature for 45 min. The resulting mixture was partitioned between water (150 mL) and EtOAc (150 mL) and the phases were
 10 separated. The aqueous portion was back-extracted with EtOAc (150 mL) then the combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo* to afford the title compound as a beige solid.

LC-MS (Method E): Rt 1.20 min; MS m/z 464.2 = [M+H]⁺ (98% @ 215 nm)

¹H NMR (400 MHz, DMSO-d₆) δ 10.81 (s, 1H), 9.38 (s, 1H), 8.50 (d, J = 5.5 Hz, 1H), 8.19
 15 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.5, 2.1 Hz, 1H), 7.33 (d, J = 5.8 Hz, 1H), 7.12 (d, J = 9.0 Hz, 1H), 3.83 (s, 2H), 1.90 – 1.84 (m, 2H), 1.78 – 1.73 (m, 2H), 1.33 – 1.26 (m, 2H), 1.21 – 1.16 (m, 2H).

Step 5: 4-[[2-[2-Fluoro-5-hydroxy-4-[1-(hydroxymethyl)cyclopropyl]phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide

20 To a cooled (-78 °C) solution of 4-[[2-(5-fluoro-2-oxo-spiro[benzofuran-3,1'-cyclopropane]-6-yl)acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (step 4) (98%, 3.12 g, 6.59 mmol) in THF (70 mL) was added dropwise 4M LiBH₄ in THF (1.81 mL, 7.25 mmol). The mixture was stirred at -78 °C for 10 min, then allowed to warm gradually to room temperature and stirred at room temperature for 5 h. The resulting mixture was
 25 cooled to 0 °C with an ice bath and quenched by the dropwise addition of 1M HCl (70 mL). The resulting mixture was warmed to room temperature, diluted with EtOAc (300 mL) and water (230 mL) and the phases were separated. The aqueous portion was extracted with EtOAc (300 mL) and the combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo* to give the crude product as a beige solid. The solid was
 30 recrystallised from EtOAc (~25 mL) to afford a white powdery solid. The mother liquor was

concentrated *in vacuo* to give a yellow solid which was purified by C18 reverse phase chromatography eluting with MeCN/water 10-100% (0.1% formic acid) to afford an off-white solid.

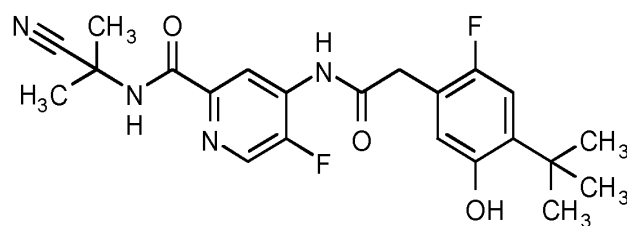
The material from the EtOAc crystallization and the reverse phase purification were combined in MeCN and concentrated *in vacuo*. The solids were azeotroped with MeCN then recrystallised from MeCN and dried in a high vacuum oven at ~40°C overnight to afford the title compound as a white solid.

LC-MS (Method A): Rt 2.84 min; MS m/z 468.3 = [M+H]⁺ (99% @ 215 nm)

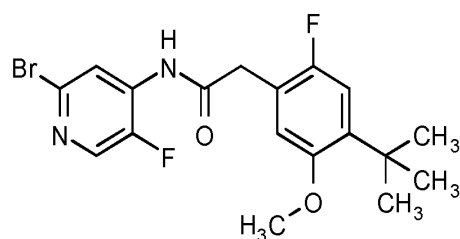
¹H NMR (400 MHz, DMSO-d₆) δ 10.79 (s, 1H), 9.38 (s, 1H), 9.24 (s, 1H), 8.51 (d, J = 5.5 Hz, 1H), 8.21 (d, J = 1.9 Hz, 1H), 7.85 (dd, J = 5.5, 2.2 Hz, 1H), 6.89 (d, J = 10.4 Hz, 1H), 6.75 (d, J = 6.7 Hz, 1H), 4.99 (t, J = 5.4 Hz, 1H), 3.67 (s, 2H), 3.47 (d, J = 5.3 Hz, 2H), 1.35 – 1.27 (m, 2H), 1.23 – 1.14 (m, 2H), 0.83 – 0.73 (m, 2H), 0.68 – 0.58 (m, 2H).

Example 3

4-[[2-(4-*tert*-Butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-1-methyl-ethyl)-5-fluoro-pyridine-2-carboxamide



Step 1: N-(2-Bromo-5-fluoro-4-pyridyl)-2-(4-*tert*-butyl-2-fluoro-5-methoxy-phenyl)acetamide



20

The title compound was prepared from 2-(4-*tert*-butyl-2-fluoro-5-methoxy-phenyl)acetic acid (Intermediate G) and 2-bromo-5-fluoro-pyridin-4-amine analogously to Example 1 step 1. DIPEA was replaced with TEA.

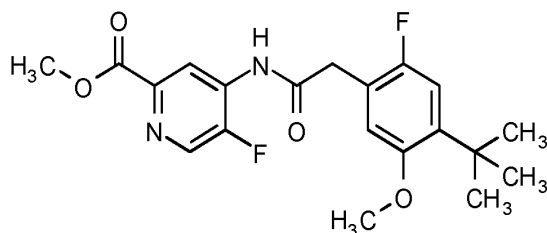
LC-MS (Method E): Rt 1.38 mins; MS m/z 413.0, 415.0 = [M+H]⁺ (94 % @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.67 (s, 1H), 8.41 (d, J = 2.6 Hz, 1H), 8.38 (d, J = 5.8 Hz, 1H), 6.98 (d, J = 6.7 Hz, 1H), 6.95 (d, J = 11.8 Hz, 1H), 3.87 (s, 2H), 3.78 (s, 3H), 1.31

25

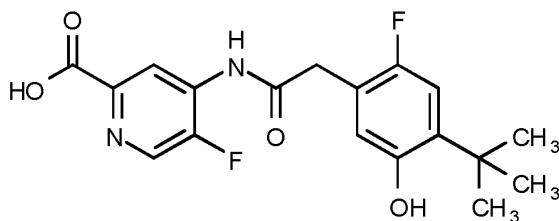
(s, 9H).

Step 2: Methyl 4-[[2-(4-*tert*-butyl-2-fluoro-5-methoxy-phenyl)acetyl]amino]-5-fluoro-pyridine-2-carboxylate



- 5 All reagents charged to COWare gas reactor system (two-chamber glass apparatus) according to the following procedure;
Chamber A was charged with N-(2-bromo-5-fluoro-4-pyridyl)-2-(4-*tert*-butyl-2-fluoro-5-methoxy-phenyl) acetamide (step 1) (500 mg, 1.21 mmol), Pd(dppf)Cl₂ (85 mg, 0.12 mmol) and the apparatus was flushed with nitrogen. To chamber B, a solution of formic acid (320
10 μ L, 8.47 mmol) and methanesulfonyl chloride (656 μ L, 8.47 mmol) in degassed toluene (5 mL) was added. Then a solution of TEA (423 μ L, 2.42 mmol) in MeOH (5 mL) was added to chamber A followed by the addition of TEA (2.96 mL, 16.94 mmol) to chamber B to generate carbon monoxide. The COWare equipment was heated to 60 °C for 16 h. The resulting mixture from chamber A was partitioned between EtOAc (100 mL) and brine (100
15 mL). The phases were separated and the aqueous portion was re-extracted with EtOAc (100 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo* and purification of the crude material by chromatography on silica eluting with 0-100% EtOAc in heptanes afforded the title compound as a pale beige foam.
LC-MS (Method E): Rt 1.25 mins; MS m/z 393.1 = [M+H]⁺ (94% @ 215 nm)
20 ¹H NMR (500 MHz, DMSO-d₆) δ 10.67 (s, 1H), 8.91 (d, J = 6.4 Hz, 1H), 8.66 (d, J = 2.4 Hz, 1H), 6.99 (d, J = 6.7 Hz, 1H), 6.96 (d, J = 11.8 Hz, 1H), 3.87 (s, 2H), 3.85 (s, 3H), 3.79 (s, 3H), 1.32 (s, 9H).

Step 3: 4-[[2-(4-*tert*-Butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-5-fluoro-pyridine-2-carboxylic acid



25

1M BBr₃ in DCM (4.34 mL, 4.34 mmol) was added to a solution of methyl 4-[[2-(4-*tert*-

butyl-2-fluoro-5-methoxy-phenyl)acetyl]amino]-5-fluoro-pyridine-2-carboxylate (step 2) (98%, 348 mg, 0.87 mmol) in DCM (10 mL) and the mixture was stirred at room temperature for 4 h. The resulting mixture was diluted with water (15 mL) and stirred at room temperature for 10 min. The volatile solvent removed *in vacuo* and the resulting mixture diluted with EtOAc (50 mL) and 1:1 water:brine (30 mL). The phases were separated and the aqueous portion was re-extracted with EtOAc (30 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo* to afford the title compound as an off-white solid.

LC-MS (Method E): Rt 1.08 mins; MS m/z 365.1 = [M+H]⁺ (95% @ 215 nm)

¹H NMR (400 MHz, DMSO-d₆) δ 10.61 (s, 1H), 9.30 (s, 1H), 8.90 (d, J = 6.5 Hz, 1H), 8.64 (d, J = 2.4 Hz, 1H), 6.87 (d, J = 11.9 Hz, 1H), 6.73 (d, J = 7.0 Hz, 1H), 3.78 (s, 2H), 1.32 (s, 9H).

Step 4: 4-[[2-(4-*tert*-Butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-1-methyl-ethyl)-5-fluoro-pyridine-2-carboxamide

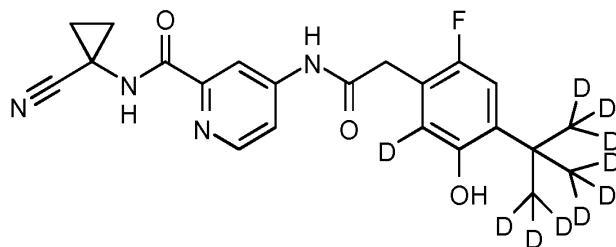
HATU (151 mg, 0.40 mmol) was added to a solution of 4-[[2-(4-*tert*-butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-5-fluoro-pyridine-2-carboxylic acid (step 3) (145 mg, 0.40 mmol), 2-amino-2-methyl-propanenitrile hydrochloride (72 mg, 0.6 mmol) and DIPEA (0.17 mL, 0.99 mmol) in DMF (3 mL) and the reaction mixture was stirred at room temperature for 2 h. The resulting mixture was diluted with EtOAc (20 mL) and water (20 mL) and the phases were separated. The organic portion was washed with brine (20 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Purification of the crude material by preparative HPLC (acidic pH, standard elution method) afforded the title compound as a white solid.

LC-MS (Method A): Rt 3.54 mins; MS m/z 431.2 = [M+H]⁺ (98% @ 215 nm)

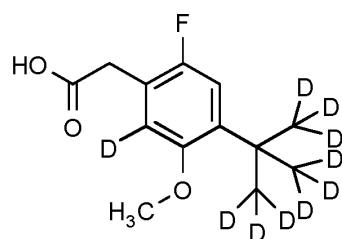
¹H NMR (500 MHz, DMSO-d₆) δ 10.63 (s, 1H), 9.31 (s, 1H), 8.88 (d, J = 6.5 Hz, 1H), 8.82 (s, 1H), 8.61 (d, J = 2.4 Hz, 1H), 6.88 (d, J = 11.9 Hz, 1H), 6.74 (d, J = 6.9 Hz, 1H), 3.79 (s, 2H), 1.71 (s, 6H), 1.32 (s, 9H).

Example 4

N-(1-Cyanocyclopropyl)-4-[[2-[2-deuterio-6-fluoro-3-hydroxy-4-[2,2,2-trideuterio-1,1-bis(trideuteriomethyl)ethyl]phenyl]acetyl]amino]pyridine-2-carboxamide

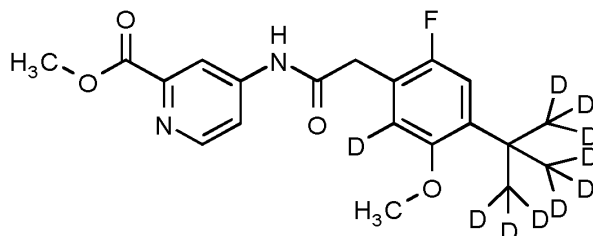


- 5 Step 1: 2-[2-Deuterio-6-fluoro-3-methoxy-4-[2,2,2-trideuterio-1,1-bis(trideuterio methyl)ethyl]phenyl]acetic acid



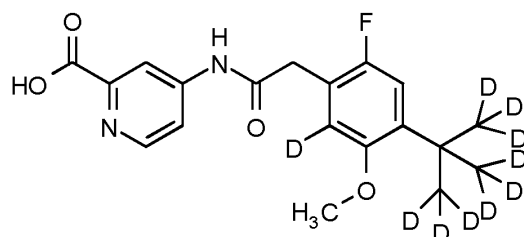
- A vessel containing 2-(2-fluoro-5-methoxy-phenyl)acetic acid (300 mg, 1.63 mmol) in DCE (16 mL) was treated with 1,1,1,3,3,3-hexadeuterio-2-deuteriooxy-2-(trideuteriomethyl) propane (1.23 mL, 13.03 mmol) and deuteriosulfuric acid (0.71 mL, 13.03 mmol) then stirred at room temperature for 3 h. The resulting mixture was diluted with water (20 mL) and the layers separated. The aqueous layer was extracted with DCM (3 x 20 mL) and the combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo*. The residue was dissolved in DCM (15 mL), treated with TFA (1.5 mL), stirred for 2 h and concentrated *in vacuo*. Purification of the resulting mixture by chromatography on silica eluting with 0-100% EtOAc (+1% formic acid) in heptanes (+1% formic acid) afforded the title compound as a colourless solid. (Note: NMR analysis indicated 80% D incorporation in the ortho-position to the phenol, and 97% D incorporation in the *tert*-butyl group.)
- 15
- 20 LC-MS (Method E): Rt 1.18 mins; (75% @ 215 nm)
- ¹H NMR (500 MHz, DMSO-d₆) δ 12.41 (s, 1H), 7.08 (d, J = 9.4 Hz, 0.2H), 6.92 (d, J = 11.7 Hz, 1H), 3.77 (s, 3H), 3.55 (d, J = 1.0 Hz, 2H), 1.25 (s, 0.3H).

Step 2: Methyl 4-[[2-[2-deuterio-6-fluoro-3-methoxy-4-[2,2,2-trideuterio-1,1-bis(trideuteriomethyl)ethyl]phenyl]acetyl]amino]pyridine-2-carboxylate



- A mixture of methyl 4-aminopyridine-2-carboxylate (178 mg, 1.17 mmol) and 2-[2-deuterio-6-fluoro-3-methoxy-4-[2,2,2-trideuterio-1,1-bis(trideuteriomethyl) ethyl]phenyl] acetic acid (step 1) (267 mg, 1.06 mmol) in 1,4-dioxane (10.7 mL) was treated with TEA (0.56 mL, 3.19 mmol) and 50% T3P® solution in EtOAc (0.63 mL, 1.06 mmol) and the mixture was stirred for 16 h. The resulting mixture was concentrated *in vacuo* and the residue was dissolved in EtOAc (30 mL). The mixture was washed with saturated aqueous sodium bicarbonate (2 x 20 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Purification of the crude material by chromatography on silica eluting with 0-100% EtOAc in heptanes followed by 0-100% MeOH in EtOAc afforded the title compound as a colourless oil. (Note: NMR analysis indicated 80% D incorporation in the ortho-position to the phenol, and 97% D incorporation in the *tert*-butyl group.)
- LC-MS (Method E): Rt 1.17 mins; MS m/z 385.1 = [M+H]⁺ (69% @ 215 nm)
- ¹H NMR (500 MHz, DMSO-d₆) δ 10.81 (s, 1H), 8.55 (d, J = 5.5 Hz, 1H), 8.30 (t, J = 2.2 Hz, 1H), 7.77 (dd, J = 5.5, 2.1 Hz, 1H), 6.99 (d, J = 6.65 Hz, 0.2H), 6.95 (d, J = 11.7 Hz, 1H), 3.87 (s, 3H), 3.79 (s, 3H), 3.75 (s, 2H), 1.26 (s, 0.3H).

- Step 3: 4-[[2-[2-Deuterio-6-fluoro-3-hydroxy-4-[2,2,2-trideuterio-1,1-bis(trideuteriomethyl) ethyl]phenyl]acetyl]amino]pyridine-2-carboxylic acid



- Methyl 4-[[2-[2-deuterio-6-fluoro-3-methoxy-4-[2,2,2-trideuterio-1,1-bis (trideuteriomethyl) ethyl]phenyl]acetyl]amino]pyridine-2-carboxylate (step 2) (69%, 471 mg, 0.85 mmol) in THF (4 mL) was treated with 1M LiOH (4.23 mL, 4.23 mmol) and stirred for 2 h.
- The volatile solvents were removed *in vacuo* and the aqueous phase was acidified to pH 1 by addition of 1M HCl. The resulting suspension was extracted with EtOAc (3 x 10 mL)

and the combined organic extracts were concentrated *in vacuo*. The crude material was dissolved in DCM (8 mL), cooled in an ice bath and treated with 1M BBr₃ in DCM (2.54 mL, 2.54 mmol). After stirring for 3 h, the reaction was quenched with water (10 mL) and the phases separated. The aqueous layer was extracted with DCM (2 x 20 mL) and EtOAc (2 x 20 mL) and the combined organic extracts were concentrated *in vacuo*. Purification of the crude material by C18 reverse phase chromatography eluting with 10-100% MeCN in water afforded the title compound as a colourless solid. (Note: NMR analysis indicated 80% D incorporation in the *ortho*-position to the phenol, and 97% D incorporation in the *tert*-butyl group.)

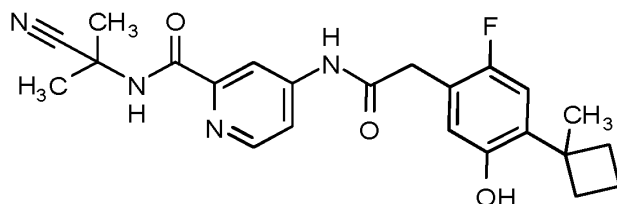
LC-MS (Method E): Rt 0.98 mins; MS m/z 357.1 = [M+H]⁺ (100% @ 215 nm)
¹H NMR (400 MHz, DMSO-d₆) δ 10.79 (s, 1H), 9.29 (s, 1H), 8.54 (d, J = 5.5 Hz, 1H), 8.27 (s, 1H), 7.79 (dd, J = 5.5, 2.1 Hz, 1H), 6.86 (d, J = 11.9 Hz, 1H), 6.74 (d, J = 7.0 Hz, 0.2H), 3.65 (s, 2H), 1.26 (s, 0.3H).

Step 4: N-(1-Cyanocyclopropyl)-4-[[2-[2-deuterio-6-fluoro-3-hydroxy-4-[2,2,2-trideuterio-1,1-bis(trideuteriomethyl)ethyl]phenyl]acetyl]amino]pyridine-2-carboxamide
4-[[2-[2-Deuterio-6-fluoro-3-hydroxy-4-[2,2,2-trideuterio-1,1-bis(trideuterio methyl)ethyl]phenyl]acetyl]amino]pyridine-2-carboxylic acid (step 3) (50 mg, 0.14 mmol) in DMF (1.4 mL) was treated with 1-aminocyclopropane carbonitrile hydrochloride (20 mg, 0.17 mmol), DIPEA (49 µL, 0.28 mmol) and HATU (50.7 mg, 0.13 mmol) and the mixture was stirred at room temperature for 2 h. Purification of the reaction mixture by preparative HPLC (acidic pH, early elution method) afforded the title compound as a colourless solid. (Note: NMR analysis indicated 80% D incorporation in the *ortho*-position to the phenol, and 97% D incorporation in the *tert*-butyl group).

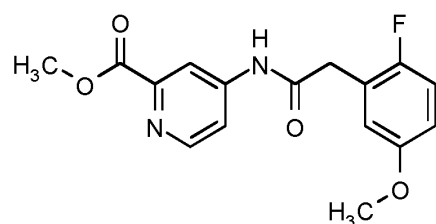
LC-MS (Method C): Rt 3.38 mins; MS m/z 421.3 = [M+H]⁺ (100% @ 215 nm)
¹H NMR (500 MHz, DMSO-d₆) δ 10.82 (s, 1H), 9.67 (s, 1H), 9.30 (s, 1H), 8.51 (d, J = 5.5 Hz, 1H), 8.24 (d, J = 2.1 Hz, 1H), 7.86 (dd, J = 5.5, 2.2 Hz, 1H), 6.87 (d, J = 11.9 Hz, 1H), 6.75 (d, J = 6.9 Hz, 0.2H), 3.66 (s, 2H), 1.57 – 1.51 (m, 2H), 1.37 – 1.30 (m, 2H), 1.27 (s, 0.3H).

30

35

Example 5**N-(1-Cyano-1-methyl-ethyl)-4-[[2-[2-fluoro-5-hydroxy-4-(1-methylcyclobutyl)phenyl]acetyl]amino]pyridine-2-carboxamide**

- 5 **Step 1:** Methyl 4-[[2-(2-fluoro-5-methoxy-phenyl)acetyl]amino]pyridine-2-carboxylate

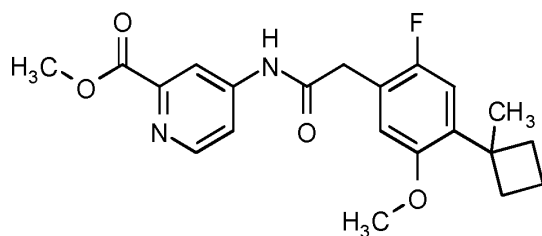


To a solution of methyl 4-aminopyridine-2-carboxylate (3.64 g, 23.89 mmol) and 2-(2-fluoro-5-methoxy-phenyl)acetic acid (4 g, 21.72 mmol) in 1,4-dioxane (108.6 mL) was added TEA (9.48 mL, 54.3 mmol) and 50% T3P® solution in EtOAc (51.67 mL, 43.44 mmol) and the mixture was stirred for 2 h. The resulting mixture was concentrated *in vacuo* and the residue was dissolved in EtOAc (100 mL) and washed with saturated aqueous sodium bicarbonate (2 x 100 mL). The organic portion was dried over Na₂SO₄ and concentrated *in vacuo*. Purification by chromatography on silica eluting with 0%-100% EtOAc in heptanes afforded the title compound as an orange gum.

- 15 LC-MS (Method E): Rt 1.00 mins; MS m/z 319.1 = [M+H]⁺ (100% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.80 (s, 1H), 8.55 (d, J = 5.4 Hz, 1H), 8.30 (d, J = 1.8 Hz, 1H), 7.77 (dd, J = 5.5, 2.2 Hz, 1H), 7.11 (t, J = 9.2 Hz, 1H), 6.96 (dd, J = 6.1, 3.2 Hz, 1H), 6.86 (dt, J = 8.9, 3.7 Hz, 1H), 3.87 (s, 3H), 3.77 (s, 2H), 3.73 (s, 3H).

- 20 **Step 2:** Methyl 4-[[2-[2-fluoro-5-methoxy-4-(1-methylcyclobutyl)phenyl]acetyl]amino]pyridine-2-carboxylate



A solution of methyl 4-[[2-(2-fluoro-5-methoxy-phenyl)acetyl]amino]pyridine-2-

carboxylate (step 1) (200 mg, 0.63 mmol) in DCE (2 mL) was treated with concentrated sulfuric acid (0.27 mL, 5.03 mmol) and the mixture was cooled to 0 °C. To this mixture was added dropwise methylenecyclobutane (214 mg, 3.14 mmol) in DCE (2 mL) and the mixture was stirred at room temperature overnight. The resulting mixture was diluted with DCM (10 mL) and water (10 mL). The organic portion was separated, dried over Na₂SO₄ and concentrated *in vacuo* to afford the title compound as yellow solid.

LC-MS (Method E): Rt 1.22 mins; MS m/z 387.1 = [M+H]⁺ (77% @ 215 nm)

Step 3: N-(1-Cyano-1-methyl-ethyl)-4-[[2-[2-fluoro-5-hydroxy-4-(1-methylcyclobutyl)phenyl]acetyl]amino]pyridine-2-carboxamide

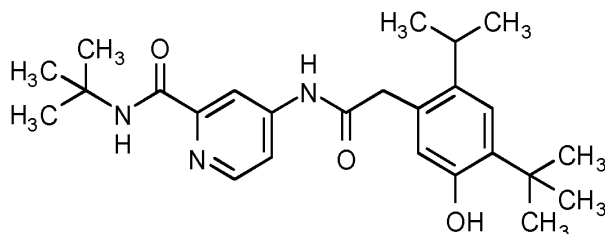
A solution of 1M BBr₃ in DCM (4.05 mL, 4.05 mmol) was added to a cooled (0 °C), stirred solution of methyl 3-[[2-[2-fluoro-5-methoxy-4-(1-methylcyclobutyl)phenyl]acetyl]amino]benzoate (260 mg, 0.67 mmol) under nitrogen, over 2 min. The mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with ice, stirring for 30 min. The organic layer was separated, dried over Na₂SO₄ and concentrated *in vacuo* to afford a brown oil. The oil was dissolved in DMF (1 mL) and 2-amino-2-methylpropanenitrile hydrochloride (36 mg, 0.29 mmol) and DIPEA (86 µL, 0.49 mmol) were added followed by HATU (80.83 mg, 0.21 mmol) and the reaction mixture was stirred at room temperature overnight. The resulting mixture was diluted with EtOAc (10 mL) and water (10 mL). The organic layer was separated, dried over Na₂SO₄ and concentrated *in vacuo*. Purification of the crude material by preparative HPLC (acidic pH, early elution method) afforded the title compound as an off-white solid.

LC-MS (Method A): Rt 3.52 mins; MS m/z 425.3 = [M+H]⁺ (96% @ 215 nm)

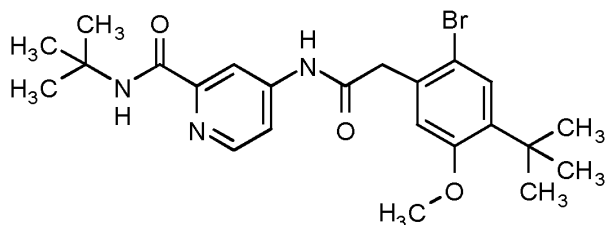
¹H NMR (500 MHz, MeOH -d₄) δ 8.47 (d, J = 5.5 Hz, 1H), 8.19 (d, J = 1.9 Hz, 1H), 7.94 (dd, J = 5.5, 2.1 Hz, 1H), 6.69 – 6.63 (m, 2H), 3.68 (s, 2H), 2.43 – 2.30 (m, 2H), 2.16 – 2.02 (m, 3H), 1.80 (s, 6H), 1.80 – 1.72 (m, 1H), 1.45 (s, 3H).

Example 6

N-*tert*-Butyl-4-[[2-(4-*tert*-butyl-5-hydroxy-2-isopropyl-phenyl)acetyl]amino]pyridine-2-carboxamide



Step 1: 4-[[2-(2-Bromo-4-*tert*-butyl-5-methoxy-phenyl)acetyl]amino]-N-*tert*-butyl-pyridine-2-carboxamide

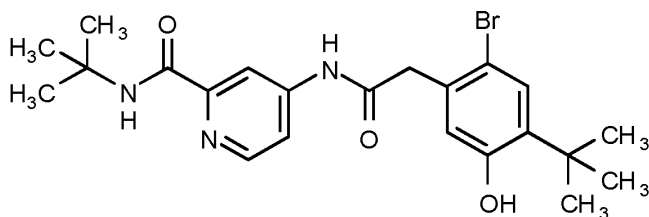


The title compound was prepared from 2-(2-bromo-4-*tert*-butyl-5-methoxy-phenyl)acetic acid (Intermediate F) and 4-amino-N-*tert*-butyl-pyridine-2-carboxamide analogously to Example 1 step 1.

LC-MS (Method E): Rt 1.42 mins; MS m/z 476.1, 478.1 = [M+H]⁺ (96% @ 215 nm)

¹H NMR (400 MHz, DMSO-d₆) δ 10.80 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.17 (d, J = 1.8 Hz, 1H), 8.03 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.30 (s, 1H), 7.09 (s, 1H), 3.86 (s, 2H), 3.81 (s, 3H), 1.40 (s, 9H), 1.32 (s, 9H).

Step 2: 4-[[2-(2-Bromo-4-*tert*-butyl-5-hydroxy-phenyl)acetyl]amino]-N-*tert*-butyl-pyridine-2-carboxamide



The title compound was prepared from 4-[[2-(2-bromo-4-*tert*-butyl-5-methoxy-phenyl)acetyl]amino]-N-*tert*-butyl-pyridine-2-carboxamide (step 1) and 1M BBr₃ in DCM analogously to Example 1 step 2.

LC-MS (Method E): Rt 1.32 mins; MS m/z 462.0, 463.9 = [M+H]⁺ (96% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.79 (s, 1H), 9.66 (s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.20 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 7.24 (s, 1H), 6.83 (s, 1H), 3.75 (s, 2H), 1.40 (s, 9H), 1.33 (s, 9H).

Step 3: N-*tert*-Butyl-4-[[2-(4-*tert*-butyl-5-hydroxy-2-isopropyl-phenyl)acetyl]amino]pyridine-2-carboxamide

A mixture of 4-[[2-(2-bromo-4-*tert*-butyl-5-hydroxy-phenyl)acetyl]amino]-N-*tert*-butyl-pyridine-2-carboxamide (step 2) (96%, 170 mg, 0.35 mmol), 2-isopropenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (119 mg, 0.71 mmol), tripotassium phosphate (300 mg, 1.41 mmol), P(Cy)₃ (40 mg, 0.14 mmol) and Pd(OAc)₂ (16 mg, 0.07 mmol) under nitrogen

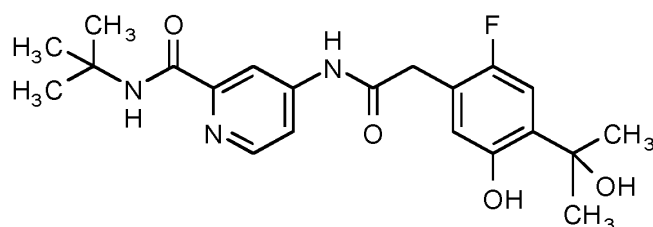
was dissolved in degassed 10:1 toluene:water (2.2 mL) and the mixture was heated at 100 °C for 4 h. The resulting mixture was concentrated *in vacuo* and the residue dissolved in EtOAc (10 mL). The mixture was washed with water (10 mL) and the aqueous wash was re-extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo*. The crude mixture was filtered through a plug of silica, washing through with EtOAc and concentrated *in vacuo*. The residue was dissolved in EtOH (2 mL) and treated with 10% Pd/C (38 mg, 0.35 mmol). The mixture was placed under a hydrogen atmosphere and stirred for 24 h. The resulting mixture was filtered through a Celite® plug, washing through with EtOAc and the filtrate was concentrated *in vacuo*. Purification by preparative HPLC (acidic pH, early elution method) afforded the title compound as a colourless solid.

LC-MS (Method A): Rt 4.32 mins; MS m/z 426.4 = [M+H]⁺ (100% @ 215 nm)

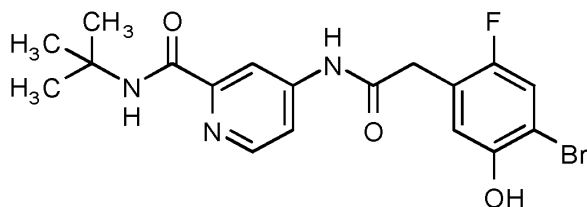
¹H NMR (500 MHz, DMSO-d₆) δ 10.72 (s, 1H), 9.03 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.20 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.03 (s, 1H), 6.62 (s, 1H), 3.64 (s, 2H), 3.05 (hept, J = 6.9 Hz, 1H), 1.40 (s, 9H), 1.33 (s, 9H), 1.12 (d, J = 6.8 Hz, 6H).

Example 7

N-tert-Butyl-4-[[2-[2-fluoro-5-hydroxy-4-(1-hydroxy-1-methyl-ethyl)phenyl]acetyl]amino]pyridine-2-carboxamide



Step 1: 4-[[2-(4-Bromo-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide

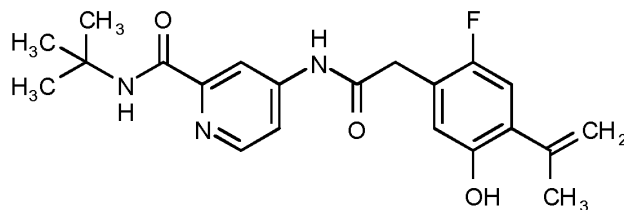


The title compound was prepared from 4-[[2-(4-bromo-2-fluoro-5-methoxy-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Intermediate I) and 1M BBr₃ in DCM analogously to Example 1 step 2.

LC-MS (Method A): Rt 3.28 mins; MS m/z 424.1, 426.1 = [M+H]⁺ (93% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.79 (s, 1H), 10.15 (s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.79 (dd, J = 5.5, 2.2 Hz, 1H), 7.40 (d, J = 9.0 Hz, 1H), 6.95 (d, J = 6.9 Hz, 1H), 3.71 (s, 2H), 1.40 (s, 9H).

- 5 Step 2: N-*tert*-Butyl-4-[[2-(2-fluoro-5-hydroxy-4-isopropenyl-phenyl)acetyl]amino]pyridine-2-carboxamide



- The title compound was prepared from 4-[[2-(4-bromo-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-*tert*-butyl-pyridine-2-carboxamide (step 1) and 2-isopropenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane analogously to Example 8 step 1.

LC-MS (Method A): Rt 3.56 mins; MS m/z 386.2 = [M+H]⁺ (91% @ 215 nm)

- ¹H NMR (500 MHz, DMSO-d₆) δ 10.78 (s, 1H), 9.43 (s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.19 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 6.91 (d, J = 10.6 Hz, 1H), 6.80 (d, J = 6.7 Hz, 1H), 5.22 – 5.19 (m, 1H), 5.14 – 5.11 (m, 1H), 3.69 (s, 2H), 2.06 (s, 3H), 1.40 (s, 9H).

Step 3: N-*tert*-Butyl-4-[[2-[2-fluoro-5-hydroxy-4-(1-hydroxy-1-methyl-ethyl)phenyl]acetyl]amino]pyridine-2-carboxamide

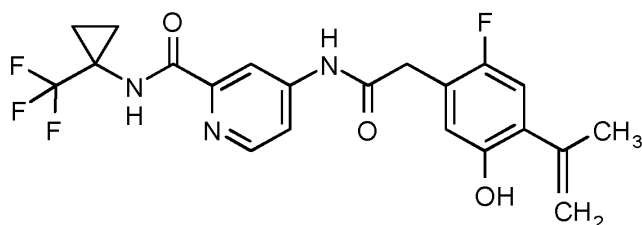
- A solution of N-*tert*-butyl-4-[[2-(2-fluoro-5-hydroxy-4-isopropenyl-phenyl)acetyl]amino]pyridine-2-carboxamide (step 2) (50 mg, 0.13 mmol) in water (2.5 mL) and 1,4-dioxane (5 mL) was treated with methanesulfonic acid (842 μL, 12.97 mmol) and stirred at 30 °C for 24 h. After standing at room temperature overnight, the mixture was partitioned between EtOAc (20 mL) and water (20 mL). The layers were separated and the aqueous portion further extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over Na₂SO₄ and concentrated *in vacuo*.
- 25 The crude material was purified by preparative HPLC (acidic pH, early elution method) to afford the title compound as a white solid.

LC-MS (Method A): Rt 2.99 mins; MS m/z 404.3 = [M+H]⁺ (100% @ 215 nm)

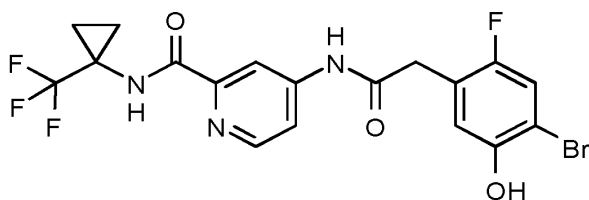
- ¹H NMR (500 MHz, MeOH -d₄) δ 8.43 (dd, J = 5.6, 0.5 Hz, 1H), 8.13 (dd, J = 2.2, 0.5 Hz, 1H), 7.90 (dd, J = 5.5, 2.2 Hz, 1H), 7.00 (d, J = 11.2 Hz, 1H), 6.73 (d, J = 6.6 Hz, 1H), 3.70 (s, 2H), 1.58 (s, 6H), 1.47 (s, 9H).

Example 7.1

4-[[2-(2-Fluoro-5-hydroxy-4-isopropenyl-phenyl)acetyl]amino]-N-[1-(trifluoromethyl) cyclopropyl]pyridine-2-carboxamide



- 5 Step 1: 4-[2-(4-Bromo-2-fluoro-5-hydroxyphenyl)acetamido]-N-[1-(trifluoromethyl) cyclopropyl] pyridine-2-carboxamide



- To a cooled (0 °C) solution of 4-[[2-(4-bromo-2-fluoro-5-methoxy-phenyl)acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Intermediate H) (19.5 g, 39.78
 10 mmol) in DCM (250 mL) was added dropwise 1M BBr₃ in DCM (119.33 mL, 119.33 mmol) over 10 min. The reaction mixture was allowed to warm to room temperature and stirred for 2.5 h. The solvent was removed *in vacuo* and the crude material was suspended in EtOAc (350 mL) at 0 °C and treated with sat. NaHCO₃ (550 mL). The mixture was stirred vigorously for 20 min at room temperature and the organic layer was separated. The
 15 aqueous layer was re-extracted with EtOAc (200 mL) and the combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo*. The crude material was suspended in MeCN (300 mL) and the mixture was heated to 100 °C for 10 min. Water (300 mL) was added and heating continued for 30 min. The resulting hot mixture was filtered and the solid was washed with MeCN (2 x 70 mL) and dried at 40 °C under high vacuum to afford
 20 the title compound as a white solid.

LC-MS (Method E): Rt 1.16 min; MS m/z 476.2, 478.1 = [M+H]⁺ (96% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.82 (s, 1H), 10.17 (s, 1H), 9.39 (s, 1H), 8.51 (d, J = 5.5 Hz, 1H), 8.20 (d, J = 2.0 Hz, 1H), 7.83 (dd, J = 5.5, 2.2 Hz, 1H), 7.40 (d, J = 9.0 Hz, 1H), 6.95 (d, J = 6.9 Hz, 1H), 3.71 (s, 2H), 1.37 – 1.23 (m, 2H), 1.22 – 1.15 (m, 2H).

- 25 Step 2: 4-[[2-(2-Fluoro-5-hydroxy-4-isopropenyl-phenyl)acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide

A solution of 2-isopropenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (12.19 g, 72.57

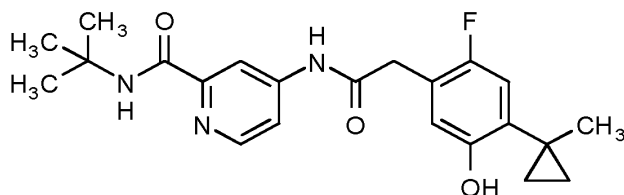
mmol), Pd(OAc)₂ (1.63 g, 7.26 mmol), 4-[[2-(4-bromo-2-fluoro-5-hydroxy-phenyl)acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (step 1)(96%, 18.0 g, 36.29 mmol) in toluene (200 mL) and water (40 mL) was degassed with nitrogen for 10 min and then treated with P(Cy)₃ (4.07 g, 14.51 mmol) and tripotassium phosphate (30.81 g, 145.14 mmol). The mixture was sparged with nitrogen, sealed and heated at 100 °C overnight. The resulting mixture was concentrated *in vacuo* and the crude residue was partitioned between EtOAc (200 mL) and water (200 mL). The organic portion was separated, dried over Na₂SO₄ and filtered through a Celite® pad, washing through with 20% MeOH in DCM (100 mL). The filtrate was concentrated *in vacuo* and the crude material suspended in toluene (200 mL). The mixture was heated to reflux for 20 minutes and then cooled and allowed to stand at 0 degrees overnight. Filtration of the resulting solid and washing with toluene (50 mL) and heptane (100 mL) afforded the title compound as an off-white solid.

The filtrate was concentrated *in vacuo* and the crude material was dissolved in MeCN (200 mL). Further material was obtained by concentration of the filtrate in vacuo and re-dissolving in MeCN (200 mL). 2,4,6-Trimercapto-s-triazine (1.5 g) and decolorizing charcoal (3.0 g) were added and the mixture was stirred at 20-25 °C for 1 h. Celite® (2.0 g) was added and the mixture was stirred at 0-5 °C for 1 h. The precipitate was removed by suction filtration through filter paper and washed with MeCN (100 mL). The filtrate was concentrated *in vacuo* and the crude material was suspended in toluene (100 mL) and heated to reflux for 20 min. The mixture was allowed to cool to room temperature and kept at 0 °C overnight. The resulting mixture was filtered, the solid was washed with cold toluene (50 mL) followed by heptane (100 mL) and dried in high vacuum oven at 40 °C to afford the title compound as an off-white solid.

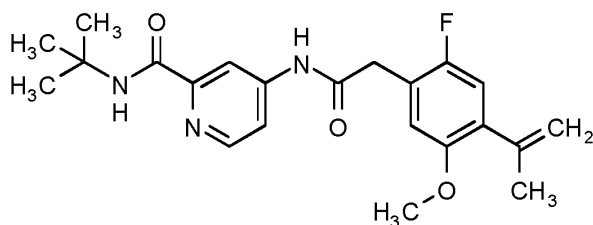
Further material was obtained by concentration of the filtrate and purification of the crude material by chromatography on silica eluting with 0-100% EtOAc in heptane followed by 0- 100% MeOH in EtOAc. The purified material from the purification steps were combined and further purified by C18 reverse phase chromatography eluting with 10-100% MeCN in water (+0.1% formic acid). The resulting solid was recrystallised from MeCN (10 mL) to afford the title compound as a white solid.

LC-MS (Method A): Rt 3.32 min; MS m/z 438.1 = [M+H]⁺ (100% @ 215 nm)

¹H NMR (500 MHz, DMSO-*d*₆) δ 10.81 (s, 1H), 9.45 (s, 1H), 9.39 (s, 1H), 8.51 (d, *J* = 5.5 Hz, 1H), 8.22 (d, *J* = 2.0 Hz, 1H), 7.84 (dd, *J* = 5.5, 2.2 Hz, 1H), 6.91 (d, *J* = 10.6 Hz, 1H), 6.80 (d, *J* = 6.7 Hz, 1H), 5.22 – 5.19 (m, 1H), 5.14 – 5.11 (m, 1H), 3.69 (s, 2H), 2.11 – 2.01 (m, 3H), 1.36 – 1.23 (m, 2H), 1.25 – 1.11 (m, 2H).

Example 8**N-*tert*-Butyl-4-[[2-[2-fluoro-5-hydroxy-4-(1-methylcyclopropyl)phenyl]acetyl]amino]pyridine-2-carboxamide**

- 5 **Step 1:** N-*tert*-Butyl-4-[[2-(2-fluoro-4-isopropenyl-5-methoxy-phenyl)acetyl]amino]pyridine-2-carboxamide

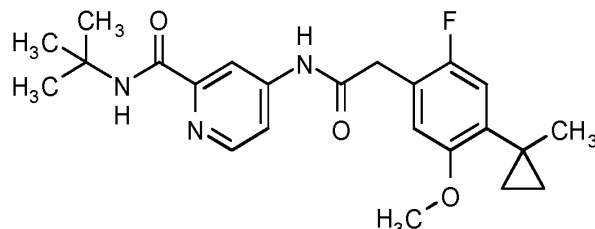


A solution of 4-[[2-(4-bromo-2-fluoro-5-methoxy-phenyl)acetyl]amino]-N-*tert*-butylpyridine-2-carboxamide (Intermediate I) (850 mg, 1.94 mmol), 2-isopropenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (729 μ L, 3.88 mmol) and tripotassium phosphate (1.65 g, 7.76 mmol) in toluene (6 mL) and water (0.6 mL) was degassed with nitrogen for 10 min and then treated with Pd(OAc)₂ (87 mg, 0.39 mmol) and P(Cy)₃ (217.54 mg, 0.78 mmol). The mixture was sparged with nitrogen, sealed and heated at 100 °C for 3 h. The resulting mixture was concentrated *in vacuo* and the crude residue was partitioned between EtOAc (50 mL) and water (50 mL). The organic portion was separated, washed with brine (50 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The resulting crude material was purified by chromatography on silica eluting with 0-100% EtOAc in heptanes followed by 0-10% MeOH in EtOAc to afford the title compound as a yellow solid.

LC-MS (Method E): Rt 1.35 mins; MS m/z 400.2 = [M+H]⁺ (91% @ 215 nm)

20 ¹H NMR (500 MHz, DMSO-d₆) δ 10.78 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.17 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.03 (d, J = 6.4 Hz, 1H), 6.97 (d, J = 10.2 Hz, 1H), 5.16 – 5.12 (m, 1H), 5.11 – 5.08 (m, 1H), 3.78 (s, 2H), 3.76 (s, 3H), 2.04 (s, 3H), 1.39 (s, 9H).

Step 2: N-*tert*-Butyl-4-[[2-[2-fluoro-5-methoxy-4-(1-methylcyclopropyl)phenyl]acetyl]amino]pyridine-2-carboxamide



To a mixture of triethylammonium bis(catecholato)iodomethylsilicate (Intermediate J) (95%, 193 mg, 0.38 mmol) and (4,4'-di-*t*-butyl-2,2'-bipyridine)bis[3,5-difluoro-2-[5-trifluoromethyl-2-pyridinyl-*k*(N)]phenyl-*k*(C)]iridium(III) hexafluorophosphate (14 mg, 0.01 mmol) in anhydrous TEA (6.59 mL) under nitrogen was added a solution of N-*tert*-butyl-4-[[2-(2-fluoro-4-isopropenyl-5-methoxy-phenyl)acetyl]amino]pyridine-2-carboxamide (step 1) (100 mg, 0.25 mmol) in anhydrous DMSO (1.5 mL). The reaction mixture was sealed with parafilm and irradiated in front of a Kessil A160WE Tuna Blue 40W LED lamp overnight maintaining the temperature at approximately 20-25°C with a fan. Additional triethylammonium bis(catecholato)iodomethylsilicate (Intermediate J) (95%, 193 mg, 0.38 mmol) and (4,4'-di-*t*-butyl-2,2'-bipyridine)bis[3,5-difluoro-2-[5-trifluoromethyl-2-pyridinyl-*k*(N)]phenyl-*k*(C)]iridium(III) hexafluorophosphate (14 mg, 0.01 mmol) were added, the mixture re-purged with nitrogen and irradiated for a further 8 h. The resulting mixture was diluted in EtOAc (10 mL) and H₂O (10 mL). A precipitate formed which was removed by filtration through a 1 g Celite® Isolute cartridge, washing with EtOAc. The filtrate phases were separated, the organic portion washed with brine (2 x 10 mL), dried over Na₂SO₄, and concentrated *in vacuo*. Purification by chromatography on silica eluting with 0-100% EtOAc in heptanes followed by further purification by C18 reverse phase chromatography eluting with 10-100% MeCN (+0.1% formic acid) in H₂O (+0.1% formic acid) afforded the title compound as a yellow viscous oil.

LC-MS (Method E): Rt 1.33 mins; MS *m/z* 414.1 = [M+H]⁺ (97% @ 215 nm)

¹H NMR (500 MHz, DMSO-*d*₆) δ 10.77 (s, 1H), 8.45 (d, *J* = 5.5 Hz, 1H), 8.17 (d, *J* = 2.0 Hz, 1H), 8.03 (s, 1H), 7.81 (dd, *J* = 5.5, 2.2 Hz, 1H), 6.98 (d, *J* = 5.1 Hz, 1H), 6.97 – 6.95 (m, 1H), 3.80 (s, 3H), 3.75 (s, 2H), 1.40 (s, 9H), 1.26 (s, 3H), 0.69 – 0.65 (m, 2H), 0.65 – 0.59 (m, 2H).

Step 3: N-*tert*-Butyl-4-[[2-[2-fluoro-5-hydroxy-4-(1-methylcyclopropyl)phenyl] acetyl]amino]pyridine-2-carboxamide

1M BCl₃ in DCM (181 μL, 0.18 mmol) was added dropwise to a cooled (0°C) solution of N-*tert*-butyl-4-[[2-[2-fluoro-5-methoxy-4-(1-methylcyclopropyl)phenyl] acetyl]

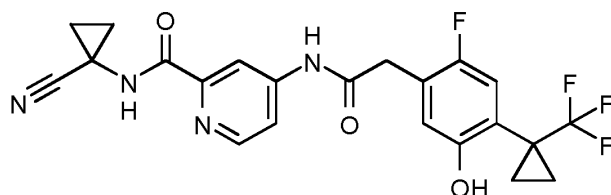
amino]pyridine-2-carboxamide (step 2) (30 mg, 0.07 mmol) and tetra-n-butylammonium iodide (67 mg, 0.18 mmol) in DCM (1 mL) under nitrogen and the mixture was stirred at 0°C for 2 h. Additional 1M BCl₃ in DCM (72 µL, 0.07 mmol) was added and stirring continued for 30 min. The reaction was quenched with ice and the organic layer separated through a hydrophobic frit. The remaining aqueous layer was washed with DCM and the organic portions were combined and concentrated *in vacuo*. Purification of the crude material by C18 reverse phase chromatography eluting with 10-100% MeCN (+0.1% formic acid) in H₂O (+0.1% formic acid) afforded the title compound as an off-white solid.

LC-MS (Method A): Rt 3.56 mins; MS m/z 400.3 = [M+H]⁺ (98 % @ 215 nm)

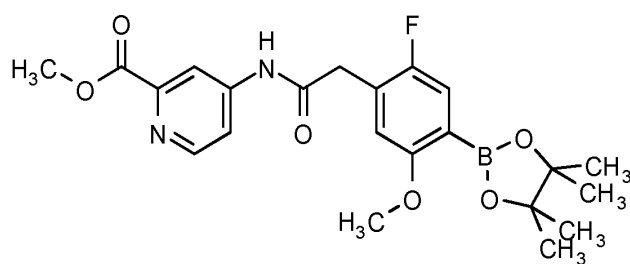
¹H NMR (500 MHz, DMSO-d₆) δ 10.76 (s, 1H), 9.17 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 6.87 (d, J = 10.4 Hz, 1H), 6.73 (d, J = 6.7 Hz, 1H), 3.64 (s, 2H), 1.40 (s, 9H), 1.26 (s, 3H), 0.69 – 0.63 (m, 2H), 0.63 – 0.55 (m, 2H).

Example 9

N-(1-Cyanocyclopropyl)-4-[[2-[2-fluoro-5-hydroxy-4-[1-(trifluoromethyl)cyclopropyl]phenyl]acetyl]amino]pyridine-2-carboxamide



Step 1: Methyl 4-[[2-[2-fluoro-5-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]acetyl]amino]pyridine-2-carboxylate



A mixture of methyl 4-[[2-(4-bromo-2-fluoro-5-methoxy-phenyl)acetyl] amino]pyridine-2-carboxylate (Intermediate I step 1) (94%, 4.5 g, 10.65 mmol), bis(pinacolato)diboron (4.06 g, 15.97 mmol), KOAc (4.42 g, 31.95 mmol) and Pd(dppf)Cl₂ (779 mg, 1.06 mmol) in 1,4-dioxane (45 mL) under nitrogen was heated at 80°C for 4 h. Additional bis(pinacolato)diboron (4.06 g, 15.97 mmol) was added and the mixture

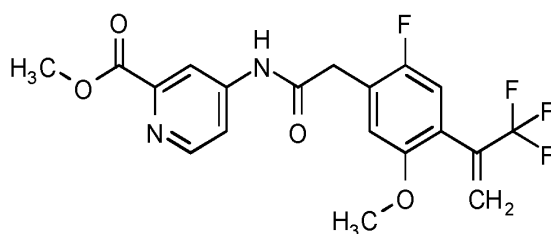
was heated at 80°C for a further 3.5 h. Additional Pd(dppf)Cl₂ (779 mg, 1.06 mmol) was then added and the mixture heated at 80°C overnight. The resulting mixture was filtered through Celite® (filter material) and concentrated *in vacuo*. Purification of the crude material by chromatography on silica eluting with 0-100% EtOAc in heptanes followed by

0-10% MeOH in EtOAc afforded the title compound as a dark brown viscous oil.

LC-MS (Method E): Rt 1.11 mins; MS m/z 445.2 = [M+H]⁺ (62% @ 215 nm)

¹H NMR (400 MHz, DMSO-d₆) δ 10.81 (s, 1H), 8.55 (d, J = 5.5 Hz, 1H), 8.29 (d, J = 1.8 Hz, 1H), 7.77 (dd, J = 5.5, 2.2 Hz, 1H), 7.20 (d, J = 9.6 Hz, 1H), 7.01 (d, J = 5.7 Hz, 1H), 3.87 (s, 3H), 3.81 (s, 2H), 3.73 (s, 3H), 1.27 (s, 12H).

Step 2: Methyl 4-[[2-[2-fluoro-5-methoxy-4-[1-(trifluoromethyl)vinyl]phenyl]acetyl]amino]pyridine-2-carboxylate



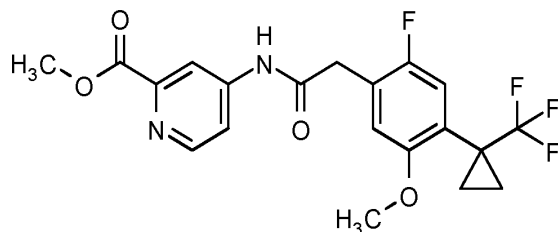
A mixture of methyl 4-[[2-[2-fluoro-5-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]acetyl]amino]pyridine-2-carboxylate (step 1) (4.5 g, 10.13 mmol), Cs₂CO₃ (3.96 g, 12.16 mmol) and Pd(dppf)Cl₂ (827 mg, 1.01 mmol) under nitrogen was dissolved in degassed monoglyme (45.5 mL) and degassed, deionised water (13 mL). 2-Bromo-3,3,3-trifluoro-prop-1-ene (2.36 mL, 22.28 mmol) was added and the mixture heated at 80°C overnight. The resulting mixture was diluted with EtOAc (150 mL) and water (150 mL). The organic portion was separated, washed with brine (150 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Purification by chromatography on silica eluting with EtOAc in heptanes 0-100% followed by MeOH in EtOAc 0-20% with subsequent purification by C18 reverse phase chromatography eluting with 10-100% MeCN (+0.1% formic acid) in H₂O (+0.1% formic acid) afforded the title compound as a colourless viscous oil.

LC-MS (Method G): Rt 0.83 mins; MS m/z 413.2 = [M+H]⁺ (91% @ 215 nm)

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Step 3: Methyl 4-[[2-[2-fluoro-5-methoxy-4-[1-(trifluoromethyl)cyclopropyl]phenyl]acetyl]amino]pyridine-2-carboxylate

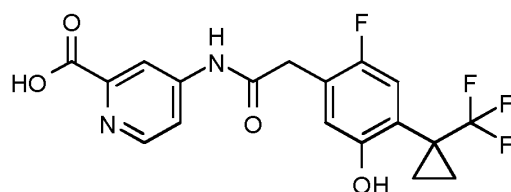


The title compound was prepared from methyl 4-[[2-[2-fluoro-5-methoxy-4-[1-(trifluoromethyl)vinyl]phenyl]acetyl]amino]pyridine-2-carboxylate (step 2) and triethylammonium bis(catecholato)iodomethylsilicate (Intermediate J) analogously to Example 8 step 2.

LC-MS (Method A): Rt 3.22 mins; MS m/z 427.2 = [M+H]⁺ (42% @ 215 nm)

¹H NMR (500 MHz, Chloroform-d) δ 8.62 (s, 1H), 8.01 (d, J = 2.1 Hz, 1H), 7.94 – 7.91 (m, 1H), 7.65 (s, 1H), 7.18 (d, J = 9.8 Hz, 1H), 6.86 – 6.82 (m, 1H), 3.99 (s, 3H), 3.85 (s, 3H), 3.74 (s, 2H), 1.40 – 1.36 (m, 2H), 1.01 – 0.97 (m, 2H).

Step 4: 4-[[2-[2-fluoro-5-hydroxy-4-[1-(trifluoromethyl)cyclopropyl]phenyl]acetyl] amino] pyridine-2-carboxylic acid



The title compound was prepared from methyl 4-[[2-[2-fluoro-5-methoxy-4-[1-(trifluoromethyl)cyclopropyl]phenyl]acetyl]amino]pyridine-2-carboxylate (step 3) and 1M BBr₃ in DCM analogously to Example 1 step 2.

LC-MS (Method E): Rt 0.96 mins; MS m/z 399.1 = [M+H]⁺ (76% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.89 (s, 1H), 9.62 (s, 1H), 8.57 – 8.53 (m, 1H), 8.28 (d, J = 2.0 Hz, 1H), 7.83 – 7.79 (m, 1H), 7.07 (d, J = 9.4 Hz, 1H), 6.84 (d, J = 6.6 Hz, 1H), 3.72 (s, 2H), 1.32 – 1.29 (m, 2H), 1.06 – 1.02 (m, 2H). [acid-OH not observed]

Step 5: N-(1-Cyanocyclopropyl)-4-[[2-[2-fluoro-5-hydroxy-4-[1-(trifluoromethyl)cyclopropyl]phenyl]acetyl]amino]pyridine-2-carboxamide

To a solution of 4-[[2-[2-fluoro-5-hydroxy-4-[1-(trifluoromethyl)cyclopropyl]phenyl]acetyl]amino]pyridine-2-carboxylic acid (step 4) (42%, 63 mg, 0.07 mmol) in DMF (1.5 mL) was added DIPEA (23 μL, 0.13 mmol), 1-aminocyclopropanecarbonitrile hydrochloride (9 mg, 0.08 mmol) followed by HATU (24 mg, 0.06 mmol) and the mixture

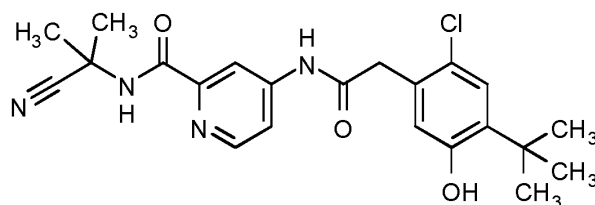
was stirred under nitrogen, at room temperature for 2 h. Additional 1-aminocyclopropanecarbonitrile hydrochloride (9 mg, 0.08 mmol), DIPEA (23 μ L, 0.13 mmol) were added followed by HATU (24 mg, 0.06 mmol) and the reaction mixture was stirred overnight. The resulting mixture was concentrated *in vacuo* and purification of the crude material by preparative HPLC (acidic pH, early elution method) afforded the title compound as a tan solid.

LC-MS (Method A): Rt 3.08 mins; MS m/z 463.2 = [M+H]⁺ (94% @ 215 nm)

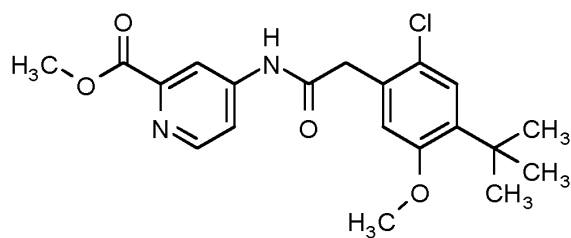
¹H NMR (500 MHz, DMSO-d₆) δ 10.85 (s, 1H), 9.68 (s, 1H), 9.62 (s, 1H), 8.50 (d, J = 5.5 Hz, 1H), 8.22 (d, J = 2.0 Hz, 1H), 7.85 (dd, J = 5.5, 2.2 Hz, 1H), 7.07 (d, J = 10.0 Hz, 1H), 6.84 (d, J = 6.6 Hz, 1H), 3.71 (s, 2H), 1.55 – 1.51 (m, 2H), 1.35 – 1.28 (m, 4H), 1.07 – 1.01 (m, 2H).

Example 10

4-[[2-(4-*tert*-Butyl-2-chloro-5-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide



Step 1: Methyl 4-[[2-(4-*tert*-butyl-2-chloro-5-methoxy-phenyl)acetyl]amino]pyridine-2-carboxylate



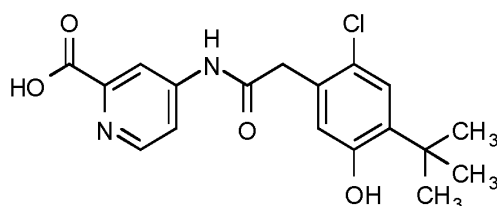
To a stirred solution of 2-(4-*tert*-butyl-2-chloro-5-methoxy-phenyl)acetic acid (Intermediate K)(1.68 g, 6.54 mmol), methyl 4-aminopyridine-2-carboxylate (1.19 g, 7.85 mmol) and DIPEA (1.49 mL, 8.51 mmol) in 1,4-dioxane (40 mL) was added 50% T3P® solution in EtOAc (5.06 mL, 8.51 mmol). The reaction mixture was stirred at room temperature for 45 min and then partitioned between EtOAc (200 mL) and water (200 mL). The resulting suspension was washed with 1M aq. HCl (100 mL) followed by 20% aqueous NaOH (2 x 100 mL). The organic layer was separated, dried over Na₂SO₄ and concentrated *in vacuo*. The crude material was purified by chromatography on silica eluting with 20-100% EtOAc

in heptanes to afford the title compound as an off-white powder.

LC-MS (Method E): Rt 1.25 mins; MS m/z 391.1, 393.1 = [M+H]⁺ (100% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.82 (s, 1H), 8.55 (d, J = 5.45 Hz, 1H), 8.31 (d, J = 2.0 Hz, 1H), 7.77 (dd, J = 5.5, 2.1 Hz, 1H), 7.16 (s, 1H), 7.08 (s, 1H), 3.86 (s, 3H), 3.85 (s, 2H), 3.81 (s, 3H), 1.32 (s, 9H).

Step 2: 4-[[2-(4-*tert*-Butyl-2-chloro-5-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid



1M BBr₃ in DCM (63.71 mL, 63.71 mmol) was added dropwise to a cooled (0 °C), stirred suspension of methyl 4-[[2-(4-*tert*-butyl-2-chloro-5-methoxy-phenyl)acetyl]amino]pyridine-2-carboxylate (step 1) (4.15 g, 10.62 mmol) in DCM (8 mL). After 30 min, the ice bath was removed and the reaction mixture was stirred at room temperature for 18 h. The resulting mixture was concentrated *in vacuo* and the crude residue was partitioned between EtOAc (100 mL) and water (100 mL). The organic layer was separated and the aqueous layer back-extracted with EtOAc (50 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo*. The residue was suspended in 1:1 MeCN:water (50 mL) and filtered, washing through with 1:1 MeCN:water. The solid was dried under vacuum to afford the title compound.

LC-MS (Method E): Rt 1.02 mins; MS m/z 363.0, 365.0 = [M+H]⁺ (100% @ 215 nm)

Step 3: 4-[[2-(4-*tert*-Butyl-2-chloro-5-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-1-methyl-ethyl) pyridine-2-carboxamide

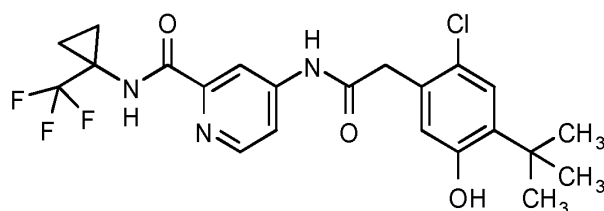
To a solution of 4-[[2-(4-*tert*-butyl-2-chloro-5-hydroxy-phenyl)acetyl]amino] pyridine-2-carboxylic acid (step 2) (2.5 g, 6.89 mmol) in DMF (25 mL) was added 2-amino-2-methyl-propanenitrile hydrochloride (914 mg, 7.58 mmol), DIPEA (2.41 mL, 13.78 mmol) followed by HATU (2.62 g, 6.89 mmol) and the mixture stirred at room temperature overnight. The resulting mixture was diluted with EtOAc and washed sequentially with 1M HCl (150 mL), sat. NaHCO₃ solution (150 mL) and brine (150 mL). The organic portion was dried over Na₂SO₄ and concentrated *in vacuo*. Purification of the crude material by chromatography on silica eluting with 0-100% EtOAc in heptanes afforded the title compound as a colourless powder.

LC-MS (Method A): Rt 3.65 mins; MS m/z 429.2, 431.2 = [M+H]⁺ (99% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.85 (s, 1H), 9.64 (s, 1H), 8.85 (s, 1H), 8.52 (d, J = 5.5 Hz, 1H), 8.24 (d, J = 2.0 Hz, 1H), 7.85 (dd, J = 5.5, 2.1 Hz, 1H), 7.09 (s, 1H), 6.82 (s, 1H), 3.75 (s, 2H), 1.72 (s, 6H), 1.33 (s, 9H).

5 Example 10.1

4-[[2-(4-*tert*-Butyl-2-chloro-5-hydroxy-phenyl)acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide



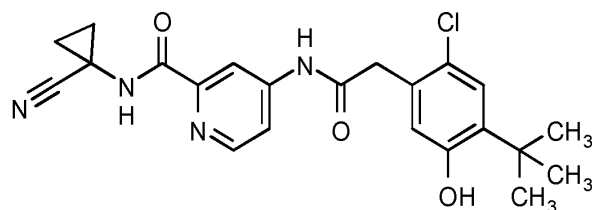
The title compound was prepared analogously to Example 10 by replacing 2-amino-2-methyl-propanenitrile hydrochloride (step 3) with 1-(trifluoromethyl)cyclopropanamine hydrochloride.

LC-MS (Method A): Rt 3.92 mins; MS m/z 470.2, 472.2 = [M+H]⁺ (98 % @ 215 nm)

¹H NMR (400 MHz, DMSO-d₆) δ 10.81 (s, 1H), 9.62 (s, 1H), 9.38 (s, 1H), 8.51 (d, J = 5.5 Hz, 1H), 8.22 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.09 (s, 1H), 6.82 (s, 1H), 3.74 (s, 2H), 1.33 (s, 9H), 1.30 – 1.14 (m, 4H).

Example 10.2

4-[[2-(4-*tert*-Butyl-2-chloro-5-hydroxy-phenyl)acetyl]amino]-N-(1-cyanocyclopropyl)pyridine-2-carboxamide



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The title compound was prepared analogously to Example 10 by replacing 2-amino-2-methyl-propanenitrile hydrochloride (step 3) with 1-aminocyclopropanecarbonitrile hydrochloride.

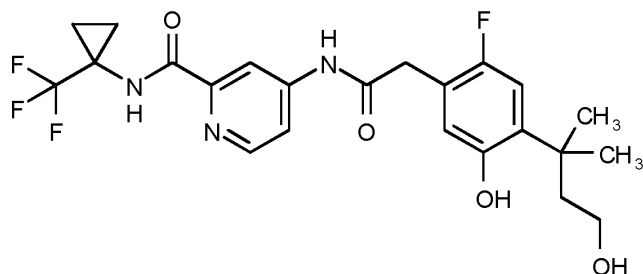
LC-MS (Method A): Rt 3.50 mins; MS m/z 427.2, 429.2 = [M+H]⁺ (97 % @ 215 nm)

¹H NMR (400 MHz, DMSO-d₆) δ 10.82 (br s, 1H), 9.66 (s, 1H), 9.63 (br s, 1H), 8.50 (d, J = 5.7 Hz, 1H), 8.24 (d, J = 1.8 Hz, 1H), 7.85 (dd, J = 5.5, 2.2 Hz, 1H), 7.09 (s, 1H), 6.82 (s, 1H), 3.75 (s, 2H), 1.56 – 1.50 (m, 2H), 1.39 – 1.27 (m, 11H).

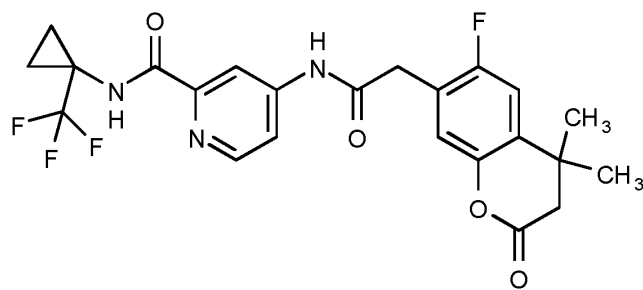
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Example 11

4-[[2-[2-Fluoro-5-hydroxy-4-(3-hydroxy-1,1-dimethyl-propyl)phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide



- 5 Step 1: 4-[[2-(6-Fluoro-4,4-dimethyl-2-oxo-chroman-7-yl)acetyl]amino]-N-[1-(trifluoromethyl) cyclopropyl]pyridine-2-carboxamide



- The title compound was prepared from 2-(6-fluoro-4,4-dimethyl-2-oxo-chroman-7-yl)acetic acid (Intermediate P) and 4-amino-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Intermediate A) analogously to Example 2 step 1.

LC-MS (Method G): Rt 0.96 min; MS m/z 480.2 = [M+H]⁺ (93% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.84 (s, 1H), 9.39 (s, 1H), 8.51 (d, J = 5.5 Hz, 1H), 8.19 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.28 (d, J = 10.2 Hz, 1H), 7.15 (d, J = 6.4 Hz, 1H), 3.80 (s, 2H), 2.73 (s, 2H), 1.34 – 1.21 (m, 8H), 1.21 – 1.17 (m, 2H).

- 15 Step 2: 4-[[2-[2-Fluoro-5-hydroxy-4-(3-hydroxy-1,1-dimethyl-propyl)phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide

- To a stirred, cooled (-78 °C) solution of 4-[[2-(6-fluoro-4,4-dimethyl-2-oxo-chroman-7-yl)acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (step 1) (93%, 345 mg, 0.67 mmol) in THF (10 mL) was added 4M LiBH₄ in THF (201 μL, 0.8 mmol) and the mixture was stirred at -78 °C for 1 h and then at room temperature overnight.

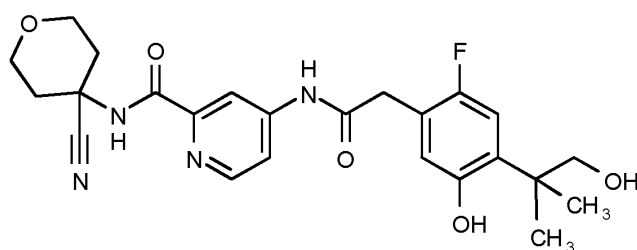
The reaction was quenched with water (20 mL) and diluted with EtOAc (10 mL). The organic layer was separated, dried over Na₂SO₄ and concentrated *in vacuo*. Purification of the crude residue by C18 reverse phase chromatography eluting with 10-100% MeCN in water (0.1% formic acid) afforded the title compound as a white solid.

LC-MS (Method A): Rt 2.98 min; MS m/z 484.2 = [M+H]⁺ (98% @ 215 nm)

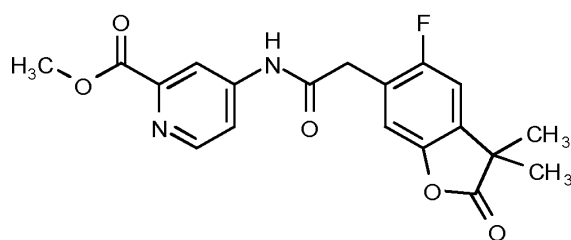
¹H NMR (500 MHz, DMSO-d₆) δ 10.81 (s, 1H), 9.39 (s, 1H), 9.30 (s, 1H), 8.50 (d, J = 5.5 Hz, 1H), 8.22 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 6.82 (d, J = 12.0 Hz, 1H), 6.73 (d, J = 7.0 Hz, 1H), 4.16 (t, J = 4.9 Hz, 1H), 3.65 (s, 2H), 3.20 – 3.10 (m, 2H), 2.03 – 1.91 (m, 2H), 1.38 – 1.22 (m, 8H), 1.21 – 1.12 (m, 2H).

Example 12

N-(4-Cyanotetrahydropyran-4-yl)-4-[[2-[2-fluoro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetyl]amino]pyridine-2-carboxamide



Step 1: Methyl 4-[[2-(5-fluoro-3,3-dimethyl-2-oxo-benzofuran-6-yl)acetyl]amino]pyridine-2-carboxylate



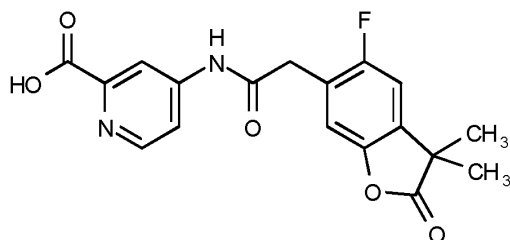
DIPEA (9.0 mL, 51.53 mmol) and 50% T3P® solution in EtOAc (20.0 mL, 33.6 mmol) were added simultaneously to a stirred solution of 2-(5-fluoro-3,3-dimethyl-2-oxo-benzofuran-6-yl)acetic acid (Intermediate U) (4.0 g, 16.79 mmol) and methyl 4-aminopyridine-2-carboxylate (2.55 g, 16.79 mmol) in DMF (60 mL) and the mixture was stirred at room temperature for 2 h. The resulting mixture was diluted with EtOAc (60 mL) and washed with brine (100 mL). The aqueous was extracted with EtOAc (2 x 75 mL) and the combined organic extracts were washed with brine (2 x 100 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Purification of the residue by chromatography on silica eluting with 0-100% EtOAc in heptanes followed by azeotroping of the product fractions with EtOAc (3 x 100 mL) afforded the title compound as a beige powder.

LC-MS (Method G): Rt 0.81 min; MS m/z 373.2 = [M+H]⁺ (100% @ 215 nm)

¹H NMR (400 MHz, DMSO-d₆) δ 10.85 (br. s, 1H), 8.56 (d, J = 5.4 Hz, 1H), 8.30 (d, J = 1.9 Hz, 1H), 7.77 (dd, J = 5.5, 2.1 Hz, 1H), 7.44 (d, J = 8.9 Hz, 1H), 7.30 (d, J = 5.8 Hz,

1H), 3.86 (s, 3H), 3.83 (s, 2H), 1.45 (s, 6H).

Step 2: 4-[[2-(5-Fluoro-3,3-dimethyl-2-oxo-benzofuran-6-yl)acetyl]amino]pyridine-2-carboxylic acid



- 5 To a solution of methyl 4-[[2-(5-fluoro-3,3-dimethyl-2-oxo-benzofuran-6-yl)acetyl]amino]pyridine-2-carboxylate (step 1) (2.0 g, 5.37 mmol) in THF (22 mL) was added a solution of lithium hydroxide hydrate (1.13 g, 26.86 mmol) in water (22 mL) and the reaction mixture was stirred at room temperature for 1 h. The pH of the resulting mixture was adjusted to pH 1 using 2M KHSO₄ (approx. 45 mL) and stirring continued at room temperature for 1
- 10 h. Dioxane (100 mL) was added to aid solubility and the mixture was heating to 50°C overnight. The mixture was extracted with EtOAc/MeCN (1:1, 4 x 100 mL) and the combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo*. The crude residue was dissolved in 4M HCl in dioxane (15 mL) and heated to 80°C for 1 h. The resulting emulsion was allowed to cool to room temperature and concentrated *in vacuo*,
- 15 azeotroping with EtOAc:MeCN (1:1, 2 x 100 mL) to afford the title compound as an off-white solid.

LC-MS (Method E): Rt 0.93 min; MS m/z 359.1 = [M+H]⁺ (97% @ 215 nm)

- ¹H NMR (400 MHz, DMSO-d₆) δ 11.26 (br. s, 1H), 8.60 (d, J = 5.9 Hz, 1H), 8.36 (d, J = 2.1 Hz, 1H), 7.95 (dd, J = 5.9, 2.2 Hz, 1H), 7.45 (d, J = 8.9 Hz, 1H), 7.32 (d, J = 5.8 Hz,
- 20 1H), 3.89 (s, 2H), 1.45 (s, 6H).

Step 3: N-(4-Cyanotetrahydropyran-4-yl)-4-[[2-[2-fluoro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetyl]amino]pyridine-2-carboxamide

- To a solution of 4-[[2-(5-fluoro-3,3-dimethyl-2-oxo-benzofuran-6-yl)acetyl]amino]pyridine-2-carboxylic acid (step 2) (87%, 150 mg, 0.36 mmol), 4-aminotetrahydropyran-4-carbonitrile (51 mg, 0.40 mmol) and HATU (166 mg, 0.44 mmol) in DMF (3 mL) was
- 25 added DIPEA (89 μL, 0.51 mmol) and the mixture was stirred at room temperature overnight. Additional HATU (166 mg, 0.44 mmol), 4-aminotetrahydropyran-4-carbonitrile (51 mg, 0.40 mmol) and DIPEA (89 μL, 0.51 mmol) were added and stirring continued for a further hour. The resulting mixture was diluted with EtOAc (8 mL), washed with water (8
- 30 mL), brine (2 x 8 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The crude residue was dissolved in THF (3 mL) and cooled to -78°C. 4M LiBH₄ in THF (0.10 mL, 0.40 mmol)

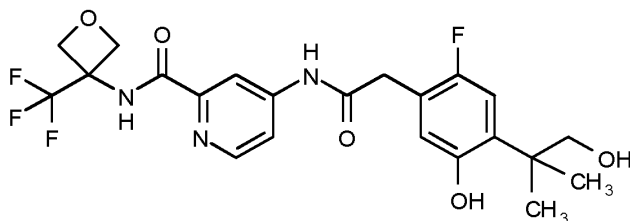
was added dropwise and stirring continued whilst gradually warming to room temperature over 45 min. The resulting mixture was re-cooled to 0°C and the reaction was quenched by the dropwise addition of 1M HCl (5 mL). The mixture was diluted with EtOAc (10 mL) and the phases were separated. The aqueous was extracted with EtOAc (10 mL) and the combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo*. Purification of the crude product by C18 reverse phase chromatography eluting with 10-100% MeCN in water (+0.1% formic acid) afforded the title compound as a beige solid.

LC-MS (Method A): Rt 2.54 min; MS m/z 471.4 = [M+H]⁺ (100% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.83 (s, 1H), 9.39 (s, 1H), 9.02 (s, 1H), 8.54 (d, J = 5.5 Hz, 1H), 8.24 (d, J = 2.0 Hz, 1H), 7.86 (dd, J = 5.5, 2.2 Hz, 1H), 6.90 (d, J = 12.1 Hz, 1H), 6.72 (d, J = 7.0 Hz, 1H), 4.77 (t, J = 5.3 Hz, 1H), 3.87 (dt, J = 12.1, 3.8 Hz, 2H), 3.65 (s, 2H), 3.62 – 3.55 (m, 4H), 2.40 – 2.33 (m, 2H), 2.11 – 2.03 (m, 2H), 1.25 (s, 6H).

Example 12.1

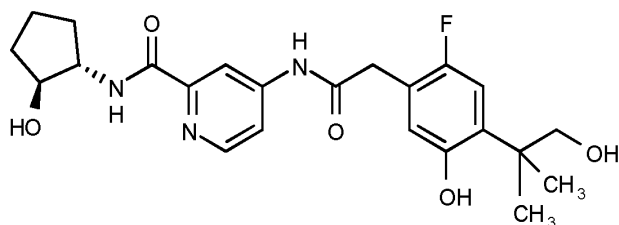
4-[[2-[2-Fluoro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetyl]amino]-N-[3-(trifluoromethyl)oxetan-3-yl]pyridine-2-carboxamide



The title compound was prepared from 4-[[2-(5-fluoro-3,3-dimethyl-2-oxo-benzofuran-6-yl)acetyl]amino]pyridine-2-carboxylic acid (Example 12 step 2) and 3-(trifluoromethyl)oxetan-3-amine hydrochloride analogously to Example 12 step 3.

LC-MS (Method A): Rt 2.75 min; MS m/z 486.3 = [M+H]⁺ (100% @ 215 nm)

¹H NMR (400 MHz, DMSO-d₆) δ 10.82 (s, 1H), 9.89 (s, 1H), 9.38 (s, 1H), 8.55 (d, J = 5.5 Hz, 1H), 8.22 (d, J = 2.0 Hz, 1H), 7.87 (dd, J = 5.5, 2.1 Hz, 1H), 6.91 (d, J = 12.1 Hz, 1H), 6.73 (d, J = 7.0 Hz, 1H), 4.93 (d, J = 7.9 Hz, 2H), 4.79 – 4.69 (m, 3H), 3.66 (s, 2H), 3.61 (d, J = 3.3 Hz, 2H), 1.26 (s, 6H).

Example 12.2**4-[[2-[2-Fluoro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetyl]amino]-N-[(1S,2S)-2-hydroxycyclopentyl]pyridine-2-carboxamide**

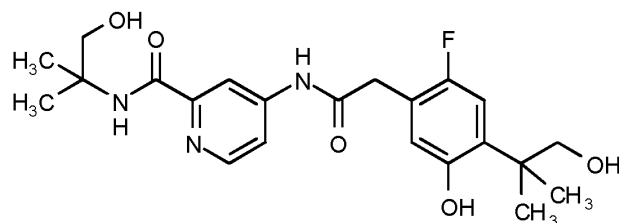
- 5 The title compound was prepared from 4-[[2-(5-fluoro-3,3-dimethyl-2-oxo-benzofuran-6-yl)acetyl]amino]pyridine-2-carboxylic acid (Example 12 step 2) and (1S,2S)-2-aminocyclopentanol hydrochloride analogously to Example 12 step 3.

LC-MS (Method A): Rt 2.37 min; MS m/z 446.3 = [M+H]⁺ (100% @ 215 nm)

- ¹H NMR (500 MHz, Methanol-d₄) δ 8.46 (d, J = 5.5 Hz, 1H), 8.34 (br. s, 1H), 8.18 (d, J = 1.9 Hz, 1H), 7.89 (dd, J = 5.5, 2.2 Hz, 1H), 6.95 (d, J = 12.0 Hz, 1H), 6.71 (d, J = 6.8 Hz, 1H), 4.16 – 4.08 (m, 2H), 3.79 (s, 2H), 3.69 (s, 2H), 2.23-2.15 (m, 1H), 2.05-1.97 (m, 1H), 1.89 – 1.73 (m, 2H), 1.70 – 1.58 (m, 2H), 1.34 (s, 6H).

Example 12.3

- 15 **4-[[2-[2-Fluoro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetyl]amino]-N-(2-hydroxy-1,1-dimethyl-ethyl)pyridine-2-carboxamide**



- 4-[[2-(5-Fluoro-3,3-dimethyl-2-oxo-benzofuran-6-yl)acetyl]amino]pyridine-2-carboxylic acid ((Example 12 step 2)(87%, 172 mg, 0.42 mmol) and DIPEA (0.22 mL, 1.26 mmol) were suspended in DMF (2 mL) and treated with HATU (191 mg, 0.5 mmol) followed by 2-amino-2-methyl-propan-1-ol (49 mg, 0.54 mmol) and the reaction mixture was stirred at room temperature for 2 h. The resulting mixture was diluted with EtOAc (25 mL) and washed with water (2 x 20 mL), brine (2 x 20 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The crude intermediate was dissolved in THF (10 mL) and cooled to -78°C. 4M LiBH₄ in THF (157 μL, 0.63 mmol) was added and stirring continued whilst gradually warming to room temperature. After stirring for a further 1.5 h, the resulting mixture was

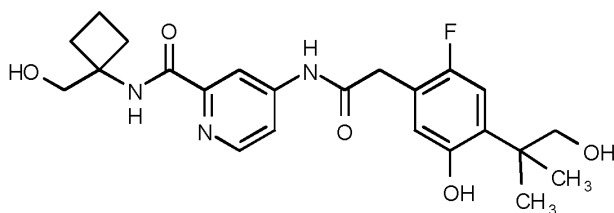
re-cooled to 0°C and the reaction was quenched by the dropwise addition of 1M HCl (10 mL). The mixture was diluted with EtOAc (20 mL) and water (20 mL) and the phases were separated. The aqueous portion was further extracted with EtOAc (2 x 10 mL) and the combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo*.
 5 Purification of the crude product by preparative HPLC (acidic pH, early elution method) gave a solid which was dried in a vacuum oven at 40°C to afford the title compound as a colourless solid.

LCMS (Method A) Rt 2.43 mins; MS m/z 434.3 = [M+H]⁺ (100% @ 215 nm)

1H NMR (400 MHz, DMSO-d₆) δ 10.76 (s, 1H), 9.37 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.25 (s, 1H), 8.19 (d, J = 1.9 Hz, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 6.90 (d, J = 12.1 Hz, 1H), 6.72 (d, J = 7.0 Hz, 1H), 5.13 (t, J = 5.5 Hz, 1H), 4.77-4.70 (m, 1H), 3.64 (s, 2H), 3.60 (d, J = 3.7 Hz, 2H), 3.44 (d, J = 5.5 Hz, 2H), 1.33 (s, 6H), 1.25 (s, 6H).

Example 12.4

15 **4-[[2-[2-Fluoro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetyl]amino]pyridine-2-carboxamide**
[1-(hydroxymethyl)cyclobutyl]pyridine-2-carboxamide



To a solution of 4-[[2-(5-fluoro-3,3-dimethyl-2-oxo-benzofuran-6-yl)acetyl]amino]pyridine-2-carboxylic acid (Example 12 step 2) (87%, 160 mg, 0.39 mmol) and DIPEA (0.24 mL, 1.36 mmol) in DMF (3 mL) was added HATU (177 mg, 0.47 mmol) followed by (1-aminocyclobutyl)methanol hydrochloride (70 mg, 0.51 mmol) and the mixture was stirred at room temperature for 40 mins. The resulting mixture was diluted with EtOAc (20 mL) and water (20 mL) and the phases were separated. The organic portion was washed with brine (20 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The crude intermediate was taken up in THF (3 mL) and cooled to -78°C. 4M LiBH₄ in THF (107 µL, 0.43 mmol) was added dropwise and the mixture was stirred whilst gradually warming to room temperature over 40 mins. The resulting mixture was re-cooled to 0°C and the reaction was quenched by the dropwise addition of 1M HCl (5 mL). The mixture was diluted with EtOAc (10 mL) and the phases were separated. The aqueous portion was further extracted with EtOAc (10 mL) and the combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo*. Purification of the crude product by preparative HPLC (acidic pH, early elution
 20
 25
 30

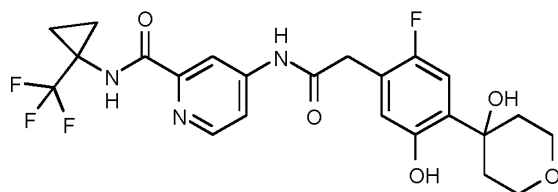
method) afforded the title compound as a colourless solid.

LC-MS (Method A): Rt 2.43 min; MS m/z 446.3 = [M+H]⁺ (100% @ 215 nm)

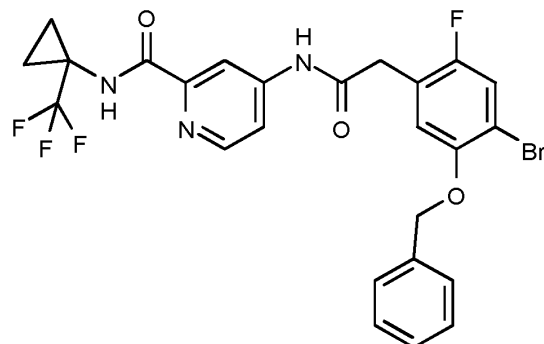
¹H NMR (500 MHz, DMSO-d₆) δ 10.79 (s, 1H), 9.34 (br. s, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.41 (s, 1H), 8.19 (d, J = 2.0 Hz, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 6.91 (d, J = 12.1 Hz, 1H), 6.73 (d, J = 7.0 Hz, 1H), 5.01 (t, J = 5.5 Hz, 1H), 4.76 (br. s, 1H), 3.65 (s, 2H), 3.62 (d, J = 5.4 Hz, 2H), 3.61 (s, 2H), 2.09 – 2.01 (m, 2H), 1.89 – 1.80 (m, 1H), 1.79 – 1.66 (m, 1H), 1.26 (s, 6H).

Example 13

10 **4-[[2-[2-Fluoro-5-hydroxy-4-(4-hydroxytetrahydropyran-4-yl)phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide**



Step 1: 4-[[2-(5-Benzyloxy-4-bromo-2-fluoro-phenyl)acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide



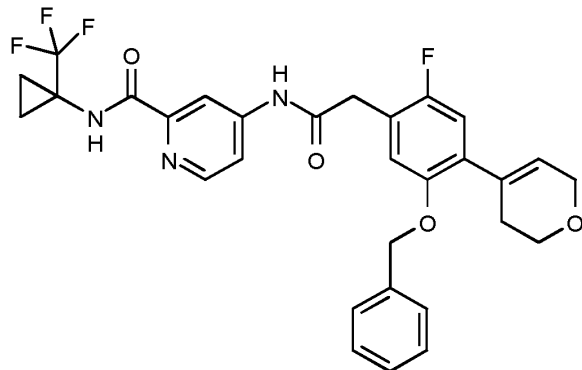
15

The title compound was prepared from 2-(5-benzyloxy-4-bromo-2-fluoro-phenyl)acetic acid (Intermediate S) and 4-amino-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Intermediate A) analogously to Example 2 step 1.

LC-MS (Method G): Rt 1.13 min; MS m/z 566.1, 568.0 = [M+H]⁺ (100% @ 215 nm)

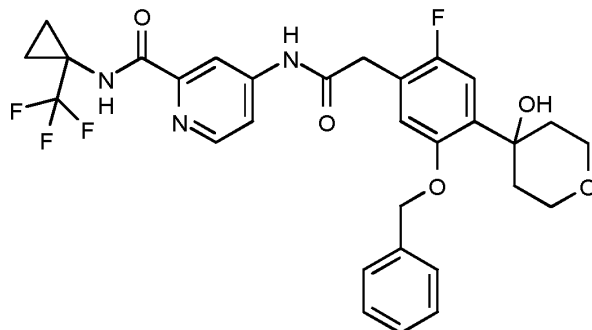
20 ¹H NMR (400 MHz, DMSO-d₆) δ 10.82 (s, 1H), 9.39 (s, 1H), 8.51 (d, J = 5.5 Hz, 1H), 8.19 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.56 (d, J = 8.9 Hz, 1H), 7.50-7.46 (m, 2H), 7.42 – 7.36 (m, 2H), 7.35-7.28 (m, 2H), 5.16 (s, 2H), 3.79 (s, 2H), 1.33-1.27 (m, 2H), 1.23-1.15 (m, 2H).

Step 2: 4-[[2-[5-Benzyloxy-4-(3,6-dihydro-2H-pyran-4-yl)-2-fluoro-phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide



- A solution of 4-[[2-(5-benzyloxy-4-bromo-2-fluoro-phenyl)acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (step 1) (220 mg, 0.39 mmol), 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (163 mg, 0.78 mmol), tripotassium phosphate (330 mg, 1.55 mmol) in toluene (5 mL) and water (0.5 mL) was degassed with nitrogen for 10 min and then treated with Pd(OAc)₂ (17 mg, 0.08 mmol) and P(Cy)₃ (44 mg, 0.16 mmol). The mixture was bubbled with nitrogen for a further 5 min, sealed and heated at 100 °C for 5 h. The resulting mixture was concentrated *in vacuo* and the residue was partitioned between EtOAc (25 mL) and water (25 mL). The layers were separated and organic portion was washed with brine (25 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The crude material was purified by chromatography on silica eluting with 0-100% EtOAc in heptanes to afford the title compound.
- LC-MS (Method E): Rt 1.35 min; MS m/z 570.3 = [M+H]⁺ (100% @ 215 nm)
- ¹H NMR (400 MHz, DMSO-d₆) δ 10.80 (s, 1H), 9.39 (s, 1H), 8.51 (d, J = 5.4 Hz, 1H), 8.20 (d, J = 1.8 Hz, 1H), 7.85 (dd, J = 5.5, 2.2 Hz, 1H), 7.46 – 7.34 (m, 4H), 7.34 – 7.28 (m, 1H), 7.15 (d, J = 6.4 Hz, 1H), 7.00 (d, J = 10.3 Hz, 1H), 5.99 – 5.95 (m, 1H), 5.07 (s, 2H), 4.19 – 4.15 (m, 2H), 3.77 (s, 2H), 3.74 (t, J = 5.4 Hz, 2H), 2.43 – 2.38 (m, 2H), 1.33 – 1.27 (m, 2H), 1.22 – 1.17 (m, 2H).

Step 3: 4-[[2-[5-Benzyloxy-2-fluoro-4-(4-hydroxytetrahydropyran-4-yl)phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide



A solution of 4-[[2-[5-benzyloxy-4-(3,6-dihydro-2H-pyran-4-yl)-2-fluoro-phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (step 2) (100%, 170 mg, 0.3 mmol), in IPA (5 mL) and DCM (1 mL) was purged with air for 10 min. The mixture was cooled to 0 °C and tris(2,2,6,6-tetramethyl-3,5-heptanedionato)manganese(III) (18 mg, 0.03 mmol) was added followed by phenylsilane (74 µL, 0.6 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction was quenched with 20% aqueous solution of sodium thiosulfate (20 mL) and stirred at room temperature for 30 min. The resulting mixture was extracted with EtOAc (2 x 25 mL), and the combined organic extracts were washed with brine (20 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification of the crude material by chromatography on silica eluting with 0-100% EtOAc in heptanes afforded the title compound as an off-white solid.

LC-MS (Method E): Rt 1.26 min; MS m/z 588.3 = [M+H]⁺ (79% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.80 (s, 1H), 9.38 (s, 1H), 8.51 (d, J = 5.5 Hz, 1H), 8.20 (d, J = 1.9 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.52 – 7.48 (m, 2H), 7.41 – 7.34 (m, 3H), 7.32-7.28 (m, 1H), 7.13 (d, J = 6.3 Hz, 1H), 5.15 (s, 2H), 5.11 (s, 1H), 3.79 – 3.71 (m, 4H), 3.66 (dd, J = 10.7, 5.2 Hz, 2H), 2.68 – 2.57 (m, 2H), 1.35 – 1.28 (m, 4H), 1.21 – 1.17 (m, 2H).

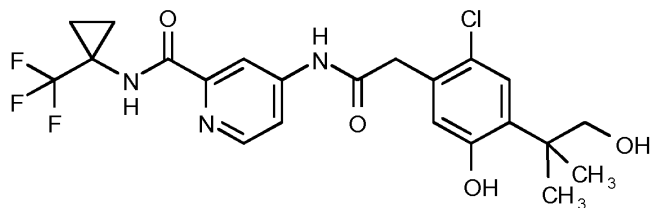
Step 4: 4-[[2-[2-Fluoro-5-hydroxy-4-(4-hydroxytetrahydropyran-4-yl)phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide

The title compound was prepared from 4-[[2-[5-benzyloxy-2-fluoro-4-(4-hydroxytetrahydropyran-4-yl)phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (step 3) and 10% Pd-C analogously to Example 2 step 2.

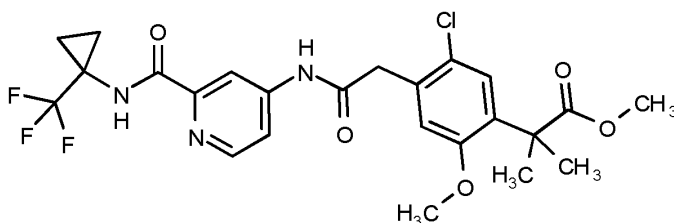
LC-MS (Method A): Rt 2.71 min; MS m/z 498.2 = [M+H]⁺ (100% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.81 (s, 1H), 9.57 (s, 1H), 9.39 (s, 1H), 8.50 (d, J = 5.5 Hz, 1H), 8.21 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.18 (d, J = 11.5 Hz, 1H), 6.76 (d, J = 6.6 Hz, 1H), 5.35 (s, 1H), 3.77-3.72 (m, 2H), 3.70-3.65 (m, 4H), 2.46 (obscured m, 2H), 1.36 (d, J = 12.9 Hz, 2H), 1.32 – 1.27 (m, 2H), 1.21-1.16 (m, 2H).

5

Example 14**4-[[2-[2-Chloro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide**

- 10 Step 1: Methyl 2-[5-chloro-2-methoxy-4-[2-oxo-2-[[2-[[1-(trifluoromethyl)cyclopropyl]carbamoyl]-4-pyridyl]amino]ethyl]phenyl]-2-methyl-propanoate



- To a stirred solution of 2-[2-chloro-5-methoxy-4-(2-methoxy-1,1-dimethyl-2-oxo-ethyl)phenyl]acetic acid (Intermediate T step 5) (771 mg, 2.56 mmol), 4-amino-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Intermediate A) (629 mg, 2.56 mmol) and TEA (672 μL, 3.85 mmol) in 1,4-dioxane (10 mL) was added 50% T3P® solution in EtOAc (2.29 mL, 3.85 mmol) and the reaction mixture was stirred at ambient temperature for 1 h.

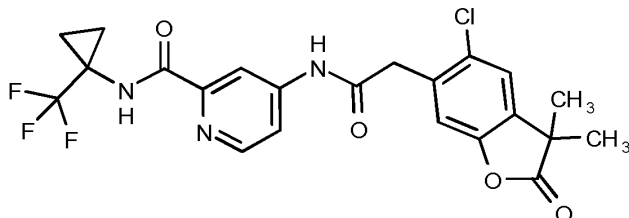
- The resulting mixture was concentrated *in vacuo* and the crude residue dissolved in EtOAc (20 mL), washed with NaHCO₃ (15 mL), brine (15 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Purification of the crude residue by chromatography on silica eluting with 0-100% EtOAc in heptanes yielded the title compound as an off-white solid.

LC-MS (Method G): Rt 1.05 min; MS m/z 528.1, 530.1 = [M+H]⁺ (99% @ 215 nm)

- ¹H NMR (500 MHz, DMSO-d₆) δ 10.87 (s, 1H), 9.40 (s, 1H), 8.51 (d, J = 5.5 Hz, 1H), 8.21 (d, J = 2.0 Hz, 1H), 7.85 (dd, J = 5.5, 2.2 Hz, 1H), 7.28 (s, 1H), 7.11 (s, 1H), 3.89 (s, 2H), 3.73 (s, 3H), 3.55 (s, 3H), 1.42 (s, 6H), 1.32 – 1.30 (m, 2H), 1.21 – 1.19 (m, 2H).

25

Step 2: 4-[[2-(5-Chloro-3,3-dimethyl-2-oxo-benzofuran-6-yl)acetyl]amino]-N-[1-(trifluoromethyl) cyclopropyl]pyridine-2-carboxamide



1M BBr₃ in DCM (2.81 mL, 2.81 mmol) was added dropwise to a solution of methyl 2-[5-chloro-2-methoxy-4-[2-oxo-2-[[2-[[1-(trifluoromethyl)cyclopropyl]carbonyl]-4-pyridyl]amino]ethyl] phenyl]-2-methyl-propanoate (step 1) (494 mg, 0.94 mmol) in DCM (12 mL) under N₂ and the mixture was stirred at room temperature overnight. The resulting mixture was diluted with water (20 mL) and extracted with DCM (30 mL). The organic extract was dried over Na₂SO₄ and concentrated *in vacuo*. Purification of the crude residue by C18 reverse phase chromatography eluting with 10-100% water (+0.1% formic acid) / MeCN (+0.1% formic acid) afforded the title compound as an off-white solid.

LC-MS (Method G): Rt 1.02 min; MS m/z 482.2, 484.1 = [M+H]⁺ (100% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.86 (s, 1H), 9.39 (s, 1H), 8.51 (d, J = 5.5 Hz, 1H), 8.19 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.67 (s, 1H), 7.38 (s, 1H), 3.94 (s, 2H), 1.46 (s, 6H), 1.32 – 1.28 (m, 2H), 1.21 – 1.17 (m, 2H).

Step 3: 4-[[2-[2-Chloro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide

To a cooled (-78 °C) solution of 4-[[2-(5-chloro-3,3-dimethyl-2-oxo-benzofuran-6-yl)acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (step 2) (197 mg, 0.41 mmol) in THF (4 mL) was added 4M LiBH₄ in THF (0.11 mL, 0.45 mmol). The resulting mixture was stirred for 5 min then allowed to warm gradually to room temperature over 1 h.

The mixture was poured onto ice cold 1M HCl (50 mL), allowed to stand for 20 min and then diluted with EtOAc (50 mL) and water (20 mL). The phases were separated and the aqueous portion was extracted with EtOAc (50 mL). The combined organic extracts were washed with saturated NaHCO₃ solution (2 x 50 mL), brine (50 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Purification of the crude residue by C18 reverse phase chromatography eluting with 10-100% water (+0.1% formic acid) / MeCN (+0.1% formic acid) afforded the title compound as an off-white solid.

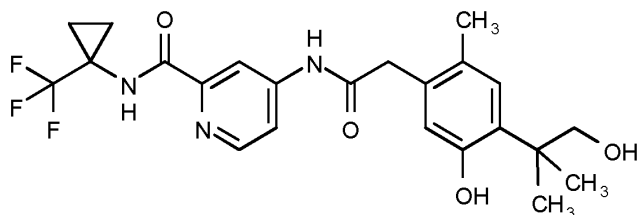
LC-MS (Method A): Rt 3.12 min; MS m/z 486.2, 488.1 = [M+H]⁺ (99% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.82 (s, 1H), 9.69 (s, 1H), 9.40 (s, 1H), 8.51 (d, J = 5.5

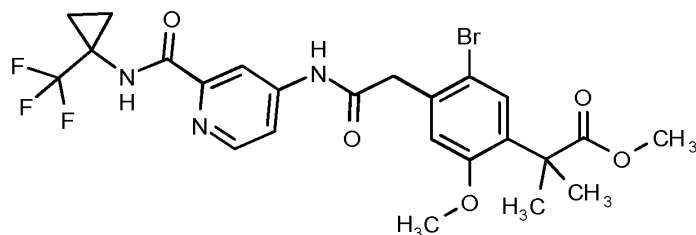
Hz, 1H), 8.23 (d, J = 2.0 Hz, 1H), 7.85 (dd, J = 5.5, 2.2 Hz, 1H), 7.13 (s, 1H), 6.80 (s, 1H), 4.77 (s, 1H), 3.75 (s, 2H), 3.61 (s, 2H), 1.33 – 1.28 (m, 2H), 1.26 (s, 6H), 1.22 – 1.17 (m, 2H).

5 Example 14.1

4-[[2-[5-Hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)-2-methyl-phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide



Step 1: Methyl 2-[5-bromo-2-methoxy-4-[2-oxo-2-[[2-[[1-(trifluoromethyl)cyclopropyl]carbamoyl]-4-pyridyl]amino]ethyl]phenyl]-2-methyl-propanoate



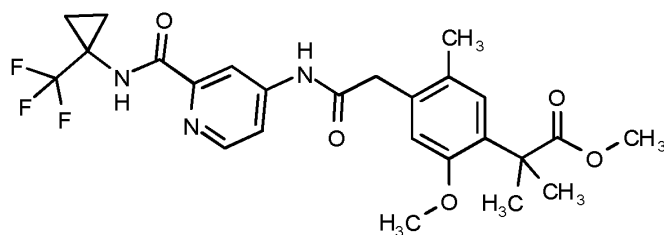
The title compound was prepared from 2-[2-bromo-5-methoxy-4-(2-methoxy-1,1-dimethyl-2-oxo-ethyl)phenyl]acetic acid (Intermediate Q) and 4-amino-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Intermediate A) analogously

Example 14 steps 1.

LC-MS (Method H): Rt 1.53 min; MS m/z 573.4 = [M+H]⁺ (99% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.87 (s, 1H), 9.40 (s, 1H), 8.51 (d, J = 5.5 Hz, 1H), 8.21 (d, J = 2.0 Hz, 1H), 7.85 (dd, J = 5.5, 2.2 Hz, 1H), 7.41 (s, 1H), 7.12 (s, 1H), 3.90 (s, 2H), 3.72 (s, 3H), 3.55 (s, 3H), 1.42 (s, 6H), 1.32 – 1.29 (m, 2H), 1.22 – 1.16 (m, 2H).

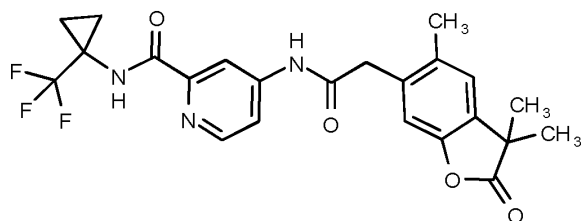
Step 2: Methyl 2-[2-methoxy-5-methyl-4-[2-oxo-2-[[2-[[1-(trifluoromethyl)cyclopropyl]carbamoyl]-4-pyridyl]amino]ethyl]phenyl]-2-methyl-propanoate



Methyl 2-[5-bromo-2-methoxy-4-[2-oxo-2-[[2-[[1-(trifluoromethyl)cyclopropyl]carbamoyl]-4-pyridyl]amino]ethyl]phenyl]-2-methyl-propanoate (step 1) (75%, 655 mg, 0.86 mmol) was dissolved in 1,4-dioxane (15 mL) and 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (50%, 0.29 mL, 1.03 mmol), Pd(dppf)₂Cl₂ (31 mg, 0.04 mmol) and K₂CO₃ (237 mg, 1.72 mmol) were added. The reaction mixture was degassed for 5 min and left to stir at 110°C for 18 h. The resulting mixture was diluted with EtOAc (40 mL) and washed with water (30 mL), brine (30 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Purification by C18 reverse phase chromatography eluting with 0-100% MeCN in water afforded the title compound.

- LC-MS (Method G): Rt 1.01 min; MS m/z 508.30 = [M+H]⁺ (79% @ 215 nm)
¹H NMR (400 MHz, DMSO-d₆) δ 10.77 (s, 1H), 9.38 (s, 1H), 8.50 (d, J = 5.5 Hz, 1H), 8.20 (d, J = 2.0 Hz, 1H), 7.86 (dd, J = 5.5, 2.1 Hz, 1H), 7.06 (s, 1H), 6.90 (s, 1H), 3.72 (s, 2H), 3.67 (s, 3H), 3.52 (s, 3H), 2.22 (s, 3H), 1.39 (s, 6H), 1.32 – 1.28 (m, 2H), 1.21 – 1.15 (m, 2H).

- Step 3:** N-[1-(Trifluoromethyl)cyclopropyl]-4-[[2-(3,3,5-trimethyl-2-oxo-benzofuran-6-yl)acetyl]amino]pyridine-2-carboxamide



- The title compound was prepared from methyl 2-[2-methoxy-5-methyl-4-[2-oxo-2-[[2-[[1-(trifluoromethyl)cyclopropyl]carbamoyl]-4-pyridyl]amino]ethyl]phenyl]-2-methyl-propanoate (step 2) and 1M BBr₃ in DCM analogously to Example 14 step 2.

LC-MS (Method G): Rt 1.02 min; MS m/z 462.2 = [M+H]⁺ (93% @ 215 nm)
¹H NMR (500 MHz, DMSO-d₆) δ 10.79 (s, 1H), 9.39 (s, 1H), 8.50 (d, J = 5.5 Hz, 1H), 8.20 (d, J = 1.9 Hz, 1H), 7.85 (dd, J = 5.5, 2.2 Hz, 1H), 7.28 (s, 1H), 7.16 (s, 1H), 3.79 (s, 2H), 2.27 (s, 3H), 1.42 (s, 6H), 1.32 – 1.27 (m, 2H), 1.21 – 1.16 (m, 2H).

- Step 4:** 4-[[2-[5-Hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)-2-methyl-phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide

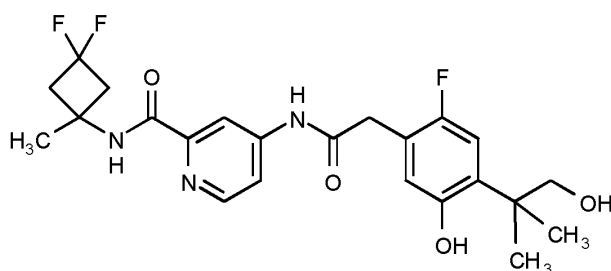
The title compound was prepared from N-[1-(trifluoromethyl)cyclopropyl]-4-[[2-(3,3,5-trimethyl-2-oxo-benzofuran-6-yl)acetyl]amino]pyridine-2-carboxamide (step 3) and 4M LiBH₄ analogously to Example 14 step 3.

- LC-MS (Method A): Rt 3.04 min; MS m/z 466.3 = [M+H]⁺ (98% @ 215 nm)
¹H NMR (500 MHz, DMSO-d₆) δ 10.73 (s, 1H), 9.39 (s, 1H), 9.15 (s, 1H), 8.50 (d, J = 5.5

Hz, 1H), 8.22 (d, J = 1.9 Hz, 1H), 7.85 (dd, J = 5.5, 2.2 Hz, 1H), 6.92 (s, 1H), 6.64 (s, 1H), 4.71 (s, 1H), 3.59 (s, 2H), 3.58 (s, 2H), 2.15 (s, 3H), 1.32 – 1.28 (m, 2H), 1.25 (s, 6H), 1.21 – 1.17 (m, 2H).

5 Example 15

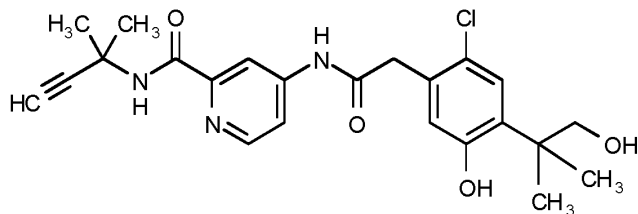
N-(3,3-Difluoro-1-methyl-cyclobutyl)-4-[[2-[2-fluoro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetyl]amino]pyridine-2-carboxamide



4-Amino-N-(3,3-difluoro-1-methyl-cyclobutyl)pyridine-2-carboxamide (Intermediate AE) (67 mg, 0.28 mmol) and 2-(5-fluoro-3,3-dimethyl-2-oxo-benzofuran-6-yl)acetic acid (Intermediate U) (60 mg, 0.25 mmol) in DMF (2.5 mL) were treated with DIPEA (0.13 mL, 0.74 mmol) and 50% T3P® solution in EtOAc (0.59 mL, 0.49 mmol) and the mixture stirred for 3 h. The resulting mixture was diluted with EtOAc (20 mL) and washed with brine (2 x 20 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The residue was dissolved in THF (2.5 mL), cooled to -78 °C and treated with 4M LiBH₄ in THF (60 µL, 0.25 mmol). The mixture was allowed to warm to 0 °C and stirred for 4 h. The reaction was quenched by adding dropwise to an ice-cold solution of 1M HCl and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (30 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Purification of the crude material by preparative HPLC (acidic pH, early elution method) afforded the title compound as a colourless solid.

LC-MS (Method A): Rt 3.02 min; MS m/z 466.3 = [M+H]⁺ (99% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.78 (s, 1H), 9.39 (br. s, 1H), 9.04 (s, 1H), 8.49 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 1.9 Hz, 1H), 7.83 (dd, J = 5.5, 2.2 Hz, 1H), 6.90 (d, J = 12.1 Hz, 1H), 6.72 (d, J = 7.0 Hz, 1H), 4.75 (br. s, 1H), 3.65 (s, 2H), 3.60 (s, 2H), 3.12 – 3.00 (m, 2H), 2.74 – 2.64 (m, 2H), 1.52 (s, 3H), 1.25 (s, 6H).

Example 15.1**4-[[2-[2-Chloro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide**

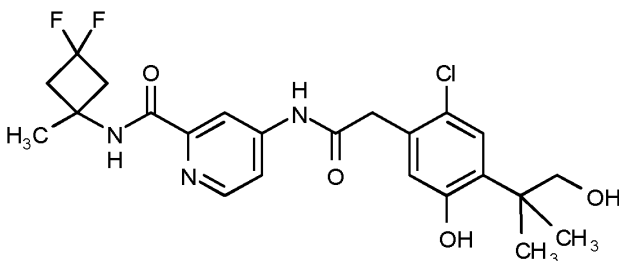
- 5 The title compound was prepared from 4-amino-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Intermediate AD) and 2-(5-chloro-3,3-dimethyl-2-oxo-benzofuran-6-yl)acetic acid (Intermediate T) analogously to Example 15.

LC-MS (Method A): Rt 3.07 min; MS m/z 444.3, 446.3 = [M+H]⁺ (100% @ 215 nm)

- ¹H NMR (500 MHz, DMSO-d₆) δ 10.82 (s, 1H), 9.68 (s, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.33 (s, 1H), 8.21 (d, J = 1.9 Hz, 1H), 7.83 (dd, J = 5.5, 2.2 Hz, 1H), 7.12 (s, 1H), 6.80 (s, 1H), 4.76 (s, 1H), 3.74 (s, 2H), 3.61 (s, 2H), 3.22 (s, 1H), 1.64 (s, 6H), 1.25 (s, 6H).
- 10

Example 15.2

- 15 **4-[[2-[2-Chloro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetyl]amino]-N-(3,3-difluoro-1-methyl-cyclobutyl)pyridine-2-carboxamide**

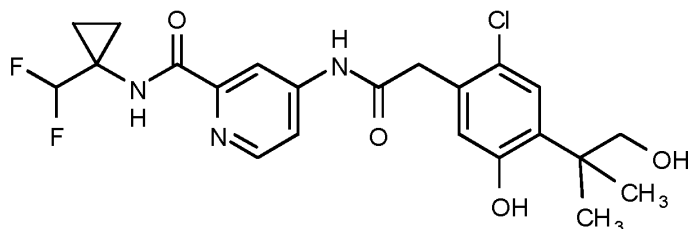


The title compound was prepared from 4-amino-N-(3,3-difluoro-1-methyl-cyclobutyl)pyridine-2-carboxamide (Intermediate AE) and 2-(5-chloro-3,3-dimethyl-2-oxo-benzofuran-6-yl)acetic acid (Intermediate T) analogously to Example 15.

- 20 LC-MS (Method A): Rt 3.18 min; MS m/z 482.3, 484.3 = [M+H]⁺ (99% @ 215 nm)
- ¹H NMR (500 MHz, DMSO-d₆) δ 10.79 (s, 1H), 9.68 (s, 1H), 9.04 (s, 1H), 8.49 (d, J = 5.5 Hz, 1H), 8.19 (d, J = 1.9 Hz, 1H), 7.83 (dd, J = 5.5, 2.2 Hz, 1H), 7.12 (s, 1H), 6.80 (s, 1H), 4.76 (t, J = 5.2 Hz, 1H), 3.74 (s, 2H), 3.61 (d, J = 4.9 Hz, 2H), 3.12 – 3.00 (m, 2H), 2.74 – 2.63 (m, 2H), 1.52 (s, 3H), 1.25 (s, 6H).

Example 15.3

4-[[2-[2-Chloro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetyl]amino]-N-[1-(difluoromethyl)cyclopropyl]pyridine-2-carboxamide



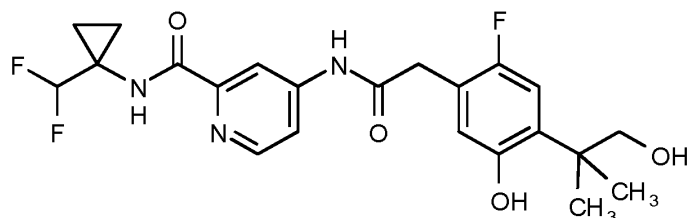
- 5 The title compound was prepared from 2-(5-chloro-3,3-dimethyl-2-oxo-benzofuran-6-yl)acetic acid (Intermediate T) and 4-amino-N-[1-(difluoromethyl)cyclopropyl]pyridine-2-carboxamide (Intermediate AC) analogously to Example 15.

LC-MS (Method A): Rt 2.96 min; MS m/z 468.2, 470.2 = [M+H]⁺ (100% @ 215 nm)

- ¹H NMR (400 MHz, DMSO-d₆) δ 10.80 (s, 1H), 9.68 (s, 1H), 9.08 (s, 1H), 8.49 (d, J = 5.5 Hz, 1H), 8.21 (d, J = 2.1 Hz, 1H), 7.83 (dd, J = 5.5, 2.1 Hz, 1H), 7.12 (s, 1H), 6.80 (s, 1H), 6.08 (t, J = 57.1 Hz, 1H), 4.75 (s, 1H), 3.74 (s, 2H), 3.61 (s, 2H), 1.25 (s, 6H), 1.11 – 1.05 (m, 2H), 1.06 – 0.99 (m, 2H).
- 10

Example 15.4

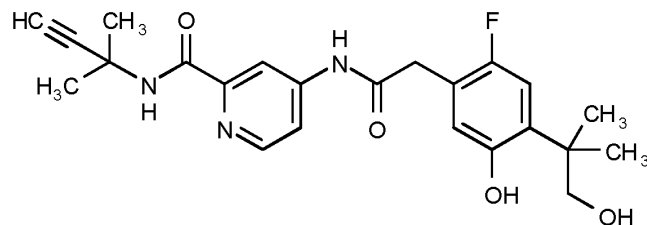
- 15 **N-[1-(Difluoromethyl)cyclopropyl]-4-[[2-[2-fluoro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetyl]amino]pyridine-2-carboxamide**



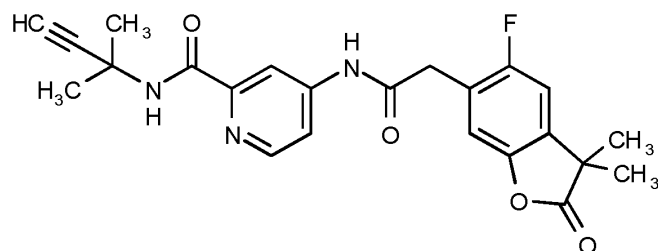
- The title compound was prepared from 2-(5-fluoro-3,3-dimethyl-2-oxo-benzofuran-6-yl)acetic acid (Intermediate U) and 4-amino-N-[1-(difluoromethyl)cyclopropyl]pyridine-2-carboxamide (Intermediate AC) analogously to Example 15.
- 20

LC-MS (Method A): Rt 2.78 min; MS m/z 452.3 = [M+H]⁺ (94% @ 215 nm)

- ¹H NMR (500 MHz, DMSO-d₆) δ 10.79 (s, 1H), 9.38 (br. s, 1H), 9.09 (s, 1H), 8.49 (d, J = 5.5 Hz, 1H), 8.21 (d, J = 1.9 Hz, 1H), 7.83 (dd, J = 5.5, 2.2 Hz, 1H), 6.90 (d, J = 12.1 Hz, 1H), 6.72 (d, J = 7.0 Hz, 1H), 6.08 (t, J = 57.1 Hz, 1H), 4.75 (br. s, 1H), 3.64 (s, 2H), 3.60 (s, 2H), 1.25 (s, 6H), 1.11 – 1.05 (m, 2H), 1.05 – 1.00 (m, 2H).
- 25

Example 16**N-(1,1-Dimethylprop-2-ynyl)-4-[[2-[2-fluoro-5-hydroxy-4-(2-hydroxy-1,1-dimethylethyl)phenyl]acetyl]amino]pyridine-2-carboxamide**

- 5 Step 1: N-(1,1-Dimethylprop-2-ynyl)-4-[[2-(5-fluoro-3,3-dimethyl-2-oxo-benzofuran-6-yl)acetyl]amino]pyridine-2-carboxamide



- A solution of 4-amino-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Intermediate AD) (176 mg, 0.87 mmol), DIPEA (0.21 mL, 1.18 mmol), 2-(5-fluoro-3,3-dimethyl-2-oxo-benzofuran-6-yl)acetic acid (Intermediate U) (94%, 200 mg, 0.79 mmol) and 50% T3P® solution in EtOAc (0.56 mL, 0.95 mmol) in DMF (5 mL) was stirred at room temperature overnight. The resulting mixture was diluted with EtOAc (10 mL) and washed with brine (20 mL). The organic portion was dried over Na₂SO₄ and concentrated *in vacuo* to afford the title compound as a white solid. This was used in the next step without further purification.

LC-MS (Method G): Rt 0.98 min; MS m/z 424.3 = [M+H]⁺ (92% @ 215 nm)

Step 2: N-(1,1-Dimethylprop-2-ynyl)-4-[[2-[2-fluoro-5-hydroxy-4-(2-hydroxy-1,1-dimethylethyl)phenyl]acetyl]amino]pyridine-2-carboxamide

- To a cooled (-78 °C), stirred solution of N-(1,1-dimethylprop-2-ynyl)-4-[[2-(5-fluoro-3,3-dimethyl-2-oxo-benzofuran-6-yl)acetyl]amino]pyridine-2-carboxamide (step 1) (92%, 330 mg, 0.72 mmol) in THF (10 mL) was added 4M LiBH₄ in THF (215 μL, 0.86 mmol) and the mixture was stirred at -78 °C for 1 h and then at room temperature for 3 h. The resulting mixture was cooled to 0 °C and the reaction was quenched with 1M HCl (10 mL). The mixture was diluted with EtOAc (10 mL) and the layers were separated. The aqueous portion was re-extracted with EtOAc (2 x 10 mL) and the combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo*. Purification of the crude product by C18

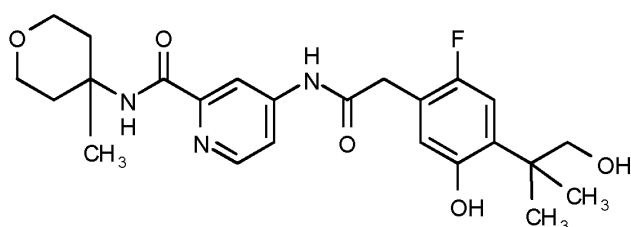
reverse phase chromatography eluting with 10-100% MeCN in water (+0.1% formic acid) followed by recrystallisation from MeCN afforded the title compound as a white solid.

LC-MS (Method C): Rt 2.97 min; MS m/z 426.5 = [M-H]⁻ (100% @ 215 nm)

¹H NMR (400 MHz, DMSO-d₆) δ 10.79 (s, 1H), 9.37 (bs, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.32 (s, 1H), 8.20 (d, J = 1.9 Hz, 1H), 7.83 (dd, J = 5.5, 2.2 Hz, 1H), 6.90 (d, J = 12.1 Hz, 1H), 6.72 (d, J = 7.0 Hz, 1H), 4.75 (bs, 1H), 3.65 (s, 2H), 3.60 (s, 2H), 3.21 (s, 1H), 1.65 (s, 6H), 1.25 (s, 6H).

Example 16.1

4-[[2-[2-Fluoro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetyl]amino]-N-(4-methyltetrahydropyran-4-yl)pyridine-2-carboxamide



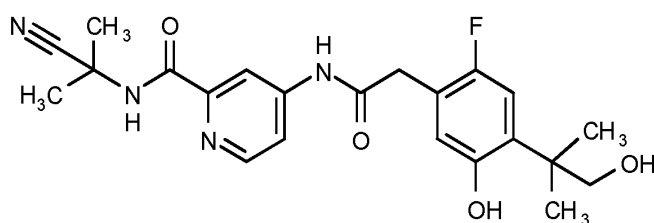
The title compound was prepared from 2-(5-fluoro-3,3-dimethyl-2-oxo-benzofuran-6-yl)acetic acid (Intermediate U) and 4-amino-N-(4-methyltetrahydropyran-4-yl)pyridine-2-carboxamide (Intermediate AF) analogously to Example 16 steps 1 and 2.

LC-MS (Method A): Rt 2.66 min; MS m/z 460.3 = [M+H]⁺ (100% @ 215 nm)

¹H NMR (400 MHz, DMSO-d₆) δ 10.79 (s, 1H), 9.38 (s, 1H), 8.49 (d, J = 5.6 Hz, 1H), 8.20 (d, J = 1.8 Hz, 1H), 8.12 (s, 1H), 7.83 (dd, J = 5.5, 2.2 Hz, 1H), 6.91 (d, J = 12.1 Hz, 1H), 6.73 (d, J = 7.0 Hz, 1H), 4.75 (br. s, 1H), 3.70 – 3.57 (m, 6H), 3.55 – 3.47 (m, 2H), 2.24 – 2.16 (m, 2H), 1.68 – 1.58 (m, 2H), 1.43 (s, 3H), 1.26 (s, 6H).

Example 16.2

N-(1-Cyano-1-methyl-ethyl)-4-[[2-[2-fluoro-5-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetyl]amino]pyridine-2-carboxamide



The title compound was prepared from 2-(5-fluoro-3,3-dimethyl-2-oxo-benzofuran-6-yl)acetic acid (Intermediate U) and 4-amino-N-(1-cyano-1-methyl-ethyl)pyridine-2-

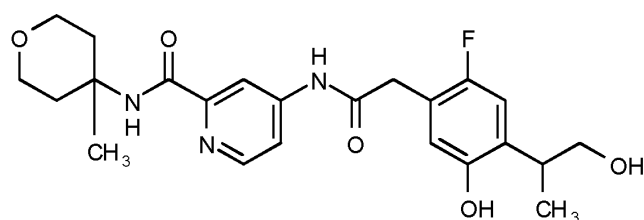
carboxamide (Intermediate AB) analogously to Example 16 steps 1 and 2.

LC-MS (Method A): Rt 2.65 min; MS m/z 429.4 = [M+H]⁺ (98% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.83 (s, 1H), 9.39 (s, 1H), 8.84 (s, 1H), 8.52 (d, J = 5.5 Hz, 1H), 8.23 (d, J = 2.0 Hz, 1H), 7.86 (dd, J = 5.5, 2.2 Hz, 1H), 6.90 (d, J = 12.1 Hz, 1H),
5 6.73 (d, J = 7.0 Hz, 1H), 4.75 (s, 1H), 3.66 (s, 2H), 3.60 (s, 2H), 1.72 (s, 6H), 1.25 (s, 6H).

Example 16.3

4-[[2-[2-Fluoro-5-hydroxy-4-(2-hydroxy-1-methyl-ethyl)phenyl]acetyl]amino]-N-(4-methyltetrahydropyran-4-yl)pyridine-2-carboxamide



10

The title compound was prepared from 2-(5-fluoro-3-methyl-2-oxo-3H-benzofuran-6-yl)acetic acid (Intermediate UA) and 4-amino-N-(4-methyltetrahydropyran-4-yl)pyridine-2-carboxamide (Intermediate AF) analogously to Example 16 steps 1 and 2.

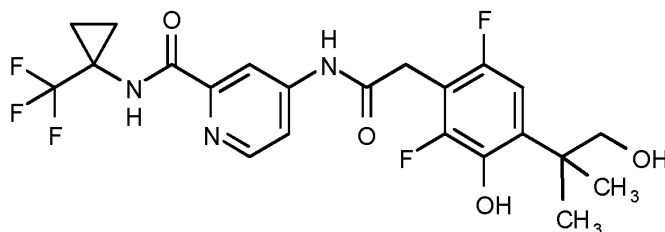
LC-MS (Method A): Rt 2.34 min; MS m/z 446.3 = [M+H]⁺ (99% @ 215 nm)

15 ¹H NMR (500 MHz, DMSO-d₆) δ 10.79 (s, 1H), 9.25 (s, 1H), 8.49 (d, J = 5.5 Hz, 1H), 8.20 (d, J = 1.9 Hz, 1H), 8.12 (s, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 6.88 (d, J = 11.0 Hz, 1H), 6.75 (d, J = 6.8 Hz, 1H), 4.64 (t, J = 5.3 Hz, 1H), 3.68 – 3.61 (m, 4H), 3.57 – 3.48 (m, 3H), 3.38 – 3.34 (m, 1H), 3.18 – 3.08 (m, 1H), 2.24 – 2.17 (m, 2H), 1.67 – 1.59 (m, 2H), 1.43 (s, 3H), 1.13 (d, J = 7.0 Hz, 3H).

20

Example 16.4

4-[[2-[2,6-Difluoro-3-hydroxy-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide



25 The title compound was prepared from 4-amino-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Intermediate A) and 2-(5,7-difluoro-3,3-dimethyl-2-oxo-benzofuran-6-

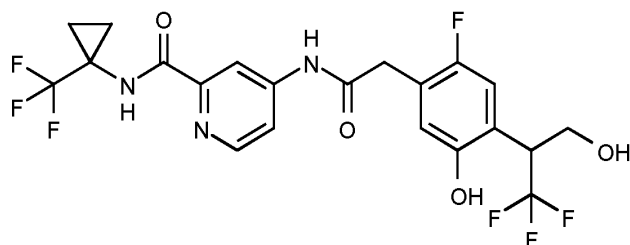
yl)acetic acid (Intermediate V) analogously to Example 16 steps 1 and 2.

LC-MS (Method A): Rt 3.04 min; MS m/z 488.3 = [M+H]⁺ (99% @ 215 nm)

¹H NMR (400 MHz, DMSO-d₆) δ 10.88 (s, 1H), 9.51 (br. s, 1H), 9.38 (s, 1H), 8.51 (d, J = 5.6 Hz, 1H), 8.18 (d, J = 2.1 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 6.82 (dd, J = 11.8, 1.7 Hz, 1H), 5.07 (br. s, 1H), 3.77 (s, 2H), 3.63 (s, 2H), 1.32 – 1.24 (m, 8H), 1.22 – 1.15 (m, 2H).

Example 17

4-[[2-[2-Fluoro-5-hydroxy-4-[2,2,2-trifluoro-1-(hydroxymethyl)ethyl]phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide



Step 1: 4-[[2-[5-Benzyloxy-4-[1-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-2,2,2-trifluoro-ethyl]-2-fluoro-phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide
tert-Butyl-chloro-dimethyl-silane (41 mg, 0.27 mmol) was added to a mixture of 2-[5-benzyloxy-2-fluoro-4-[2,2,2-trifluoro-1-(hydroxymethyl)ethyl]phenyl]acetic acid (Intermediate R) (51 mg, 0.14 mmol) and imidazole (23 mg, 0.34 mmol) in DMF (1.5 mL) and the resulting mixture was stirred at room temperature overnight. Additional Imidazole (23 mg, 0.34 mmol) and *tert*-butyl-chloro-dimethyl-silane (41 mg, 0.27 mmol) were added and stirring continued for a further 30 min. More imidazole (46 mg) and *tert*-butyl-chloro-dimethyl-silane (82 mg) were added and stirring continued for 30 min. The resulting mixture was diluted with EtOAc (10 mL) and saturated ammonium chloride solution (10 mL) and the phases were separated. The aqueous portion was extracted with EtOAc (10 mL) and the combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo*. The residue was dissolved in 1,4-dioxane (1.5 mL) and treated with 4-amino-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Intermediate A) (40 mg, 0.16 mmol), DIPEA (47.95 μL, 0.27 mmol) followed by 50% T3P® solution in EtOAc (0.1 mL, 0.16 mmol) and the resulting mixture was stirred at room temperature for 45 min. The resulting mixture was diluted with EtOAc (15 mL) and water (15 mL) and the phases were separated. The aqueous portion was extracted with EtOAc (10 mL) and the combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo*. Purification of the

crude material by chromatography on silica eluting with 0-50% EtOAc in heptanes afforded the title compound as a colourless oil.

LC-MS (Method H): Rt 2.10 min; MS m/z 714.5 = [M+H]⁺ (98% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.84 (s, 1H), 9.40 (s, 1H), 8.51 (d, J = 5.5 Hz, 1H), 8.20 (d, J = 1.9 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.45 – 7.41 (m, 2H), 7.40 – 7.35 (m, 2H), 7.35 – 7.30 (m, 1H), 7.28 (d, J = 10.4 Hz, 1H), 7.25 (d, J = 6.4 Hz, 1H), 5.15-5.08 (m, 2H), 4.21 – 4.11 (m, 1H), 4.07 – 4.01 (m, 1H), 3.98 – 3.93 (m, 1H), 3.80 (s, 2H), 1.31 – 1.17 (m, 4H), 0.80 (s, 9H), -0.02 (s, 3H), -0.04 (s, 3H).

Step 2: 4-[[2-[2-Fluoro-5-hydroxy-4-[2,2,2-trifluoro-1-(hydroxymethyl)ethyl]phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide

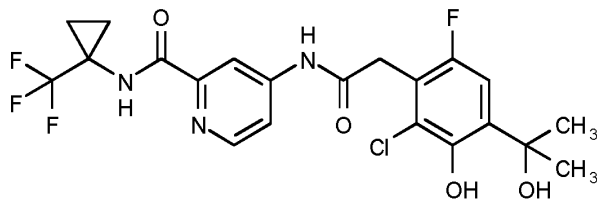
4M HCl in dioxane (0.5 mL, 2.0 mmol) was added to mixture of 4-[[2-[5-benzyloxy-4-[1-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-2,2,2-trifluoro-ethyl]-2-fluoro-phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (step 1) (46 mg, 0.06 mmol) in MeOH (0.5 mL). The mixture was stirred at room temperature for 15 min and then concentrated *in vacuo* azeotroping with EtOH (2 x 5 mL). The residue was dissolved in EtOH (3 mL) and placed under a nitrogen atmosphere. 10% Pd/C (6.85 mg, 0.01 mmol) was added and the reaction mixture was stirred under a hydrogen atmosphere for 2 h. The resulting mixture was filtered through a Celite® pad rinsing through with 9:1 EtOAc:MeOH. The filtrate was concentrated *in vacuo* and purification of the crude material by C18 reverse phase chromatography eluting with 10-100% MeCN/water (+0.1% formic acid) afforded the title compound as an off-white solid.

LC-MS (Method A): Rt 2.91 min; MS m/z 510.0 = [M+H]⁺ (99% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.84 (s, 1H), 9.80 (s, 1H), 9.39 (s, 1H), 8.51 (d, J = 5.5 Hz, 1H), 8.21 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.08 (d, J = 10.6 Hz, 1H), 6.87 (d, J = 6.7 Hz, 1H), 5.11 (t, J = 4.9 Hz, 1H), 4.11 – 4.00 (m, 1H), 3.93 – 3.86 (m, 1H), 3.82 – 3.75 (m, 1H), 3.71 (s, 2H), 1.33 – 1.25 (m, 2H), 1.24 – 1.15 (m, 2H).

Example 18

4-[[2-[2-Chloro-6-fluoro-3-hydroxy-4-(1-hydroxy-1-methylethyl)phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide



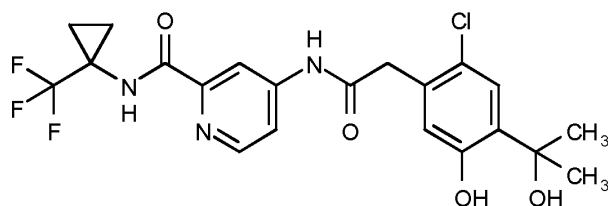
N-Chlorosuccinimide (59 mg, 0.44 mmol) was added to a mixture of 4-[[2-[2-fluoro-5-hydroxy-4-(1-hydroxy-1-methyl-ethyl)phenyl]acetyl]amino]-*N*-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Example 2) (100 mg, 0.22 mmol) in DMF (2 mL) and the mixture was stirred at room temperature for 18 h. Additional *N*-chlorosuccinimide (59 mg, 0.44 mmol) was added and stirring continued for 24 h. The resulting mixture was diluted with EtOAc (10 mL) and 1:1 brine:water (10 mL) and the phases were separated. The organic portion was dried over Na₂SO₄ and concentrated *in vacuo* to give the crude product as a yellow oil. Purification of the oil by C18 reverse phase chromatography eluting with 10-100% MeCN/water (+0.1% formic acid) afforded the title compound as an off-white solid.

LC-MS (Method A): Rt 3.16 min; MS *m/z* 490.3 = [M+H]⁺ (100% @ 215 nm)

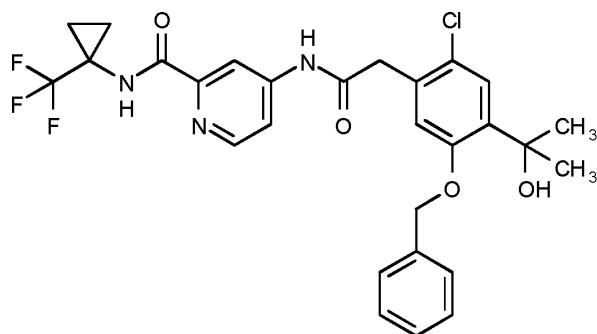
¹H NMR (500 MHz, DMSO-*d*₆) δ 10.93 (s, 1H), 9.39 (s, 1H), 8.50 (d, *J* = 5.5 Hz, 1H), 8.18 (d, *J* = 2.0 Hz, 1H), 7.83 (dd, *J* = 5.5, 2.2 Hz, 1H), 7.06 (d, *J* = 10.8 Hz, 1H), 3.88 (s, 2H), 1.52 (s, 6H), 1.32 – 1.26 (m, 2H), 1.21 – 1.15 (m, 2H).

Example 19

4-[[2-[2-Chloro-5-hydroxy-4-(1-hydroxy-1-methyl-ethyl)phenyl]acetyl]amino]-*N*-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide



Step 1: 4-[[2-[5-Benzyloxy-2-chloro-4-(1-hydroxy-1-methyl-ethyl)phenyl]acetyl]amino]-*N*-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide



To a solution of 2-[5-benzyloxy-2-chloro-4-(1-hydroxy-1-methyl-ethyl)phenyl]acetic acid (Intermediate BE)(150 mg, 0.45 mmol), 4-amino-*N*-[1-

(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Intermediate A)(100 mg, 0.41 mmol) and DIPEA (178 μ L, 1.02 mmol) in 1,4-dioxane (1 mL) was added 50% T3P® solution in EtOAc (364 μ L, 0.61 mmol) and the mixture was stirred at ambient temperature for 2 h then allowed to stand over the weekend. The resulting mixture was partitioned between DCM (5 mL) and water (5 mL) and the organics were separated via filtration through a hydrophobic PTFE fritted tube. The filtrate was concentrated *in vacuo* and purification of the residue by chromatography on silica eluting with 0-100% EtOAc in heptanes followed by 0-100% MeOH in EtOAc afforded the title compound as a pale yellow powdery solid.

LC-MS (Method G): Rt 1.05 min; MS m/z 562.2, 564.2 = [M+H]⁺ (91% @ 215 nm)

¹H NMR (500 MHz, DMSO-*d*₆) δ 10.83 (s, 1H), 9.40 (s, 1H), 8.52 (d, *J* = 5.6 Hz, 1H), 8.21 (d, *J* = 2.0 Hz, 1H), 7.85 (dd, *J* = 5.5, 2.2 Hz, 1H), 7.59 (s, 1H), 7.49 – 7.44 (m, 2H), 7.43 – 7.37 (m, 2H), 7.36 – 7.31 (m, 1H), 7.19 (s, 1H), 5.15 (s, 1H), 5.11 (s, 2H), 3.86 (s, 2H), 1.47 (s, 6H), 1.33 – 1.28 (m, 2H), 1.22 – 1.17 (m, 2H).

Step 2: 4-[[2-[2-Chloro-5-hydroxy-4-(1-hydroxy-1-methyl-ethyl)phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide

To 4-[[2-[5-benzyloxy-2-chloro-4-(1-hydroxy-1-methyl-ethyl)phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (196 mg, 0.35 mmol) (step 1) and 10% Pd/C (20 mg, 0.35 mmol) under an atmosphere of nitrogen was added degassed EtOH (3.5 mL) and the mixture was purged with nitrogen and then placed under a hydrogen atmosphere for 60 min. Further 10% Pd/C (20 mg, 0.35 mmol) was added then the reaction was again purged with nitrogen and placed under a hydrogen atmosphere for a further 65 min. The resulting mixture was diluted with MeOH (~10 mL) and filtered through Celite®, washing through with further MeOH. The filtrate was concentrated *in vacuo* and the residue was purified by chromatography on silica eluting with 0-100% EtOAc in heptanes and 0-100% MeOH in EtOAc followed by preparative HPLC (acidic pH, early elution method) using water/MeCN with 0.1% formic acid. The combined product fractions were concentrated *in vacuo* to remove the bulk of the organic solvents and the aqueous residue was treated with saturated aq. NaHCO₃ (10 mL). The mixture was extracted with EtOAc (2 x 15 mL) and the combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo* to afford the title compound as a white crystalline solid.

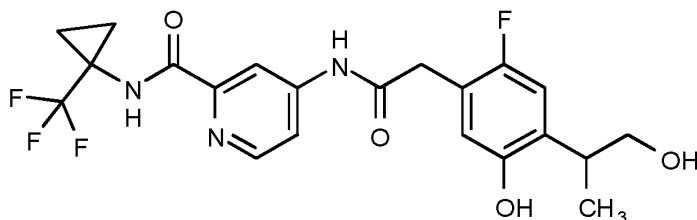
LC-MS (Method A): Rt 3.11 min; MS m/z 472.2, 474.2 = [M+H]⁺ (100% @ 215 nm)

UPLC (MSQ1, 7MIN_HIRES_UPLC) 100%; Rt 3.11 mins; MS m/z 472.2, 474.2 = [M+H]⁺

¹H NMR (500 MHz, DMSO-*d*₆) δ 10.82 (s, 1H), 9.40 (s, 1H), 8.51 (d, *J* = 5.5 Hz, 1H), 8.22 (d, *J* = 2.0 Hz, 1H), 7.84 (dd, *J* = 5.5, 2.2 Hz, 1H), 7.35 (s, 1H), 6.79 (s, 1H), 3.76 (s, 2H), 1.49 (s, 6H), 1.33 – 1.28 (m, 2H), 1.22 – 1.17 (m, 2H).

Example 20

4-[[2-[2-Fluoro-5-hydroxy-4-(2-hydroxy-1-methyl-ethyl)phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide



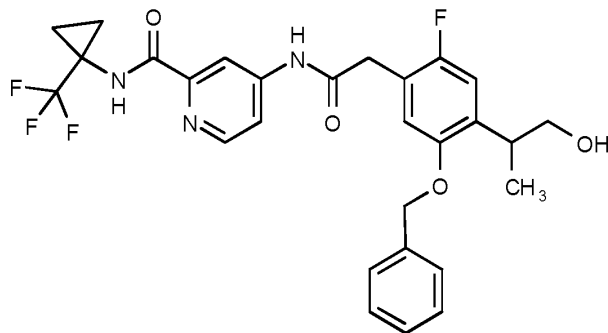
- 5 Step 1: Methyl 2-[2-benzyloxy-5-fluoro-4-[2-oxo-2-[[2-[[1-(trifluoromethyl)cyclopropyl]carbamoyl]-4-pyridyl]amino]ethyl]phenyl]propanoate

A solution of [(E)-1-methoxyprop-1-en-1-yl]-trimethyl-silane (130 μ L, 0.71 mmol) in degassed DMF (2 mL) was added to a mixture of 4-[[2-(5-benzyloxy-4-bromo-2-fluorophenyl)acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Example 10
10 13, step 1) (200 mg, 0.35 mmol), ZnF_2 (37 mg, 0.35 mmol) and $\text{Pd}(\text{P}^t\text{Bu}_3)_2$ (18 mg, 0.04 mmol) under nitrogen and the resulting mixture was heated to 80 $^\circ\text{C}$ for 16 h. The resulting mixture was diluted with EtOAc (20 mL) and washed with water (2 x 20 mL), brine (2 x 20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting crude material was purified by chromatography on silica eluting with 0-100% EtOAc in heptanes to afford the
15 title compound as a white solid.

LC-MS (Method G): Rt 1.09 min; MS m/z 574.2 = $[\text{M}+\text{H}]^+$ (83% @ 215 nm)

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.82 (s, 1H), 9.39 (s, 1H), 8.51 (d, J = 5.5 Hz, 1H), 8.20 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.43 – 7.35 (m, 4H), 7.33 – 7.29 (m, 1H), 7.14 (d, J = 6.3 Hz, 1H), 7.06 (d, J = 10.2 Hz, 1H), 5.10 – 5.04 (m, 2H), 3.98 (q, J =
20 7.2 Hz, 1H), 3.77 (s, 2H), 3.51 (s, 3H), 1.37 (d, J = 7.2 Hz, 3H), 1.32 – 1.28 (m, 2H), 1.21-1.17 (m, 2H).

Step 2: 4-[[2-[5-Benzyloxy-2-fluoro-4-(2-hydroxy-1-methyl-ethyl)phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide



A cooled (-78 °C) solution of methyl 2-[2-benzyloxy-5-fluoro-4-[2-oxo-2-[[2-[[1-(trifluoromethyl) cyclopropyl]carbonyl]-4-pyridyl]amino]ethyl]phenyl]propanoate (step 1) (83%, 100 mg, 0.14 mmol) in THF (10 mL) under an inert atmosphere was treated with a solution of 2.4M LiAlH₄ in THF (121 µL, 0.29 mmol) and the mixture was allowed to stir at -78 °C for 1.5 h and then warmed to 0 °C. The reaction was quenched with water and allowed to warm to room temperature. The resulting mixture was diluted with water (25 mL) and EtOAc (25 mL). The layers were separated and the organic portion was washed with a saturated Rochelles salt solution (10 mL), brine (10 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The crude material was purified by C18 reverse phase chromatography eluting with 10-100% MeCN/water (+0.1% formic acid). The product fractions were concentrated *in vacuo* to afford a colourless oil. The oil was azeotroped with MeOH and concentrated under high vacuum to afford the title compound as a light yellow solid.

LC-MS (Method G): Rt 1.00 min; MS m/z 546.2 = [M+H]⁺ (90% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.79 (s, 1H), 9.39 (s, 1H), 8.50 (d, J = 5.5 Hz, 1H), 8.19 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.47 – 7.41 (m, 2H), 7.40 – 7.35 (m, 2H), 7.35 – 7.28 (m, 1H), 7.08 (d, J = 6.5 Hz, 1H), 7.00 (d, J = 10.8 Hz, 1H), 5.07 (s, 2H), 4.66 – 4.61 (m, 1H), 3.74 (s, 2H), 3.58 – 3.52 (m, 1H), 3.30 – 3.22 (partial obscured m, 2H), 1.32 – 1.26 (m, 2H), 1.22 – 1.17 (m, 2H), 1.14 (d, J = 7.0 Hz, 3H).

Step 3: 4-[[2-[2-Fluoro-5-hydroxy-4-(2-hydroxy-1-methyl-ethyl)phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide

The title compound was prepared from 4-[[2-[5-benzyloxy-2-fluoro-4-(2-hydroxy-1-methyl-ethyl)phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (step 2) and 10% Pd-C analogously to Example 2 step 2.

LC-MS (Method A): Rt 2.70 min; MS m/z 456.3 = [M+H]⁺ (96% @ 215 nm)

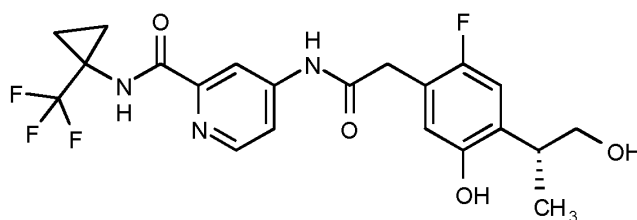
¹H NMR (500 MHz, DMSO-d₆) δ 10.80 (s, 1H), 9.38 (s, 1H), 9.26 (s, 1H), 8.50 (d, J = 5.5 Hz, 1H), 8.21 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 6.87 (d, J = 11.0 Hz, 1H), 6.75 (d, J = 6.7 Hz, 1H), 4.66-4.61 (m, 1H), 3.65 (s, 2H), 3.57-3.51 (m, 1H), 3.17-3.08 (m, 1H), 1.32-1.28 (m, 2H), 1.21-1.16 (m, 2H), 1.13 (d, J = 7.0 Hz, 3H). Signal at ~3.3-3.4 hidden under water peak but observed in HSQC (below).

Examples 20a and 20b

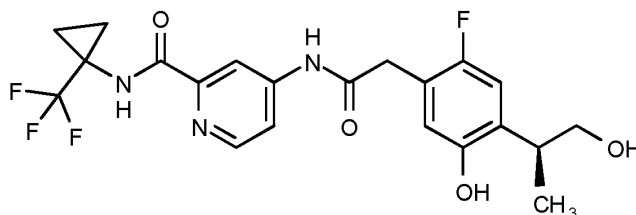
Chiral separation of racemic 4-[[2-[2-fluoro-5-hydroxy-4-(2-hydroxy-1-methyl-ethyl)phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Example 20) using Supercritical Fluid Chromatography [15% IPA : 85% CO₂ with

Chiralpak AD-H 10 x 250 mm column at 15 mL/min] afforded the individual enantiomers:

- Example 20a:** 4-[[2-[2-Fluoro-5-hydroxy-4-[(1S)-2-hydroxy-1-methyl-ethyl]phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide or 4-[[2-[2-fluoro-5-hydroxy-4-[(1R)-2-hydroxy-1-methyl-ethyl]phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide



(R)-Isomer

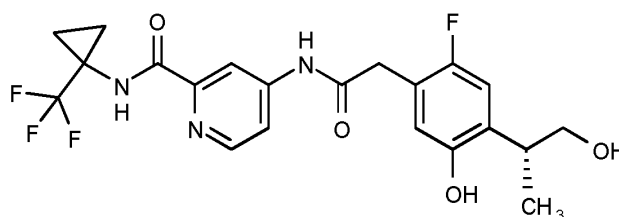


(S)-Isomer

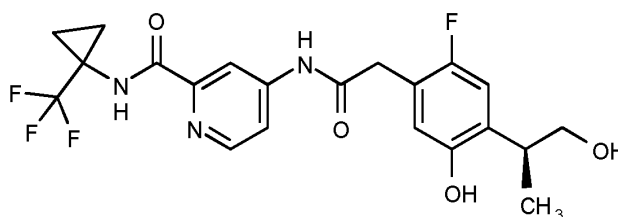
First eluted peak: SFC retention time = 17.13 min

- 10 LC-MS (Method A): Rt 2.69 min; MS m/z 456.3 = $[M+H]^+$ (91% @ 215 nm)
 ^1H NMR (500 MHz, DMSO- d_6) δ 10.80 (s, 1H), 9.39 (s, 1H), 9.21 (br. s, 1H), 8.50 (d, J = 5.5 Hz, 1H), 8.21 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 6.87 (d, J = 11.0 Hz, 1H), 6.74 (d, J = 6.8 Hz, 1H), 4.65 (br. s, 1H), 3.65 (s, 2H), 3.53 (dd, J = 10.2, 5.6 Hz, 1H), 3.40-3.30 (obscured m, 1H), 3.14–3.10 (m, 1H), 1.32–1.28 (m, 2H), 1.21–1.17 (m, 2H),
 15 1.13 (d, J = 7.0 Hz, 3H).

Example 20b: 4-[[2-[2-Fluoro-5-hydroxy-4-[(1S)-2-hydroxy-1-methyl-ethyl]phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide or 4-[[2-[2-fluoro-5-hydroxy-4-[(1R)-2-hydroxy-1-methyl-ethyl]phenyl]acetyl]amino]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide



(R)-Isomer



(S)-Isomer

Second eluted peak: SFC retention time = 20.28 min

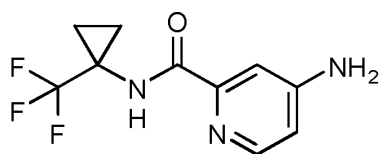
LC-MS (Method A): Rt 2.69 min; MS m/z 456.3 = [M+H]⁺ (99% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.80 (s, 1H), 9.39 (s, 1H), 9.25 (br. s, 1H), 8.50 (d, J = 5.5 Hz, 1H), 8.21 (d, J = 2.1 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 6.87 (d, J = 11.0 Hz, 1H), 6.74 (d, J = 6.7 Hz, 1H), 4.65 (br. s, 1H), 3.65 (s, 2H), 3.53 (dd, J = 10.2, 5.6 Hz, 1H), 3.40-3.30 (obscured m, 1H), 3.15–3.10 (m, 1H), 1.31–1.28 (m, 2H), 1.20–1.17 (m, 2H), 1.13 (d, J = 7.0 Hz, 3H).

15 Preparation of Intermediates

Intermediate A

4-Amino-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide



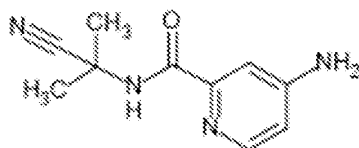
4-Aminopyridine-2-carboxylic acid (1 g, 7.24 mmol) in DMF (36.2 mL) was treated with TEA (3.68 mL, 26.43 mmol), 1-(trifluoromethyl)cyclopropanamine hydrochloride (1.29 g, 7.96 mmol) followed by TBTU (3.14 g, 9.77 mmol) and stirred at room temperature for 4 days. The resulting mixture was filtered and the solid washed with DMF (2 x 30 mL). The filtrate was concentrated *in vacuo* and the crude residue dissolved in EtOAc (300 mL) and washed with sat. NaHCO₃ solution (2 x 300 mL). The aqueous portion was re-extracted with EtOAc (30 mL) and the combined organic extracts were washed with brine (2 x 160 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Purification by C18 reverse column chromatography eluting with 10-100% MeCN in water afforded the title compound as an off-white solid.

LC-MS (Method F): Rt 1.32 mins; MS m/z 246.1 = [M+H]⁺ (100% @ 215 nm)

¹H NMR (500 MHz, DMSO-*d*₆) δ 9.13 (s, 1H), 8.02 (d, *J* = 5.6 Hz, 1H), 7.20 (d, *J* = 2.3 Hz, 1H), 6.61 (dd, *J* = 5.6, 2.4 Hz, 1H), 6.36 (s, 2H), 1.32 – 1.22 (m, 2H), 1.21 – 1.11 (m, 2H).

15 Intermediate AB

4-Amino-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide



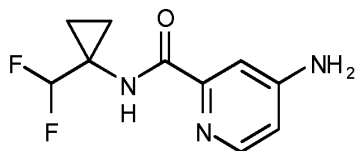
The title compound was prepared from 4-aminopyridine-2-carboxylic acid and 2-amino-2-methyl-propanenitrile hydrochloride analogously to Intermediate A.

20 LC-MS (Method E): Rt 0.35 mins; MS m/z 205.0 = [M+H]⁺ (100% @ 215 nm)

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.60 (s, 1H), 8.03 (d, *J* = 5.6 Hz, 1H), 7.21 (d, *J* = 2.3 Hz, 1H), 6.62 (dd, *J* = 5.6, 2.4 Hz, 1H), 6.40 (s, 2H), 1.70 (s, 6H).

Intermediate AC

25 4-Amino-N-[1-(difluoromethyl)cyclopropyl]pyridine-2-carboxamide



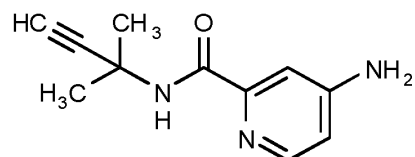
The title compound was prepared from 4-aminopyridine-2-carboxylic acid and 1-(difluoromethyl)cyclopropanamine hydrochloride analogously to Intermediate A.

LC-MS (Method I): Rt 0.39 min; MS m/z 228.0 = [M+H]⁺ (100% @ 215 nm)

¹H NMR (400 MHz, DMSO-d₆) δ 8.85 (s, 1H), 8.00 (d, J = 5.6 Hz, 1H), 7.19 (d, J = 2.1 Hz, 1H), 6.60 (dd, J = 5.6, 2.4 Hz, 1H), 6.36 (s, 2H), 6.05 (t, J = 57.2 Hz, 1H), 1.09 – 1.03 (m, 2H), 1.03 – 0.97 (m, 2H).

5 Intermediate AD

4-Amino-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide



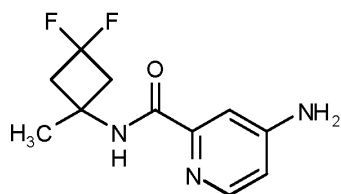
The title compound was prepared from 4-aminopyridine-2-carboxylic acid and 2-methylbut-3-yn-2-amine analogously to Intermediate A.

10 LC-MS (Method I): Rt 0.42 min; MS m/z 203.9 = [M+H]⁺ (100% @ 215 nm)

¹H NMR (400 MHz, DMSO-d₆) δ 8.23 (s, 1H), 7.99 (d, J = 5.6 Hz, 1H), 7.19 (d, J = 2.3 Hz, 1H), 6.58 (dd, J = 5.6, 2.4 Hz, 1H), 6.36 (s, 2H), 3.19 (s, 1H), 1.62 (s, 6H).

Intermediate AE

15 4-Amino-N-(3,3-difluoro-1-methyl-cyclobutyl)pyridine-2-carboxamide



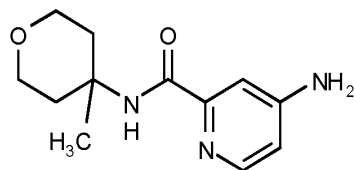
The title compound was prepared from 3,3-difluoro-1-methyl-cyclobutanamine hydrochloride and 4-aminopyridine-2-carboxylic acid analogously to Intermediate A.

LC-MS (Method G): Rt 0.63 min; MS m/z 242.2 = [M+H]⁺ (98% @ 215 nm)

20 ¹H NMR (400 MHz, DMSO-d₆) δ 8.79 (s, 1H), 8.01 (d, J = 5.6 Hz, 1H), 7.18 (d, J = 2.2 Hz, 1H), 6.59 (dd, J = 5.6, 2.4 Hz, 1H), 6.32 (br. s, 2H), 3.11 – 2.96 (m, 2H), 2.72 – 2.59 (m, 2H), 1.50 (s, 3H).

Intermediate AF

25 4-Amino-N-(4-methyltetrahydropyran-4-yl)pyridine-2-carboxamide



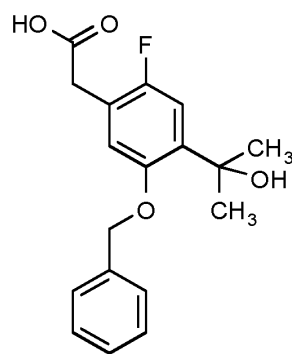
The title compound was prepared from 4-methyltetrahydropyran-4-amine hydrochloride and 4-aminopyridine-2-carboxylic acid analogously to Intermediate A.

LC-MS (Method I): Rt 0.36 min; MS m/z 236.0 = [M+H]⁺ (93% @ 215 nm)

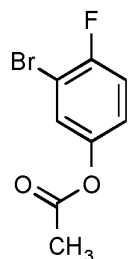
¹H NMR (500 MHz, DMSO-d₆) δ 8.08 (s, 1H), 8.00 (d, J = 5.6 Hz, 1H), 7.18 (d, J = 2.2 Hz, 1H), 6.58 (dd, J = 5.6, 2.4 Hz, 1H), 6.34 (s, 2H), 3.67 – 3.60 (m, 2H), 3.51 – 3.45 (m, 2H), 2.18 – 2.12 (m, 2H), 1.63 – 1.56 (m, 2H), 1.39 (s, 3H).

Intermediate B

2-[5-Benzyloxy-2-fluoro-4-(1-hydroxy-1-methyl-ethyl)phenyl]acetic acid



Step 1: (3-Bromo-4-fluoro-phenyl) acetate

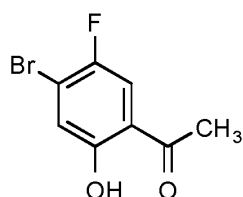


A cooled (0 °C) solution of 3-bromo-4-fluoro-phenol (5 g, 26.18 mmol) and TEA (6.86 mL, 49.22 mmol) in DCM (100 mL) was treated dropwise with acetyl chloride (2.61 mL, 36.65 mmol) and the mixture was stirred at room temperature for 45 min. The resulting mixture was diluted with DCM (100 mL) and washed sequentially with 0.5M HCl (120 mL), water (120 mL), sat. NaHCO₃ (120 mL) and brine (120 mL). The organic portion was dried over Na₂SO₄ and concentrated *in vacuo* to afford the title compound as a tan solid.

LC-MS (Method E): Rt 1.14 min (85% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 7.59 (dd, J = 6.0, 2.8 Hz, 1H), 7.43 (t, J = 8.8 Hz, 1H), 7.26 – 7.17 (m, 1H), 2.26 (s, 3H).

Step 2: 1-(4-Bromo-5-fluoro-2-hydroxy-phenyl)ethanone

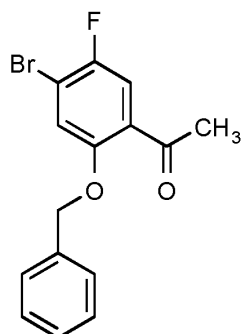


A mixture of (3-bromo-4-fluoro-phenyl) acetate (step 1) (90%, 6.3 g, 24.33 mmol) and aluminium trichloride (5.84 g, 43.8 mmol) was stirred at 165 °C for 3 h. The melt was allowed to cool to room temperature and the resulting solid was suspended in DCM (100 mL). 2N HCl (100 mL) was added and the insoluble material was removed by filtration through Celite® (filter material). The layers were separated and the aqueous portion was re-extracted with DCM (60 mL). The combined organic extracts were washed with water (140 mL), brine (140 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The crude material was purified by chromatography on silica eluting with 0-30% EtOAc in heptanes to afford the title compound as an off-white solid.

LC-MS (Method E): Rt 1.17 min (96% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 11.62 (s, 1H), 7.79 (d, J = 9.4 Hz, 1H), 7.33 (d, J = 5.8 Hz, 1H), 2.61 (s, 3H).

Step 3: 1-(2-Benzyloxy-4-bromo-5-fluoro-phenyl)ethanone

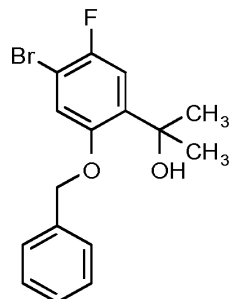


Benzyl bromide (3.23 mL, 27.19 mmol) was added to a stirred mixture of 1-(4-bromo-5-fluoro-2-hydroxy-phenyl)ethanone (step 2) (96%, 5.5 g, 22.66 mmol) and K₂CO₃ (7.83 g, 56.65 mmol) in DMF (25 mL) and the mixture was stirred at 80 °C for 1 hour. The resulting mixture was allowed to cool to room temperature and partitioned between EtOAc (150 mL) and water (150 mL). The aqueous layer was further extracted with EtOAc (100 mL). The combined organic extracts were washed with water (2 x 150 mL), brine (150 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The crude material was purified by chromatography on silica eluting with 0-60% EtOAc in heptanes to afford the title compound as an off-white solid.

LC-MS (Method E): Rt 1.35 min (87% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 7.65 (d, J = 5.5 Hz, 1H), 7.55 – 7.46 (m, 3H), 7.44 – 7.40 (m, 2H), 7.39 – 7.35 (m, 1H), 5.26 (s, 2H), 2.49 (s, 3H).

Step 4: 2-(2-Benzyloxy-4-bromo-5-fluoro-phenyl)propan-2-ol



To a stirred solution of 1-(2-benzyloxy-4-bromo-5-fluoro-phenyl)ethanone (step 3) (90%, 100 mg, 0.28 mmol) in THF (1 mL) at -78 °C was added bromo(methyl)magnesium (3M in Et₂O) (121 μL, 0.36 mmol). The dry ice bath was removed and the mixture was stirred at room temperature for 1 hour. The resulting mixture was diluted with sat. aq. NH₄Cl (10 mL) and EtOAc (10 mL). The organic layer was separated, dried over Na₂SO₄ and concentrated *in vacuo* to afford the title compound as a pale yellow solid.

LC-MS (Method E): Rt 1.31 mins; MS m/z 320.9, 322.9 [M+H-H₂O]⁺ (95% @ 215 nm)

¹H NMR (400 MHz, DMSO-d₆) δ 7.57 – 7.27 (m, 7H), 5.23 (s, 1H), 5.14 (s, 2H), 1.45 (s, 6H).

Step 5: 2-[5-Benzyloxy-2-fluoro-4-(1-hydroxy-1-methyl-ethyl)phenyl]acetic acid

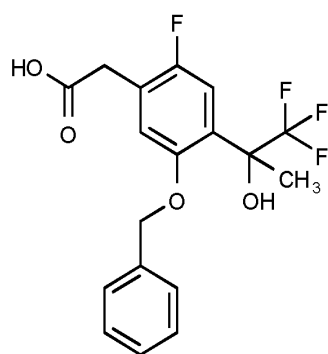
To a stirred solution of potassium 3-ethoxy-3-oxo-propanoate (75 mg, 0.44 mmol) and 2-(2-benzyloxy-4-bromo-5-fluoro-phenyl)propan-2-ol (step 4) (100 mg, 0.29 mmol) in toluene (2 mL) was added DMAP (3.6 mg, 0.03 mmol). The resulting mixture was degassed for 5 min. Diallyldipalladium dichloride (2.2 mg, 0.01 mmol) and BINAP (11.0 mg, 0.02 mmol) were added and the sealed reaction mixture was stirred at 140 °C for 3.5 h. The resulting mixture was concentrated *in vacuo* and the residue dissolved in THF (3 mL). The insoluble material was removed by filtration and the filtrate was diluted with MeOH (0.5 mL) and treated with 2M aq LiOH solution (0.44 mL, 0.88 mmol). The resulting mixture was stirred at room temperature for 16 h. The mixture was diluted with 2M NaOH (10 mL) and extracted with EtOAc (3 x 10 mL). The organic extracts were discarded and the aqueous portion was acidified to pH 3 using 2M aq. HCl. The mixture was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo* to the title compound as an off-white solid.

LC-MS (Method E): Rt 1.10 mins; MS m/z 301.0 [M+H-H₂O]⁺ (93% @ 215 nm)

^1H NMR (500 MHz, DMSO- d_6) δ 12.40 (s, 1H), 7.49 – 7.45 (m, 2H), 7.45 – 7.40 (m, 2H), 7.37 – 7.33 (m, 1H), 7.31 (d, J = 11.5 Hz, 1H), 7.05 (d, J = 6.3 Hz, 1H), 5.08 (s, 1H), 5.06 (s, 2H), 3.57 (s, 2H), 1.46 (s, 6H).

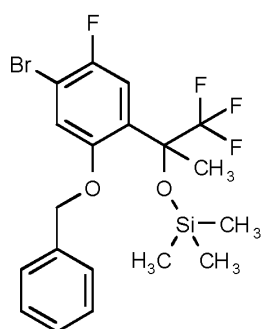
5 Intermediate BA

2-[5-Benzyloxy-2-fluoro-4-(2,2,2-trifluoro-1-hydroxy-1-methyl-ethyl)phenyl] acetic acid



Step 1: [1-(2-benzyloxy-4-bromo-5-fluoro-phenyl)-2,2,2-trifluoro-1-methyl-ethoxy]-trimethyl-silane

10



15

To a stirred solution of trimethyl(trifluoromethyl)silane (257 μL , 1.74 mmol) in THF (1 mL) at -50°C was added a solution of 1-(2-benzyloxy-4-bromo-5-fluoro-phenyl)ethanone (Intermediate B step 3) (90%, 500 mg, 1.39 mmol) in THF (1 mL) followed by TBAF (2.5 mg, 0.01 mmol). The reaction mixture was stirred at -50°C for 30 min then allowed to warm to room temperature for 1 hour. The resulting mixture was diluted with EtOAc (10 mL) and water (10 mL). The organic layer was separated, washed with water (10 mL), dried over Na_2SO_4 and concentrated *in vacuo* to form the title compound as a yellow oil.

LC-MS (Method H): R_t 2.03 mins; (85% @ 215 nm)

20

^1H NMR (500 MHz, Chloroform- d) δ 7.38 (d, J = 10.3 Hz, 1H), 7.31 – 7.11 (m, 5H), 6.99 (d, J = 5.7 Hz, 1H), 4.88 (s, 2H), 1.79 (s, 3H), 0.05 (s, 9H).

Step 2: 2-[5-Benzyloxy-2-fluoro-4-(2,2,2-trifluoro-1-hydroxy-1-methyl-ethyl)phenyl]acetic acid

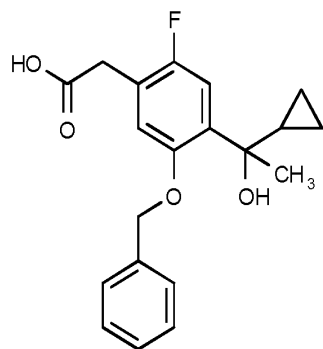
The title compound was prepared from [1-(2-benzyloxy-4-bromo-5-fluoro-phenyl)-2,2,2-trifluoro-1-methyl-ethoxy]-trimethyl-silane (step 1) and potassium 3-ethoxy-3-oxo-

LC-MS (Method E): Rt 1.18 mins; MS m/z 743.2 [2M-H]⁻ (100% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 12.60 (s (br), 1H), 7.47 – 7.39 (m, 5H), 7.37 – 7.31 (m, 1H), 7.19 (d, J = 6.4 Hz, 1H), 6.59 (s, 1H), 5.10 – 5.03 (m, 2H), 3.61 (s, 2H), 1.78 (s, 3H).

10 Intermediate BB

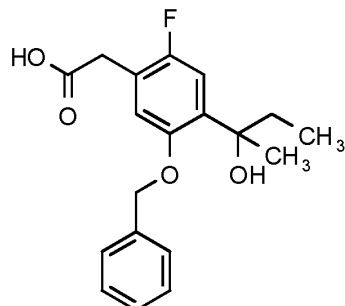
2-[5-Benzyloxy-4-(1-cyclopropyl-1-hydroxy-ethyl)-2-fluoro-phenyl]acetic acid



The title compound was prepared from 1-(2-benzyloxy-4-bromo-5-fluoro-phenyl)ethanone (Intermediate B step 3) and bromo(cyclopropyl)magnesium solution (1M in Me-THF) analogously to Intermediate B steps 4 and 5.

LC-MS (Method E): Rt 1.23 mins; MS m/z 345.1 [M+H]⁺ (86% @ 215 nm)

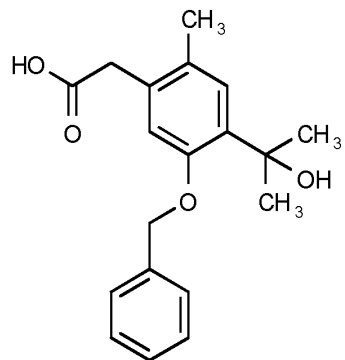
¹H NMR (500 MHz, DMSO-d₆) δ 12.47 (s (br), 1H), 7.49 – 7.45 (m, 2H), 7.43 – 7.39 (m, 2H), 7.36 – 7.32 (m, 1H), 7.23 (d, J = 11.5 Hz, 1H), 7.06 (d, J = 6.4 Hz, 1H), 5.08 (s, 2H), 4.64 (s, 1H), 3.56 (s, 2H), 1.64-1.58 (m, 1H), 1.54 (s, 3H), 0.50 – 0.42 (m, 1H), 0.24 – 0.16 (m, 2H), 0.06 – 0.00 (m, 1H).

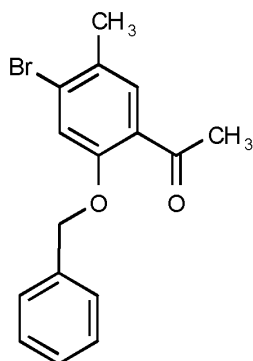
Intermediate BC**2-[5-benzyloxy-2-fluoro-4-(1-hydroxy-1-methyl-propyl)phenyl]acetic acid**

The title compound was prepared from 1-(2-benzyloxy-4-bromo-5-fluoro-phenyl)ethanone (Intermediate B step 3) and bromo(ethyl)magnesium solution (1M in THF) analogously to Intermediate B steps 4 and 5.

LC-MS (Method E): Rt 1.17 mins; MS m/z 315.1 [M+H-H₂O]⁺ (96% @ 215 nm)

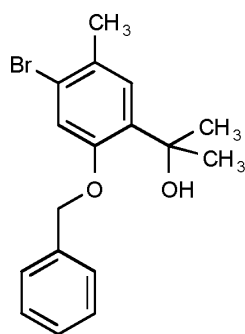
¹H NMR (500 MHz, DMSO-*d*₆) δ 12.43 (br. s, 1H), 7.47 – 7.39 (m, 4H), 7.37 – 7.32 (m, 1H), 7.28 (d, *J* = 11.6 Hz, 1H), 7.04 (d, *J* = 6.3 Hz, 1H), 5.05 (s, 2H), 4.85 (s, 1H), 3.59 – 3.54 (m, 2H), 2.02 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.65 (dq, *J* = 14.5, 7.3 Hz, 1H), 1.44 (s, 3H), 0.61 (t, *J* = 7.4 Hz, 3H).

Intermediate BD**2-[5-Benzyloxy-4-(1-hydroxy-1-methyl-ethyl)-2-methyl-phenyl]acetic acid**

Step 1: 1-(2-Benzyloxy-4-bromo-5-methyl-phenyl)ethanone

The title compound was prepared from 1-(4-bromo-2-hydroxy-5-methyl-phenyl)ethanone and bromomethylbenzene analogously to Intermediate B step 3.

- 5 LC-MS (Method G): Rt 1.18 min; MS m/z 319.0, 321.0 = [M+H]⁺ (98% @ 215 nm)
¹H NMR (400 MHz, DMSO-d₆) δ 7.56 – 7.46 (m, 4H), 7.45 – 7.39 (m, 2H), 7.38 – 7.33 (m, 1H), 5.24 (s, 2H), 2.48 (s, 3H), 2.30 (s, 3H).

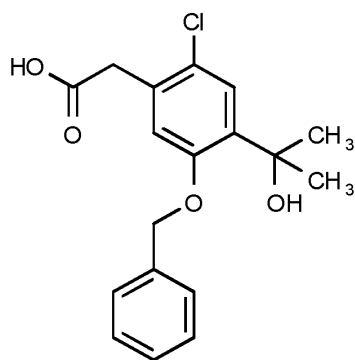
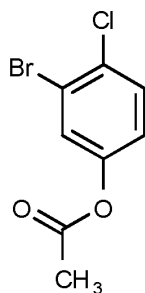
Step 2: 2-(2-Benzyloxy-4-bromo-5-methyl-phenyl)propan-2-ol

- 10 A cooled (0 °C) suspension of cerium trichloride (2.27 g, 9.21 mmol) in THF (100 mL) was treated with 3M methyl magnesium bromide in ether (3.07 mL, 9.21 mmol) and stirred for 1 h. 1-(2-Benzyloxy-4-bromo-5-methyl-phenyl)ethanone (step 1)(98%, 2 g, 6.14 mmol) was added in one portion and the reaction mixture was stirred at 0 °C for 90 min. The reaction was quenched with the addition of water (150 mL) followed by EtOAc (100 mL).
- 15 The organics were separated, washed with water (100 mL), brine (100 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The crude material was purified by chromatography on silica eluting with 0-100% EtOAc in heptanes to afford the title compound as a colourless oil.
- LC-MS (Method G): Rt 1.16 min; MS m/z 317.1, 319.1 = [M-H₂O+H]⁺ (100% @ 215 nm)
- 20 ¹H NMR (400 MHz, DMSO-d₆) δ 7.54 (s, 1H), 7.47 – 7.39 (m, 4H), 7.37 – 7.31 (m, 1H), 7.22 (s, 1H), 5.12 (s, 2H), 5.02 (s, 1H), 2.27 (s, 3H), 1.45 (s, 6H).

Step 3: 2-[5-Benzyloxy-4-(1-hydroxy-1-methyl-ethyl)-2-methyl-phenyl]acetic acid

The title compound was prepared from 2-(2-benzyloxy-4-bromo-5-methyl-phenyl)propan-2-ol (step 2) and potassium 3-ethoxy-3-oxo-propanoate analogously to Intermediate B step 5.

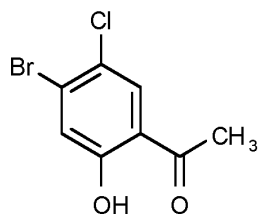
- 5 LC-MS (Method G): Rt 0.87 min; MS m/z 297.2 = [M-H₂O+H]⁺ (95% @ 215 nm)
¹H NMR (400 MHz, DMSO-d₆) δ 12.32 (br. s, 1H), 7.49 – 7.44 (m, 2H), 7.44 – 7.38 (m, 2H), 7.38 – 7.31 (m, 2H), 6.92 (s, 1H), 5.05 (s, 2H), 4.86 (s, 1H), 3.52 (s, 2H), 2.16 (s, 3H), 1.46 (s, 6H).

10 **Intermediate BE****2-[5-Benzyloxy-2-chloro-4-(1-hydroxy-1-methyl-ethyl)phenyl]acetic acid**Step 1: (3-Bromo-4-chloro-phenyl) acetate

- 15 A cooled (ice bath) solution of 3-bromo-4-chloro-phenol (5.0 g, 24.1 mmol) and TEA (6.31 mL, 36.15 mmol) in DCM (75 mL) was treated dropwise with acetyl chloride (2.4 mL, 33.74 mmol) in DCM (25 mL) and stirred at room temperature for 1 h. The resulting mixture was washed with 0.5M HCl (100 mL), 1:1 saturated NaHCO₃/water (100 mL), dried over Na₂SO₄, and concentrated *in vacuo* to afford the title compound as a brown
- 20 oil.
- LC-MS (Method E): Rt 1.22 min; no ionisation (90% @ 215 nm)

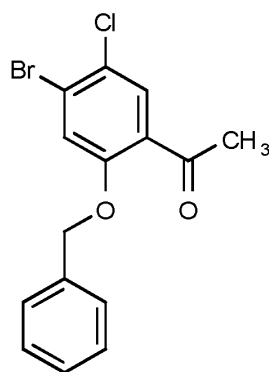
^1H NMR (400 MHz, DMSO- d_6) δ 7.68 (d, J = 8.9 Hz, 1H), 7.66 (d, J = 2.8 Hz, 1H), 7.23 (dd, J = 8.7, 2.7 Hz, 1H), 2.27 (s, 3H).

Step 2: 1-(4-Bromo-5-chloro-2-hydroxy-phenyl)ethanone



- 5 A mixture of (3-bromo-4-chloro-phenyl) acetate (step 1) (6.35 g, 25.47 mmol) and aluminium trichloride (6.11 g, 45.84 mmol) under nitrogen was heated to 165 °C for 3 h. The resulting melt was cooled to 130 °C, toluene (50 mL) was added and the mixture was heated to reflux to dissolve the solids for 1 h. The resulting mixture was cooled to room temperature then EtOAc (10 mL) and 0.5M HCl (40 mL) were added and the mixture
- 10 stirred with a secondary stirrer. The organics were separated and the aqueous was re-extracted with EtOAc (20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was treated with heptane (25 mL) and the resultant suspension was filtered, washed with further heptane and dried under suction to afford the title compound as a tan crystalline solid.
- 15 LC-MS (Method E): Rt 1.26 min; no ionisation (96% @ 215 nm)
 ^1H NMR (500 MHz, DMSO- d_6) δ 11.76 (s, 1H), 7.97 (s, 1H), 7.41 (s, 1H), 2.62 (s, 3H).

Step 3: 1-(2-Benzyloxy-4-bromo-5-chloro-phenyl)ethanone



- 1-(4-Bromo-5-chloro-2-hydroxy-phenyl)ethanone (step 2) (96%, 3.56 g, 13.69 mmol)
- 20 and 1-(4-bromo-5-chloro-2-hydroxy-phenyl)ethanone (78%, 2.35 g, 7.33 mmol) were dissolved in DMF (30 mL) and treated with K_2CO_3 (11.62 g, 84.1 mmol) and benzyl bromide (4.5 mL, 37.85 mmol). The reaction mixture was stirred at room temperature for 18 h. The resulting mixture was filtered through Celite®, washing with MeOH and the

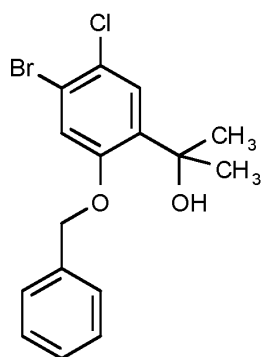
filtrate was concentrated *in vacuo*. The residue was partitioned between 4:1 EtOAc/heptane (150 mL) and water (100 mL). The organic portion was separated, washed with water (100 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by chromatography on silica eluting with a gradient of 0 to 30% EtOAc in heptanes.

- 5 The product fractions were concentrated *in vacuo* and recrystallisation of the residue from 1:1 TBME/heptane (20 mL) afforded the title compound as a brown crystalline solid.

LC-MS (Method G): Rt 1.19 min; (76% @ 215 nm)

¹H NMR (500 MHz, Chloroform-d) δ 7.83 (s, 1H), 7.44-7.40 (m, 5H), 7.32 (s, 1H), 5.14 (s, 2H), 2.55 (s, 3H).

- 10 Step 4: 2-(2-Benzyloxy-4-bromo-5-chloro-phenyl)propan-2-ol



A cooled (-78°C) solution of 1-(2-benzyloxy-4-bromo-5-chloro-phenyl)ethanone (step 3) (1.29 g, 3.8 mmol) in THF (25 mL) was treated with methyl magnesium bromide (3M in Et₂O) (1.65 mL, 4.94 mmol) and allowed to warm to room temperature, stirring for 1.5 h.

- 15 The resulting mixture was cooled to 0 °C and treated with 10% aq NH₄Cl (10 mL) and EtOAc (10 mL). The organic portion was separated, dried over Na₂SO₄ and concentrated *in vacuo*. Purification of the crude material by chromatography on basic silica eluting with a gradient of 0 to 50% EtOAc in heptanes afforded the title compound as a light tan oil which crystallised on standing.

- 20 LC-MS (Method G): Rt 1.17 min; MS m/z 337.0, 339.0 = [M+H-H₂O]⁺ (68% @ 215 nm)
¹H NMR (500 MHz, Chloroform-d) δ 7.47 (s, 1H), 7.45 – 7.36 (m, 5H), 7.21 (s, 1H), 5.10 (s, 2H), 3.45 (s, 1H), 1.58 (s, 6H).

Step 5: 2-[5-Benzyloxy-2-chloro-4-(1-hydroxy-1-methyl-ethyl)phenyl]acetic acid

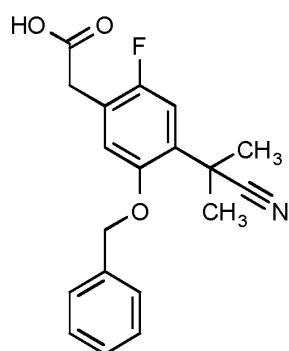
- 25 2-(2-Benzyloxy-4-bromo-5-chloro-phenyl)propan-2-ol (step 4) (1.04 g, 2.91 mmol), potassium 3-ethoxy-3-oxo-propanoate (991 mg, 5.82 mmol), diallyldipalladium dichloride (106 mg, 0.29 mmol), BINAP (362 mg, 0.58 mmol) and DMAP (36 mg, 0.29 mmol) were suspended in toluene (9.7 mL) and heated in a sealed tube to 140°C for 18 h. The reaction solvent was concentrated *in vacuo* and the resulting residue was treated with

MeOH (20 mL) and 2M aq. LiOH (4.37 mL, 8.73 mmol) then stirred at room temperature for 3 h. Further 2M aq. LiOH (4.37 mL, 8.73 mmol) and MeOH (10 mL) were added and stirring continued for an additional 2 h. The mixture was concentrated *in vacuo* to remove the bulk of the organics and the aqueous residue was diluted with water (20 mL) and DCM (30 mL). The aqueous portion was separated, washed with DCM and acidified with 2M KHSO₄ (25 mL). The mixture was extracted with DCM (2 x 30 mL) and the combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo*. The crude material was purified by chromatography on silica eluting with 0 to 100% EtOAc in heptanes followed by 0 to 100% MeOH in EtOAc. The product fractions were concentrated *in vacuo* and the residue was dissolved in 1:1 DMSO/MeOH (1.2 mL). Purification of the crude material by preparative HPLC (acidic pH, early elution method) afforded the title compound as a white crystalline solid

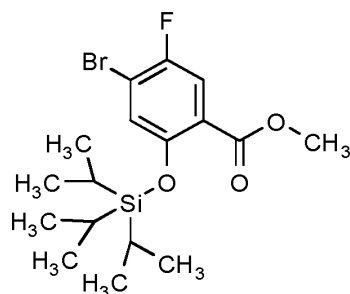
LC-MS (Method E): Rt 1.12 min; MS m/z 316.9, 318.9 = [M+H-H₂O]⁺ (100% @ 215 nm)
¹H NMR (400 MHz, DMSO-d₆) δ 7.57 (s, 1H), 7.50 – 7.45 (m, 2H), 7.45 – 7.39 (m, 2H), 7.38 – 7.33 (m, 1H), 7.15 (s, 1H), 5.11 (s, 1H), 5.09 (s, 2H), 3.65 (s, 2H), 1.45 (s, 6H).

Intermediate C

2-[5-Benzyloxy-4-(1-cyano-1-methyl-ethyl)-2-fluoro-phenyl]acetic acid



20 Step 1: Methyl 4-bromo-5-fluoro-2-triisopropylsilyloxy-benzoate



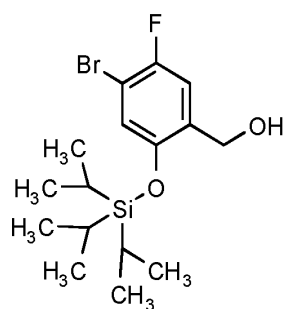
A stirred mixture of methyl 4-bromo-5-fluoro-2-hydroxy-benzoate (3 g, 12.05 mmol), TEA

(3.69 mL, 26.5 mmol) and DMAP (147 mg, 1.2 mmol) in DCM (20 mL) under nitrogen was treated dropwise with triisopropylsilyl chloride (3.09 mL, 14.46 mmol) and the mixture was stirred at room temperature overnight. The resulting mixture was diluted with water (20 mL) and the organic layer was separated, dried over Na₂SO₄ and concentrated *in vacuo* to afford the title compound as a yellow oil.

LC-MS (Method H): Rt 2.09 mins; MS m/z 405.1, 407.1 = [M+H]⁺ (97% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 7.61 (d, J = 8.8 Hz, 1H), 7.12 (d, J = 5.6 Hz, 1H), 3.81 – 3.74 (m, 3H), 1.29 (hept, J = 7.3 Hz, 3H), 1.05 (d, J = 7.6 Hz, 18H).

Step 2: (4-Bromo-5-fluoro-2-triisopropylsilyloxy-phenyl)methanol



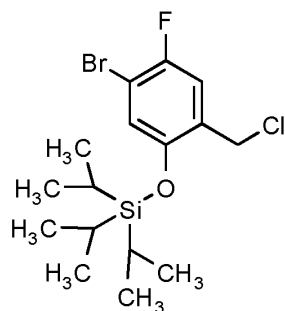
A stirred solution of methyl 4-bromo-5-fluoro-2-triisopropylsilyloxy-benzoate (step 1) (76%, 5.4 g, 10.12 mmol) in THF (100 mL) was treated with 4M LiBH₄ in THF (7.59 mL, 30.37 mmol) and the mixture was stirred at room temperature overnight.

The mixture was cooled (0 °C) and the reaction was quenched carefully with ice (20 mL) stirring for 30 min then allowed to warm to room temperature. EtOAc (20 mL) was added and the organic layer was separated, dried over Na₂SO₄ and concentrated *in vacuo*. Purification of the crude material by chromatography on silica (Biotage® Isolera 55g KP-NH) eluting with 0-100% EtOAc in heptanes afforded the title compound as a yellow oil.

LC-MS (Method H): Rt 1.60 mins; MS m/z 400.1 = [M+Na]⁺ (90% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 7.28 (d, J = 9.5 Hz, 1H), 6.92 (d, J = 5.7 Hz, 1H), 5.32 (t, J = 5.2 Hz, 1H), 4.48 (d, J = 4.4 Hz, 2H), 1.28 (dq, J = 14.5, 7.5 Hz, 3H), 1.09 – 1.03 (m, 18H).

Step 3: [5-Bromo-2-(chloromethyl)-4-fluoro-phenoxy]-triisopropyl-silane



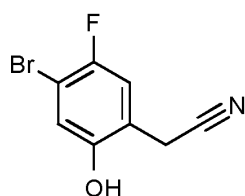
A cooled (0 °C), stirred solution of (4-bromo-5-fluoro-2-triisopropylsilyloxy-phenyl)methanol (4.8 g, 12.72 mmol) and DMF (941 μ L, 12.14 mmol) in DCM (80 mL) was treated dropwise with thionyl chloride (2.24 mL, 30.88 mmol) in DCM (40 mL) and the mixture was stirred at room temperature for 2 h.

The solvents were removed *in vacuo* and the residue was diluted with EtOAc (100 mL). The mixture was washed with saturated NaHCO_3 (100 mL), brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude material by chromatography on silica eluting with 0-100% EtOAc in heptanes afforded the title compound as a yellow oil.

LC-MS (Method H): Rt 2.12 min (87% @ 215 nm)

^1H NMR (400 MHz, DMSO-d_6) δ 7.51 (d, J = 9.0 Hz, 1H), 7.02 (d, J = 5.8 Hz, 1H), 4.66 (s, 2H), 1.35 (hept, J = 7.4 Hz, 3H), 1.08 (d, J = 7.5 Hz, 18H).

Step 4: 2-(4-Bromo-5-fluoro-2-hydroxy-phenyl)acetonitrile



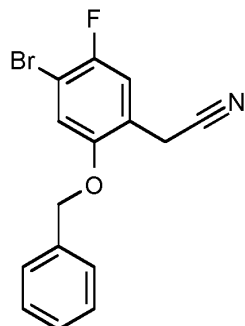
Sodium cyanide (576 mg, 11.75 mmol) was added to a solution of [5-bromo-2-(chloromethyl)-4-fluoro-phenoxy]-triisopropyl-silane (step 3) (3.1 g, 7.83 mmol) in DMF (20 mL) and the mixture was stirred at room temperature overnight. The resulting mixture was diluted with EtOAc (20 mL) and washed with sat. sodium carbonate (30 mL), brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude material by chromatography on silica eluting with 0-100% EtOAc in heptanes afforded the title compound as a yellow solid.

LC-MS (Method E): Rt 1.04 mins; MS m/z 227.8, 229.8 = $[\text{M-H}]^-$ (98% @ 215 nm)

^1H NMR (500 MHz, DMSO-d_6) δ 10.43 (s, 1H), 7.30 (d, J = 9.1 Hz, 1H), 7.08 (d, J = 6.1

Hz, 1H), 3.78 (s, 2H).

Step 5: 2-(2-Benzyloxy-4-bromo-5-fluoro-phenyl)acetonitrile

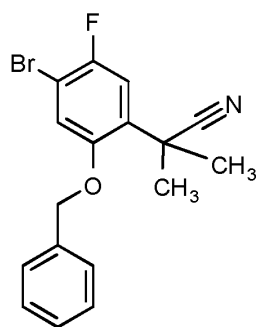


5 Benzyl bromide (614 μ L, 5.16 mmol) was added to a stirred mixture of 2-(4-bromo-5-fluoro-2-hydroxy-phenyl)acetonitrile (step 4) (990 mg, 4.3 mmol) and K_2CO_3 (1.49 g, 10.76 mmol) in DMF (10 mL) and the mixture was stirred at 80 $^{\circ}C$ for 1 hour. The resulting mixture was allowed to cool to room temperature and partitioned between EtOAc (20 mL) and water (50 mL). The layers were separated and the aqueous portion was further extracted with EtOAc (10 mL). The combined organic extracts were washed with brine (50 mL), dried
10 over Na_2SO_4 and concentrated *in vacuo*. Purification by chromatography on silica eluting with 0-100% EtOAc in heptanes afforded the title compound as a yellow oil.

LC-MS (Method E): Rt 1.30 min (68% @ 215 nm)

1H NMR (400 MHz, DMSO- d_6) δ 7.56 – 7.45 (m, 3H), 7.46 – 7.37 (m, 3H), 7.40 – 7.32 (m, 1H), 5.22 (s, 2H), 3.90 (s, 2H).

15 Step 6: 2-(2-Benzyloxy-4-bromo-5-fluoro-phenyl)-2-methyl-propanenitrile



To a cooled (0 $^{\circ}C$) solution of 2-(2-benzyloxy-4-bromo-5-fluoro-phenyl)acetonitrile (0.51 g, 1.59 mmol) in DMF (10 mL) under nitrogen was added methyl iodide (100%, 0.2 mL, 3.19 mmol) followed by NaH, (60% dispersion in mineral oil, 127 mg, 3.19 mmol). The mixture
20 was allowed to warm to room temperature and stirred overnight. The resulting mixture was carefully poured onto ice (20 mL), EtOAc (20 mL) was added and the mixture was stirred for 20 min. The organic portion was separated, dried over Na_2SO_4 and concentrated *in*

vacuo. The residual DMF was removed by drying in a high vacuum oven at 40 °C overnight to afford the title compound as a yellow oil.

LC-MS (Method E): Rt 1.37 mins; MS m/z 347.9, 350.0 = [M+H]⁺ (66% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 7.56 (m, 2H), 7.53 (d, J = 6.0 Hz, 1H), 7.45 – 7.38 (m, 2H), 7.38 – 7.32 (m, 2H), 5.27 (s, 2H), 1.69 (s, 6H).

Step 7: 2-[5-Benzyloxy-4-(1-cyano-1-methyl-ethyl)-2-fluoro-phenyl]acetic acid

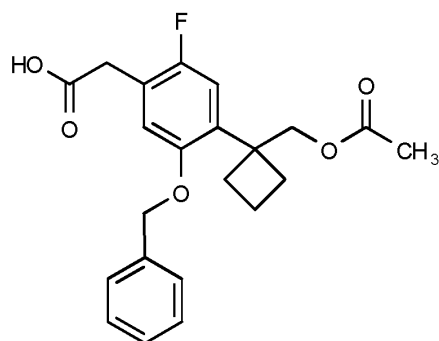
The title compound was prepared from potassium 3-ethoxy-3-oxo-propanoate and 2-(2-benzyloxy-4-bromo-5-fluoro-phenyl)-2-methyl-propanenitrile (step 6) analogously to Intermediate B step 5.

LC-MS (Method E): Rt 1.20 mins; MS m/z 328.0 = [M+H]⁺ (48% @ 215 nm)

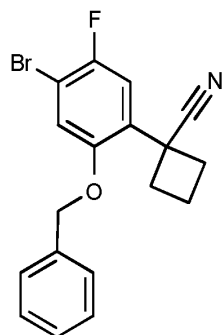
¹H NMR (400 MHz, DMSO-d₆) δ 12.50 (s, 1H), 7.61 – 7.54 (m, 2H), 7.45 – 7.37 (m, 2H), 7.39 – 7.31 (m, 1H), 7.24 (d, J = 6.5 Hz, 1H), 7.15 (d, J = 10.9 Hz, 1H), 5.19 (s, 2H), 3.62 (s, 2H), 1.69 (s, 6H).

Intermediate CA

2-[4-[1-(Acetoxymethyl)cyclobutyl]-5-benzyloxy-2-fluoro-phenyl]acetic acid



Step 1: 1-(2-Benzyloxy-4-bromo-5-fluoro-phenyl)cyclobutanecarbonitrile



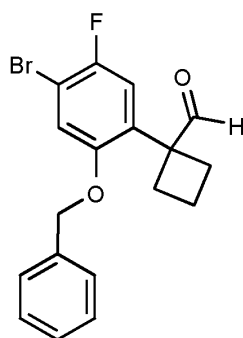
To a cooled (0 °C) suspension of NaH (60% dispersion in mineral oil, 394 mg, 9.84 mmol) in DMF (15 mL) was added a solution of 2-(2-benzyloxy-4-bromo-5-fluoro-

phenyl)acetonitrile (Intermediate C step 5)(1.5 g, 4.69 mmol) in DMF (5 mL). The mixture was stirred for 15 min and then treated dropwise with a solution of 1,3-dibromopropane (523 μ L, 5.15 mmol) in DMF (5 mL) over 10 min. The mixture was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched with saturated aqueous NH_4Cl solution (100 mL) and extracted with DCM (100 mL). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude material by chromatography on silica eluting with 0-50% TBME in heptanes afforded the title compound as a colourless crystalline solid.

LC-MS (Method G): Rt 1.18 min; MS m/z 360.1, 362.0 = $[\text{M}+\text{H}]^+$ (99% @ 215 nm)

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.53 – 7.46 (m, 3H), 7.45 – 7.39 (m, 2H), 7.39 – 7.32 (m, 2H), 5.21 (s, 2H), 2.67 – 2.53 (m, 4H), 2.29 – 2.17 (m, 1H), 1.92-1.83 (m, 1H).

Step 2: 1-(2-Benzyloxy-4-bromo-5-fluoro-phenyl)cyclobutanecarbaldehyde

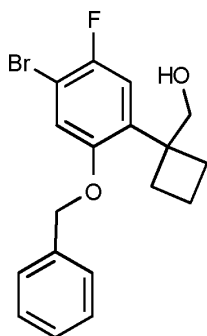


To a cooled (-78°C) solution of 1-(2-benzyloxy-4-bromo-5-fluoro-phenyl)cyclobutanecarbonitrile (step 1) (99%, 556 mg, 1.53 mmol) in THF (7.5 mL) was added 1.2M DIBAL in toluene (1.91 mL, 2.29 mmol) and the mixture was allowed to warm to 0°C and maintained at 0°C overnight. The resulting mixture was cooled to -78°C and treated with a further 0.5 equiv. of 1.2M DIBAL in toluene and allowed to warm to -40°C . The reaction was quenched by addition of 1M HCl (2 mL) at -30°C then warmed to room temperature and stirred for 30 min. The resulting mixture was diluted with EtOAc (30 mL) and washed with sat. NaHCO_3 (30 mL) solution and brine (30 mL). The organics were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue purified by chromatography on silica eluting with 0-50% TBME in heptanes to afford the title compound as a colourless oil, which crystallised on standing at room temperature.

LC-MS (Method G): Rt 1.23 min; (97% @ 215 nm)

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.61 (s, 1H), 7.42 – 7.30 (m, 6H), 7.26 (d, $J = 9.4$ Hz, 1H), 5.07 (s, 2H), 2.40 – 2.32 (m, 2H), 2.00 – 1.90 (m, 1H), 1.86 – 1.78 (m, 1H), 2.56 – 2.45 (obscured m, 2H)

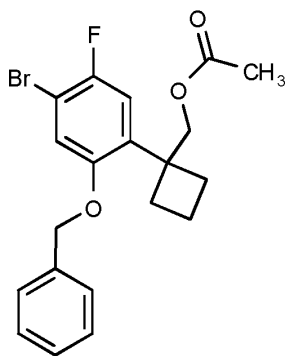
Step 3: [1-(2-Benzyloxy-4-bromo-5-fluoro-phenyl)cyclobutyl]methanol



To a cooled (0 °C) solution of 1-(2-benzyloxy-4-bromo-5-fluoro-phenyl)cyclobutane carbaldehyde (step 2) (97%, 200 mg, 0.53 mmol) in MeOH (2.5 mL) was added NaBH₄ (21 mg, 0.56 mmol) and the mixture stirred for 30 min. The reaction was quenched by addition of sat. NaHCO₃ solution (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (30 mL), dried over Na₂SO₄ and concentrated to afford the title compound as a colourless oil which crystallised on standing at room temperature.

LC-MS (Method G): Rt 1.17 min; MS m/z 363.1, 365.1 = [M-H]⁻ (99% @ 215 nm)
¹H NMR (400 MHz, DMSO-d₆) δ 7.45 – 7.38 (m, 4H), 7.36 – 7.32 (m, 1H), 7.29 (d, J = 5.9 Hz, 1H), 6.88 (d, J = 9.7 Hz, 1H), 5.07 (s, 2H), 4.62 (t, J = 5.8 Hz, 1H), 3.62 (d, J = 5.7 Hz, 2H), 2.25 – 2.11 (m, 4H), 1.97 – 1.89 (m, 1H), 1.74 – 1.66 (m, 1H).

Step 4: [1-(2-Benzyloxy-4-bromo-5-fluoro-phenyl)cyclobutyl]methyl acetate

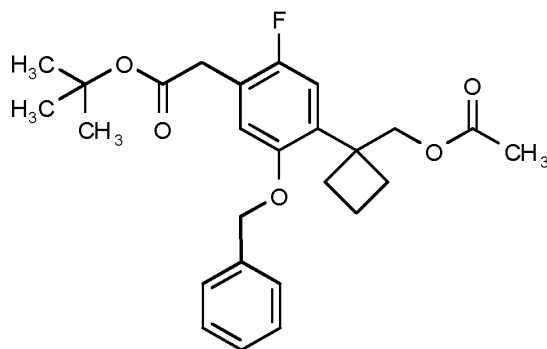


To a solution of [1-(2-benzyloxy-4-bromo-5-fluoro-phenyl)cyclobutyl]methanol (step 3) (99%, 191 mg, 0.52 mmol), TEA (99 µL, 0.57 mmol) and DMAP (6.32 mg, 0.05 mmol) in DCM (3 mL) was added acetic anhydride (54 µL, 0.57 mmol) and the mixture stirred at room temperature overnight. The resulting mixture was diluted with DCM (20 mL) and washed with 1M HCl (15 mL), brine (15 mL), dried over Na₂SO₄ and concentrated *in vacuo* to afford the title compound as a colourless oil.

LC-MS (Method E): Rt 1.55 min; (95% @ 215 nm)

^1H NMR (400 MHz, DMSO- d_6) δ 7.45 – 7.38 (m, 4H), 7.36 – 7.31 (m, 2H), 6.98 (d, J = 9.6 Hz, 1H), 5.09 (s, 2H), 4.31 (s, 2H), 2.33 – 2.25 (m, 2H), 2.17 – 2.10 (m, 2H), 2.07 – 1.98 (m, 1H), 1.88 (s, 3H), 1.78 – 1.69 (m, 1H).

5 Step 5: *tert*-Butyl 2-[4-[1-(acetoxymethyl)cyclobutyl]-5-benzyloxy-2-fluoro-phenyl]acetate



To a solution of [1-(2-benzyloxy-4-bromo-5-fluoro-phenyl)cyclobutyl]methyl acetate (step 4) (170 mg, 0.42 mmol) in THF (1.5 mL) was added Pd(dba) $_2$ (12 mg, 0.02 mmol) and Q-Phos (15 mg, 0.02 mmol). The mixture was degassed for 5 min then 0.5M bromo-(2-*tert*-butoxy-2-oxo-ethyl)zinc in THF (1.25 mL, 0.63 mmol) was added and the mixture was heated at 60 °C for 2 h. After cooling to room temperature, the resulting mixture was diluted with EtOAc (10 mL) and washed with sat. NaHCO $_3$ (10 mL) solution, brine (10 mL), dried over Na $_2$ SO $_4$ and concentrated *in vacuo*. Purification of the crude residue by chromatography on silica eluting with 0-50% TBME in heptanes afforded the title compound as a pale orange oil.

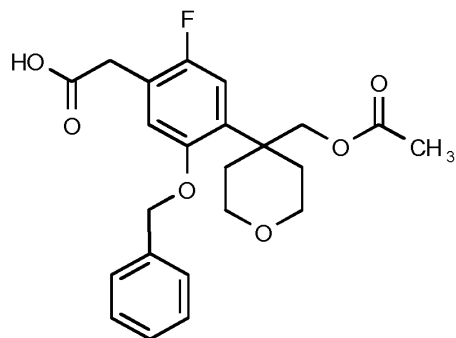
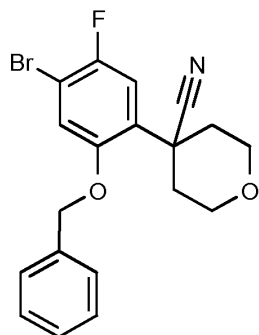
LC-MS (Method E): Rt 1.57 min; MS m/z 465.2 [M+Na] $^+$ (72% @ 215 nm)

^1H NMR (400 MHz, DMSO- d_6) δ 7.45 – 7.38 (m, 4H), 7.35 – 7.31 (m, 1H), 7.00 (d, J = 6.4 Hz, 1H), 6.79 (d, J = 10.5 Hz, 1H), 5.02 (s, 2H), 4.31 (s, 2H), 3.56 (s, 2H), 2.34 – 2.26 (m, 2H), 2.17 – 2.11 (m, 2H), 2.05 – 1.97 (m, 1H), 1.88 (s, 3H), 1.77 – 1.70 (m, 1H), 1.40 (s, 9H).

Step 6: 2-[4-[1-(Acetoxymethyl)cyclobutyl]-5-benzyloxy-2-fluoro-phenyl]acetic acid

To a cooled (0 °C) solution of *tert*-butyl 2-[4-[1-(acetoxymethyl)cyclobutyl]-5-benzyloxy-2-fluoro-phenyl]acetate (step 5)(90%, 192 mg, 0.39 mmol) in DCM (1.5 mL) was added TFA (0.5 mL, 6.53 mmol) and the mixture was allowed to warm to room temperature, stirring for a further 2 h. The resulting mixture was concentrated *in vacuo* and the crude product was azeotroped with DCM to afford the title compound as an orange oil.

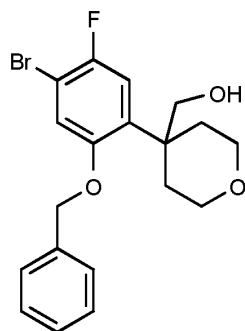
LC-MS (Method E): Rt 1.31 min; MS m/z 409.1 [M+Na] $^+$ (94% @ 215 nm)

Intermediate CB**2-[4-[4-(Acetoxymethyl)tetrahydropyran-4-yl]-5-benzyloxy-2-fluoro-phenyl]acetic acid****5 Step 1: 4-(2-Benzyloxy-4-bromo-5-fluoro-phenyl)tetrahydropyran-4-carbonitrile**

The title compound was prepared from 2-(2-benzyloxy-4-bromo-5-fluoro-phenyl)acetonitrile (Intermediate C step 5) and 1-bromo-2-(2-bromoethoxy)ethane analogously to Intermediate C step 6.

- 10 LC-MS (Method G): Rt 1.11 min; MS m/z 390.1, 392.1 = [M+H]⁺ (95% @ 215 nm)
¹H NMR (400 MHz, Chloroform-d) δ 7.52 – 7.50 (m, 1H), 7.45 – 7.35 (m, 4H), 7.18 (d, J = 5.8 Hz, 1H), 7.09 (d, J = 9.5 Hz, 1H), 5.18 (s, 2H), 4.06 – 3.99 (m, 2H), 3.91 (td, J = 12.2, 1.6 Hz, 2H), 2.36 – 2.27 (m, 2H), 2.09 – 1.99 (m, 2H).

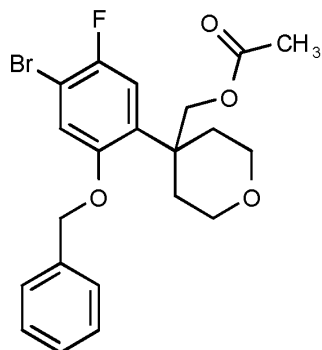
Step 2: [4-(2-Benzyloxy-4-bromo-5-fluoro-phenyl)tetrahydropyran-4-yl]methanol



To a stirred solution of 4-(2-benzyloxy-4-bromo-5-fluoro-phenyl)tetrahydropyran-4-carbonitrile (step 1) (1.85 g, 4.74 mmol) in DCM (50 mL) at -78 °C was added dropwise 1M DIBAL in hexane (5.21 mL, 5.21 mmol) and the mixture was stirred at -78 °C for 1 h. The reaction was quenched dropwise addition of MeOH, the diluted with saturated aqueous Rochelle's salt (10 mL), water (30 mL) and the phases were separated. The organic phase was washed with 1M HCl (30 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The crude solid was dissolved in DCM (50 mL) and re-treated with 1M DIBAL in hexane (5.21 mL, 5.21 mmol) at -78 °C and left to stir overnight. Additional 1 M DIBAL in hexane (3.0 mL, 3.0 mmol) was added at -78 °C and stirred for 40 min. The reaction was quenched with dropwise addition of MeOH leading to the formation of a 'hydrogel-like' material. The mixture was diluted with further DCM (30 mL), physically broken up, filtered through a sinter funnel and concentrated *in vacuo*. The filter cake was dissolved in 1 M NaOH (200 mL) and stirred for 2 h. The aqueous layer was extracted with TBME (2 x 100 mL) and the combined organic extracts were concentrated *in vacuo*. Purification by chromatography on silica eluting with 0-100% EtOAc in heptanes afforded the title compound as an off-white gum.

LC-MS (Method G): Rt 1.02 min; MS m/z 395.1, 397.2 = [M+H]⁺ (78% @ 215 nm)

¹H NMR (400 MHz, DMSO-d₆) δ 7.46 – 7.28 (m, 6H), 7.16 (d, J = 11.2 Hz, 1H), 5.12 (s, 2H), 4.49 (t, J = 5.6 Hz, 1H), 3.71 – 3.58 (m, 4H), 3.43 – 3.35 (m, 2H), 2.23 – 2.14 (m, 2H), 1.84 – 1.75 (m, 2H).

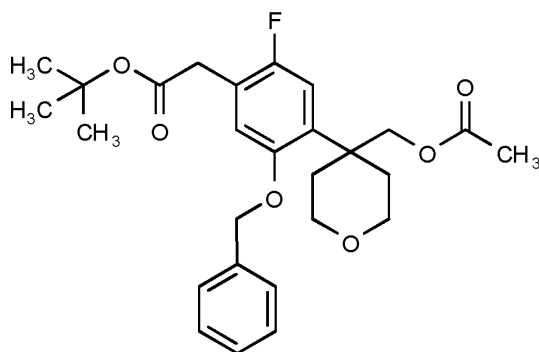
Step 3: [4-(2-Benzyloxy-4-bromo-5-fluoro-phenyl)tetrahydropyran-4-yl]methyl acetate

To a cooled (0 °C) solution of [4-(2-benzyloxy-4-bromo-5-fluoro-phenyl)tetrahydropyran-4-yl]methanol (step 2)(574 mg, 1.45 mmol) in DCM (10 mL) was added TEA (507 μ L, 2.9 mmol) followed by DMAP (17.73 mg, 0.15 mmol) and acetic anhydride (274 μ L, 2.9 mmol) and the reaction mixture was allowed to warm to room temperature and stirred overnight. The resulting mixture was diluted with DCM (20 mL) and washed with water (2 x 15 mL). The organic portion was dried over Na₂SO₄ and concentrated *in vacuo*. Purification by C18 reverse phase chromatography eluting with 10-100% MeCN in water (+0.1% formic acid) afforded the title compound as a pale yellow gum.

LC-MS (Method E): Rt 1.42 min; (100% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 7.47 – 7.38 (m, 5H), 7.39 – 7.31 (m, 1H), 7.25 (d, J = 11.0 Hz, 1H), 5.14 (s, 2H), 4.37 (s, 2H), 3.65 (ddd, J = 11.5, 5.7, 3.6 Hz, 2H), 3.41 (ddd, J = 11.5, 8.9, 2.5 Hz, 2H), 2.27 – 2.19 (m, 2H), 1.87 – 1.77 (m, 5H).

Step 4: *tert*-Butyl 2-[4-[4-(acetoxymethyl)tetrahydropyran-4-yl]-5-benzyloxy-2-fluoro-phenyl]acetate



The title compound was prepared from [4-(2-benzyloxy-4-bromo-5-fluoro-phenyl)tetrahydropyran-4-yl]methyl acetate (step 3) and 0.5M bromo-(2-*tert*-butoxy-2-oxo-ethyl)zinc in THF analogously to Intermediate CA step 5.

LC-MS (Method G): Rt 1.17 min; MS m/z 495.2 = [M+Na]⁺ (99% @ 215 nm)

¹H NMR (400 MHz, DMSO-d₆) δ 7.48 – 7.43 (m, 2H), 7.43 – 7.37 (m, 2H), 7.38 – 7.30 (m, 1H), 7.10 (d, J = 6.7 Hz, 1H), 7.05 (d, J = 11.9 Hz, 1H), 5.07 (s, 2H), 4.37 (s, 2H), 3.69 – 3.60 (m, 2H), 3.58 (s, 2H), 3.46 – 3.36 (m, 2H), 2.29 – 2.19 (m, 2H), 1.88 – 1.78 (m, 5H), 1.40 (s, 9H).

5 **Step 5:** 2-[4-[4-(Acetoxymethyl)tetrahydropyran-4-yl]-5-benzyloxy-2-fluoro-phenyl]acetic acid

The title compound was prepared from *tert*-butyl 2-[4-[4-(acetoxymethyl)tetrahydropyran-4-yl]-5-benzyloxy-2-fluoro-phenyl]acetate (step 4) and TFA analogously to Intermediate CA step 6.

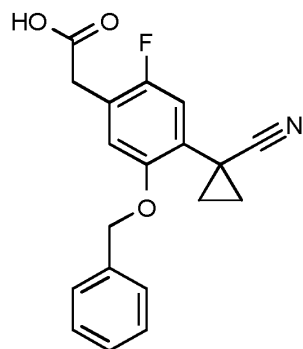
10 LC-MS (Method G): Rt 0.91 min; MS m/z 439.2 = [M+Na]⁺ (99% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 12.51 (br. s, 1H), 7.48 – 7.43 (m, 2H), 7.43 – 7.38 (m, 2H), 7.38 – 7.31 (m, 1H), 7.14 (d, J = 6.7 Hz, 1H), 7.04 (d, J = 11.8 Hz, 1H), 5.06 (s, 2H), 4.37 (s, 2H), 3.65 (ddd, J = 11.3, 5.5, 3.5 Hz, 2H), 3.59 (s, 2H), 3.46 – 3.38 (m, 2H), 2.27 – 2.19 (m, 2H), 1.87 – 1.79 (m, 5H).

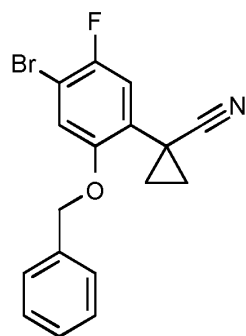
15

Intermediate D

2-[5-Benzyloxy-4-(1-cyanocyclopropyl)-2-fluoro-phenyl]acetic acid



Step 1: 1-(2-Benzyloxy-4-bromo-5-fluoro-phenyl)cyclopropanecarbonitrile



20

To solid potassium hydroxide (210 mg, 3.75 mmol) was added 60% aq. potassium

hydroxide (779 mg, 3.28 mmol) followed by 2-(2-benzyloxy-4-bromo-5-fluorophenyl)acetonitrile (Intermediate C step 5) (500 mg, 1.56 mmol) and tetrabutylammonium bromide (5 g, 15.62 mmol). The resulting mixture was treated dropwise with 1,2-dibromoethane (0.27 mL, 3.12 mmol) (exotherm observed and temperature was maintained at 50 °C by external cooling) and stirring continued at 50 °C overnight. The resulting mixture was diluted with water (15 mL) and extracted with EtOAc (2 x 10 mL). The organic extracts were combined, dried over Na₂SO₄ and concentrated *in vacuo*. Purification of the crude material by chromatography on silica eluting with 0-100% EtOAc in heptanes afforded the title compound as a yellow solid.

LC-MS (Method E): Rt 1.33 min (100% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 7.55 (d, J = 7.1 Hz, 2H), 7.48 (d, J = 5.9 Hz, 1H), 7.47 – 7.39 (m, 3H), 7.35 (t, J = 7.3 Hz, 1H), 5.28 (s, 2H), 1.64 – 1.58 (m, 2H), 1.41 – 1.35 (m, 2H).

Step 2: 2-[5-Benzyloxy-4-(1-cyanocyclopropyl)-2-fluoro-phenyl]acetic acid

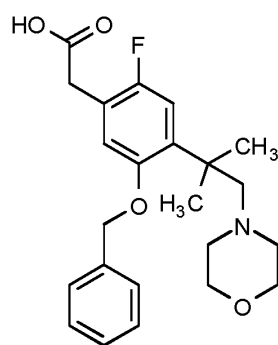
The title compound was prepared from 1-(2-benzyloxy-4-bromo-5-fluorophenyl)cyclopropanecarbonitrile (step 1) and potassium 3-ethoxy-3-oxo-propanoate analogously to Intermediate B step 5 substituting toluene with mesitylene as the solvent.

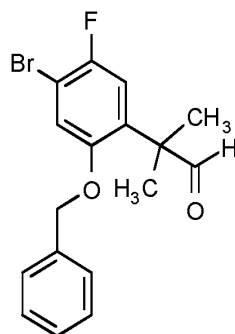
LC-MS (Method E): Rt 1.12 mins; MS m/z 326.1 = [M+H]⁺ (71 % @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 12.55 (s, 1H), 7.57 (d, J = 7.1 Hz, 2H), 7.45 – 7.38 (m, 2H), 7.38 – 7.32 (m, 1H), 7.20 (d, J = 9.8 Hz, 1H), 7.17 (d, J = 6.4 Hz, 1H), 5.20 (s, 2H), 3.60 (s, 2H), 1.62 – 1.55 (m, 2H), 1.38 – 1.32 (m, 2H).

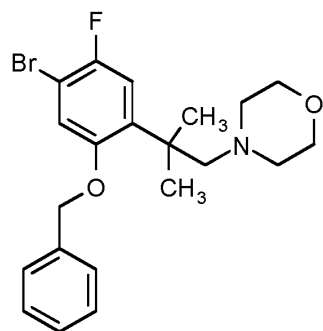
Intermediate E

2-[5-Benzyloxy-4-(1,1-dimethyl-2-morpholino-ethyl)-2-fluoro-phenyl]acetic acid



Step 1: 2-(2-Benzyloxy-4-bromo-5-fluoro-phenyl)-2-methyl-propanal

- To a solution of 2-(2-benzyloxy-4-bromo-5-fluoro-phenyl)-2-methyl-propanenitrile (Intermediate C step 6) (80% purity, 1 g, 2.30 mmol) in DCM (20 mL) at -78 °C was added
- 5 1M DIBAL in hexane (6.03 mL, 6.03 mmol). The mixture was allowed to slowly warm to room temperature and was stirred overnight. The reaction was quenched with 1M HCl (50 mL) and stirred for 30 min. The organic layer was separated, dried over Na₂SO₄ and concentrated *in vacuo*. Purification of the crude material by chromatography on silica eluting with 0-30% EtOAc in heptanes afforded the title compound as a white solid.
- 10 LC-MS (Method E): Rt 1.40 min (99 % @ 215 nm)
- ¹H NMR (400 MHz, DMSO-d₆) δ 9.46 (s, 1H), 7.46 (d, J = 6.0 Hz, 1H), 7.44 – 7.37 (m, 1H), 7.41 – 7.28 (m, 5H), 5.12 (s, 2H), 1.31 (s, 6H).

Step 2: 4-[2-(2-Benzyloxy-4-bromo-5-fluoro-phenyl)-2-methyl-propyl]morpholine

- 15 To a solution of 2-(2-benzyloxy-4-bromo-5-fluoro-phenyl)-2-methyl-propanal (step 1) (520 mg, 1.48 mmol) and AcOH (127 μL, 2.22 mmol) in THF (10 mL) was added morpholine (256 μL, 2.96 mmol) and sodium triacetoxyborohydride (377 mg, 1.78 mmol) and the resulting mixture was stirred at room temperature for 16 h. The resulting mixture was diluted with EtOAc (10 mL) and saturated sodium bicarbonate solution (20 mL). The
- 20 phases were separated and the organic portion was washed with brine (20 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Purification of the crude material by chromatography on silica eluting with 0-100% EtOAc in heptanes afforded the title compound as a

colourless oil.

LC-MS (Method E): Rt 0.99 mins; MS m/z 422.1, 424.1 = [M+H]⁺ (100% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 7.52 – 7.46 (m, 2H), 7.43 (t, J = 7.5 Hz, 2H), 7.40 – 7.33 (m, 1H), 7.34 (d, J = 6.2 Hz, 1H), 7.14 (d, J = 10.9 Hz, 1H), 5.12 (s, 2H), 3.40 – 3.34 (m, 4H), 2.59 (s, 2H), 2.21 – 2.11 (m, 4H), 1.26 (s, 6H).

Step 3: 2-[5-Benzyloxy-4-(1,1-dimethyl-2-morpholino-ethyl)-2-fluoro-phenyl]acetic acid

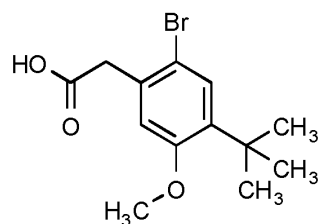
The title compound was prepared from 4-[2-(2-benzyloxy-4-bromo-5-fluoro-phenyl)-2-methyl-propyl]morpholine (step 1) and potassium 3-ethoxy-3-oxo-propanoate analogously to Intermediate B step 5 substituting toluene with mesitylene as the solvent.

LC-MS (Method E): Rt 0.90 mins; MS m/z 402.5 = [M+H]⁺ (83% @ 215 nm)

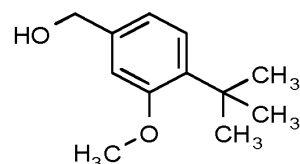
¹H NMR (400 MHz, DMSO-d₆) δ 7.54 – 7.47 (m, 2H), 7.47 – 7.38 (m, 2H), 7.40 – 7.31 (m, 1H), 7.05 (d, J = 6.7 Hz, 1H), 6.93 (d, J = 11.8 Hz, 1H), 5.04 (s, 2H), 3.51 (s, 2H), 3.42 – 3.34 (m, 4H), 2.60 (s, 2H), 2.22 – 2.10 (m, 4H), 1.26 (s, 6H).

Intermediate F

2-(2-Bromo-4-*tert*-butyl-5-methoxy-phenyl)acetic acid



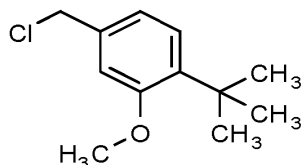
Step 1: (4-*tert*-Butyl-3-methoxy-phenyl)methanol



1M borane in THF (134.45 mL, 134.45 mmol) was added to a stirred solution of 4-*tert*-butyl-3-methoxy-benzoic acid (10 g, 48.02 mmol) in THF (100 mL) and the mixture was stirred at 50 °C for 1 hour. After cooling to room temperature, the resulting mixture was quenched cautiously with MeOH (10 mL) and the volatile solvents were removed *in vacuo*. Additional MeOH (10 mL) was added and the mixture was concentrated *in vacuo* to afford the title compound as a pale yellow oil.

LC-MS (Method E): Rt 1.14 min (97% @ 215 nm)

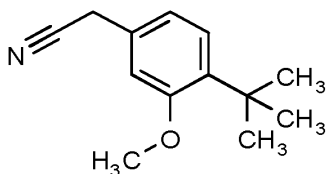
¹H NMR (500 MHz, DMSO-d₆) δ 7.14 (d, J = 7.9 Hz, 1H), 6.94 (s, 1H), 6.81 (d, J = 7.8 Hz, 1H), 5.12 (s, 1H), 4.46 (s, 2H), 3.79 (s, 3H), 1.32 (s, 9H).

Step 2: 1-tert-Butyl-4-(chloromethyl)-2-methoxy-benzene

Thionyl chloride (6.09 mL, 83.88 mmol) in DCM (40 mL) was added dropwise to a cooled (0 °C) solution of (4-tert-butyl-3-methoxy-phenyl)methanol (step 1) (97%, 8.4 g, 41.94 mmol) and DMF (3.25 mL, 41.94 mmol) in DCM (80 mL) and the mixture was stirred at room temperature for 1 hour. The resulting mixture was concentrated *in vacuo* and the residue was partitioned between EtOAc (100 mL) and saturated NaHCO₃ (100 mL). The phases were separated and the organic portion was washed with brine (30 mL), dried over Na₂SO₄ and concentrated *in vacuo* to afford the title compound as a yellow oil.

LC-MS (Method E): Rt 1.38 min (79% @ 215 nm)

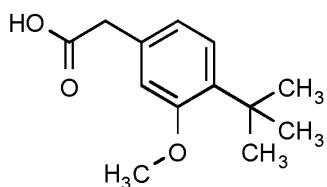
¹H NMR (500 MHz, DMSO-d₆) δ 7.20 (d, J = 7.9 Hz, 1H), 7.04 (d, J = 1.7 Hz, 1H), 6.94 (dd, J = 7.9, 1.7 Hz, 1H), 4.71 (s, 2H), 3.81 (s, 3H), 1.32 (s, 9H).

Step 3: 2-(4-tert-Butyl-3-methoxy-phenyl)acetonitrile

Sodium cyanide (1.88 g, 38.33 mmol) was added to a solution of 1-tert-butyl-4-(chloromethyl)-2-methoxy-benzene (step 2) (79%, 8.6 g, 31.94 mmol) in DMF (100 mL) and the mixture was stirred at room temperature overnight. The resulting mixture was diluted with EtOAc (100 mL) and washed with saturated aqueous sodium carbonate (300 mL), brine (50 mL), dried over Na₂SO₄ and concentrated *in vacuo* to afford the title compound as a brown oil.

LC-MS (Method E): Rt 1.25 min (84% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 7.21 (d, J = 7.9 Hz, 1H), 6.94 (d, J = 1.5 Hz, 1H), 6.86 (dd, J = 7.9, 1.7 Hz, 1H), 3.95 (s, 2H), 3.81 (s, 3H), 1.31 (s, 9H).

Step 4: 2-(4-tert-Butyl-3-methoxy-phenyl)acetic acid

To a solution of 2-(4-*tert*-butyl-3-methoxy-phenyl)acetonitrile (step 3) (84%, 8.0 g, 33.06 mmol) in water (50 mL) was added lithium hydroxide hydrate (9.27 g, 165.29 mmol) and the mixture was heated at reflux overnight. After cooling to room temperature, the resulting mixture was acidified with conc. HCl solution and extracted with DCM (2 x 30 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo* to afford the title compound as a pale yellow solid.

LC-MS (Method E): Rt 1.13 min (88% @ 215 nm)

¹H NMR (400 MHz, DMSO-d₆) δ 12.27 (s, 1H), 7.13 (d, J = 7.9 Hz, 1H), 6.86 (d, J = 1.6 Hz, 1H), 6.75 (dd, J = 7.9, 1.7 Hz, 1H), 3.78 (s, 3H), 3.50 (s, 2H), 1.31 (s, 9H).

10 **Step 5:** 2-(2-Bromo-4-*tert*-butyl-5-methoxy-phenyl)acetic acid

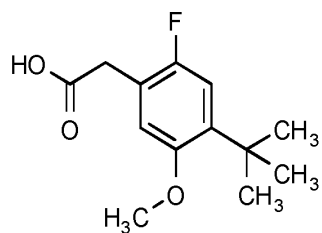
2-(4-*tert*-Butyl-3-methoxy-phenyl)acetic acid (step 4) (340 mg, 1.53 mmol) in acetic acid (2.19 mL) was treated with bromine (176 μL, 3.06 mmol) and stirred for 90 min. The reaction was quenched with saturated aqueous sodium thiosulfate and the resulting mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo*. Purification of the crude material by C18 reverse phase chromatography eluting with 10-100% MeCN in water afforded the title compound as a colourless solid.

LC-MS (Method E): Rt 1.24 min (97% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 12.43 (s, 1H), 7.28 (s, 1H), 7.04 (s, 1H), 3.79 (s, 3H), 3.65 (s, 2H), 1.31 (s, 9H).

Intermediate G

2-(4-*tert*-Butyl-2-fluoro-5-methoxy-phenyl)acetic acid



25 2-(2-Fluoro-5-methoxy-phenyl)acetic acid (585 mg, 3.17 mmol) was treated with concentrated sulfuric acid (677 μL, 12.7 mmol) and *tert*-butanol (1.21 mL, 12.7 mmol) and stirred for 3 h. The reaction mixture was concentrated *in vacuo*. During transfer of material MeOH was used, which resulted in the formation of the methyl ester. The residue was purified by C18 reverse phase chromatography eluting with 10-100% MeCN in water.

30 The resulting material was dissolved in 2M LiOH (7 mL) and THF (7 mL) and stirred for 2 h. The volatile solvents were removed *in vacuo* and the aqueous solution was acidified

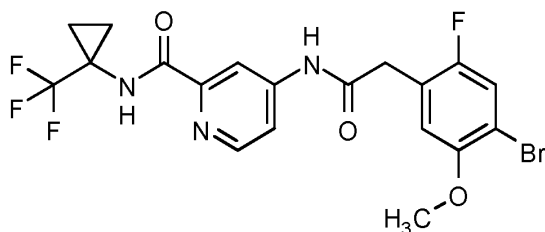
with 1M HCl. The suspension was extracted with DCM (3 x 20 mL) and the combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo* to afford the title compound as a pale yellow solid.

LC-MS (Method E): Rt 1.17 mins; MS m/z 239.0 = [M-H]⁻ (96% @ 215 nm)

- 5 ¹H NMR (500 MHz, DMSO-d₆) δ 12.42 (s, 1H), 6.94 (d, J = 7.0 Hz, 1H), 6.92 (d, J = 1.9 Hz, 1H), 3.77 (s, 3H), 3.57 – 3.53 (m, 2H), 1.31 (s, 9H).

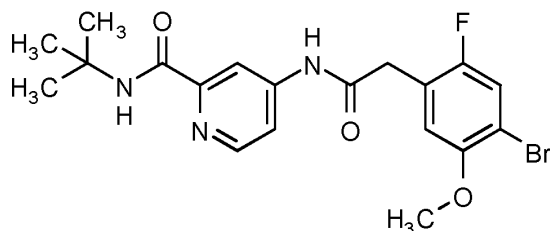
Intermediate H

- 10 **4-[2-(4-Bromo-2-fluoro-5-methoxyphenyl)acetamido]-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide**

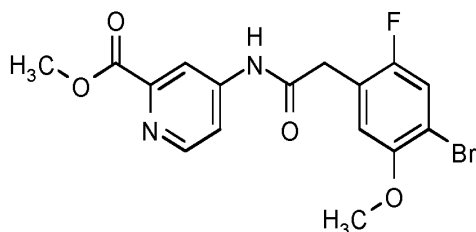


- To a solution of 2-(4-bromo-2-fluoro-5-methoxy-phenyl)acetic acid (Intermediate U step 1) (99%, 15.5 g, 58.33 mmol) in DMF (150 mL) was added DIPEA (15.28 mL, 87.5 mmol) and 4-amino-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide (Intermediate A) (15.02 g, 61.25 mmol) and the mixture was cooled to 0 °C. 50% T3P® solution in EtOAc (41.67 mL, 70. mmol) was added dropwise over 5 min and the reaction mixture was allowed to warm to room temperature gradually and stirred for 4 h. The resulting mixture was diluted with EtOAc (200 mL) and washed with brine (500 mL). The aqueous wash was back-extracted with EtOAc (200 mL) and the combined organic portions were washed with sat. NaHCO₃ (200 mL) and 1M HCl (200 mL). A precipitate formed which was filtered, washed with EtOAc (100 mL) and dried to yield a white solid. The solid was suspended in EtOAc (200 mL) and sat. NaHCO₃ (500 mL) was added. After stirring vigorously for 30 min, the organic layer was separated, dried over Na₂SO₄ and concentrated *in vacuo* to afford the title compound as a white solid.

- 25 LC-MS (Method G): Rt 1.01 min; MS m/z 490.0, 492.0 = [M+H]⁺ (100% @ 215 nm)
¹H NMR (500 MHz, DMSO-d₆) δ 10.83 (s, 1H), 9.39 (s, 1H), 8.50 (d, J = 5.6 Hz, 1H), 8.19 (d, J = 1.8 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.18 (d, J = 6.6 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 2H), 1.36 – 1.23 (m, 2H), 1.22 – 1.12 (m, 2H).

Intermediate I**4-[[2-(4-Bromo-2-fluoro-5-methoxy-phenyl)acetyl]amino]-N-*tert*-butyl-pyridine-2-carboxamide**

- 5 **Step 1:** Methyl 4-[[2-(4-bromo-2-fluoro-5-methoxy-phenyl)acetyl]amino]pyridine-2-carboxylate

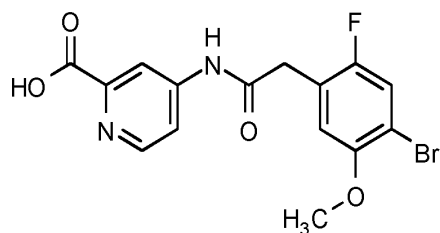


To a stirred solution of 2-(4-bromo-2-fluoro-5-methoxy-phenyl)acetic acid (Intermediate U step 1)) (91%, 2.92 g, 10.09 mmol), methyl 4-aminopyridine-2-carboxylate (1.54 g, 10.09 mmol) and DIPEA (5.29 mL, 30.26 mmol) in 1,4-dioxane (20 mL) was added 50% T3P® solution in EtOAc (6.6 mL, 11.1 mmol) and the mixture was stirred at room temperature for 17 h. The resulting mixture was diluted with EtOAc (100 mL) and water (100 mL). The phases were separated and the aqueous layer was further extracted with EtOAc (60 mL). The organic extracts were combined, washed with water (2 x 100 mL), brine (100 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The crude material was purified by chromatography on silica eluting with 0-100% EtOAc to afford the title compound as an off-white solid.

LC-MS (Method E): Rt 1.05 mins; MS m/z 397.0, 399.0 = [M+H]⁺ (99% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.82 (s, 1H), 8.55 (d, J = 5.5 Hz, 1H), 8.29 (d, J = 1.9 Hz, 1H), 7.76 (dd, J = 5.5, 2.2 Hz, 1H), 7.52 (d, J = 8.9 Hz, 1H), 7.17 (d, J = 6.6 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.80 (s, 2H).

Step 2: 4-[[2-(4-Bromo-2-fluoro-5-methoxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid



2M aq. LiOH (7.55 mL, 15.11 mmol) was added to a stirred solution of methyl 4-[[2-(4-bromo-2-fluoro-5-methoxy-phenyl)acetyl]amino]pyridine-2-carboxylate (step 1) (2 g, 5.04 mmol) in THF (10 mL) and the mixture was stirred at room temperature for 1 hour. The volatile solvent was removed *in vacuo* and the resulting aqueous layer was acidified to pH 3 with 1M aqueous HCl. The precipitate was collected by filtration and dried in a vacuum oven at 40 °C for 8 h to afford the title compound as an off-white solid.

LC-MS (Method E): Rt 0.91 mins; MS m/z 382.9, 384.9 = [M+H]⁺ (97% @ 215 nm)

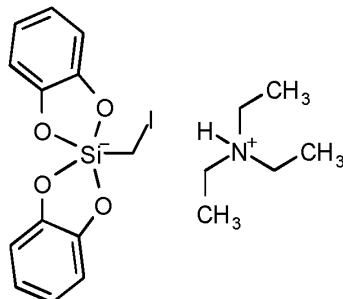
¹H NMR (500 MHz, DMSO-d₆) δ 11.10 (s, 1H), 8.55 (d, J = 5.6 Hz, 1H), 8.31 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.6, 2.1 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.21 (d, J = 6.5 Hz, 1H), 3.84 (s, 2H), 3.83 (s, 3H).

Step 3: 4-[[2-(4-Bromo-2-fluoro-5-methoxy-phenyl)acetyl]amino]-N-*tert*-butyl-pyridine-2-carboxamide

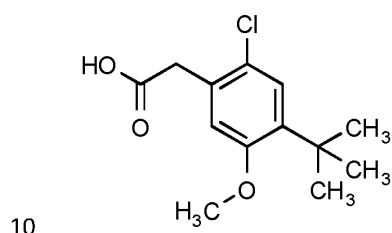
To a solution of 4-[[2-(4-bromo-2-fluoro-5-methoxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid (step 2) (930 mg, 2.43 mmol), 2-methylpropan-2-amine (306 μL, 2.91 mmol) and DIPEA (636 μL, 3.64 mmol) in DMF (5 mL) was added HATU (1 g, 2.67 mmol) and the mixture was stirred at room temperature for 1 hour. The resulting mixture was concentrated *in vacuo* and the residue partitioned between EtOAc (10 mL) and water (10 mL). The phases were separated and the organic portion was washed with water (2 x 10 mL), brine (10 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The crude material was purified by chromatography on silica eluting with 0-100% EtOAc in heptanes to afford the title compound as an off-white solid.

LC-MS (Method E): Rt 1.28 mins; MS m/z 438.1, 440.0 = [M+H]⁺ (100% @ 215 nm)

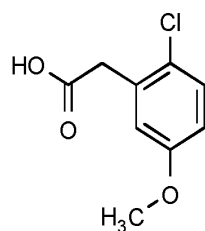
¹H NMR (500 MHz, DMSO-d₆) δ 10.80 (s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.17 (d, J = 1.9 Hz, 1H), 8.03 (s, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.18 (d, J = 6.6 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 2H), 1.40 (s, 9H).

Intermediate J**Triethylammonium bis(catecholato)iodomethylsilicate**

This compound was prepared according to the procedure described in J. Am. Chem. Soc.
 5 2018, 140, 8037–8047. Redox-Neutral Photocatalytic Cyclopropanation via Radical/Polar Crossover.

Intermediate K**2-(4-*tert*-Butyl-2-chloro-5-methoxy-phenyl)acetic acid**

10 Step 1: 2-(2-Chloro-5-methoxy-phenyl)acetic acid



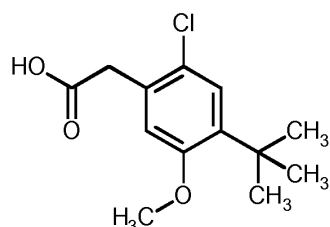
To a stirred solution of 2-(3-methoxyphenyl)acetic acid (10 g, 60.18 mmol) in DCM (301 mL) was added triphenylphosphine sulfide (1.77 g, 6.02 mmol) followed by *N*-chlorosuccinimide (9.64 g, 72.22 mmol) and the reaction mixture was stirred at room
 15 temperature for 20 hours. The resulting mixture was filtered through a silica plug washing through with TBME (2 x 500 mL). The filtrate was concentrated *in vacuo* and the residue dissolved in 1M NaOH (1 L) solution, stirring vigorously for 10 min. The aqueous mixture was extracted with TBME (2 x 200 mL) to remove the organic impurities, then acidified to
 20 pH 1 using 6 M HCl and extracted with DCM (2 x 200 mL). The DCM extracts were washed

with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The crude material was purified further by hot filtration from boiling heptanes. The solids were suspended in heptanes (1 L) and heated to reflux until all solids had dissolved while an insoluble oily residue remained. The product crystallised from the hot heptane solution once decanted away from the insoluble oily impurity. The crystallised solid was filtered and dried in a vacuum oven to afford the title compound as a pale yellow crystalline solid.

LC-MS (Method E): Rt 1.00 min; (98% @ 215 nm)

¹H NMR (400 MHz, DMSO-d₆) δ 12.43 (s, 1H), 7.32 (d, J = 8.8 Hz, 1H), 6.99 (d, J = 3.1 Hz, 1H), 6.87 (dd, J = 8.8, 3.1 Hz, 1H), 3.74 (s, 3H), 3.66 (s, 2H).

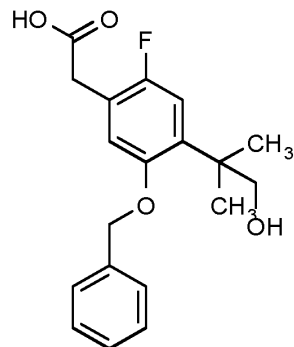
10 Step 2: 2-(4-*tert*-butyl-2-chloro-5-methoxy-phenyl)acetic acid



2-(2-Chloro-5-methoxy-phenyl)acetic acid (step 1)(20.0 g, 99.69 mmol) in DCE (498.45 mL) was treated with *t*-butanol (114.41 mL, 1196.29 mmol) followed by concentrated sulfuric acid (63.77 mL, 1196.29 mmol) added dropwise via a dropping funnel over 40 min at room temperature and stirred for 1 hr. Additional *t*-butanol (38 mL) and concentrated sulfuric acid (21 mL) were added at 90 minute intervals until the full consumption of starting material was observed. The layers were separated, then the sulphuric acid layer was extracted with DCE (2 x 200 mL), and the combined DCE layers were concentrated *in vacuo* (heating at 60 °C and high vacuum required). The resulting solid was triturated with heptane followed by 1M HCl and then washed with water to afford the title compound as an off-white solid.

LC-MS (Method A): Rt 3.65 min; (98% @ 215 nm)

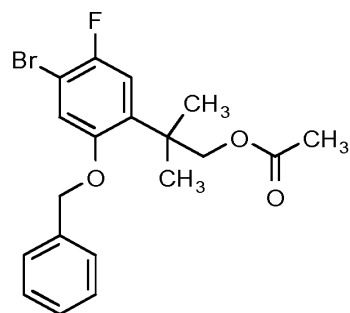
¹H NMR (500 MHz, DMSO-d₆) δ 12.42 (br. s, 1H), 7.14 (s, 1H), 7.03 (s, 1H), 3.80 (s, 3H), 3.64 (s, 2H), 1.31 (s, 9H).

Intermediate L**2-[5-Benzyloxy-2-fluoro-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetic acid****Step 1: 2-(2-Benzyloxy-4-bromo-5-fluoro-phenyl)-2-methyl-propan-1-ol**

- 5 Sodium borohydride (96.17 mg, 2.54 mmol) was added to a stirred solution of 2-(2-benzyloxy-4-bromo-5-fluoro-phenyl)-2-methyl-propanal (Intermediate E step 1) (72%, 620 mg, 1.27 mmol) in MeOH (10 mL) and the mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* then treated with saturated aq. NH_4Cl (20 mL), stirring for 30 min. EtOAc (20 mL) was added and the organic portion was separated, dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a colourless oil.

LC-MS (Method E): Rt 1.32 mins; MS m/z 351.0, 353.0 = $[\text{M}-\text{H}]^-$ (89% @ 215 nm)

- ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.50 – 7.45 (m, 2H), 7.46 – 7.39 (m, 2H), 7.39 – 7.32 (m, 1H), 7.33 (d, J = 6.2 Hz, 1H), 7.18 (d, J = 11.1 Hz, 1H), 5.13 (s, 2H), 4.59 (t, J = 5.5 Hz, 1H), 3.59 (d, J = 5.4 Hz, 2H), 1.23 (s, 6H).

Step 2: [2-(2-Benzyloxy-4-bromo-5-fluoro-phenyl)-2-methyl-propyl] acetate

- A solution of 2-(2-benzyloxy-4-bromo-5-fluoro-phenyl)-2-methyl-propan-1-ol (step 1) (85%, 520 mg, 1.25 mmol) in DCM (10 mL) was treated with DMAP (15 mg, 0.13 mmol), acetic anhydride (237 μL , 2.5 mmol) and TEA (349 μL , 2.5 mmol) and the mixture was stirred at room temperature for 4 h. The resulting mixture was washed with saturated Na_2CO_3 (20 mL) and the organic layer was separated, dried over Na_2SO_4 and

concentrated *in vacuo*. Purification of the crude material by chromatography on silica eluting with 0-100% EtOAc in heptanes afforded the title compound as a colourless oil.

LC-MS (Method E): Rt 1.47 min (94% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 7.49 – 7.44 (m, 2H), 7.42 (t, J = 7.4 Hz, 2H), 7.40 – 7.32 (m, 2H), 7.17 (d, J = 10.8 Hz, 1H), 5.15 (s, 2H), 4.28 (s, 2H), 1.90 (s, 3H), 1.30 (s, 6H).

Step 3: 2-[5-Benzyloxy-2-fluoro-4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]acetic acid

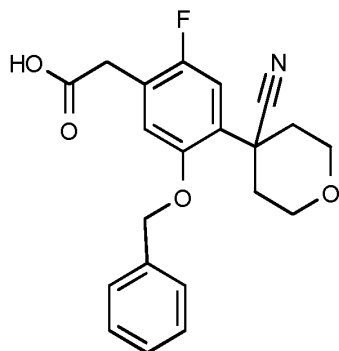
The title compound was prepared from potassium 3-ethoxy-3-oxo-propanoate and [2-(2-benzyloxy-4-bromo-5-fluoro-phenyl)-2-methyl-propyl] acetate (step 2) analogously to Intermediate B step 5.

LC-MS (Method E): Rt 1.16 mins; MS m/z 663.4 = [2M-H]⁻ (96% @ 215 nm)

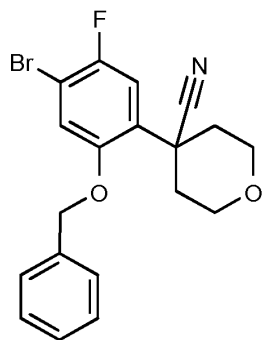
¹H NMR (500 MHz, DMSO-d₆) δ 12.44 (br. s, 1H), 7.50 – 7.47 (m, 2H), 7.44 – 7.40 (m, 2H), 7.37 – 7.33 (m, 1H), 7.05 (d, J = 6.7 Hz, 1H), 6.99 (d, J = 11.9 Hz, 1H), 5.05 (s, 2H), 4.56 (t, J = 5.3 Hz, 1H), 3.59 (d, J = 5.1 Hz, 2H), 3.55 (s, 2H), 1.24 (s, 6H).

Intermediate M

2-[5-Benzyloxy-4-(4-cyanotetrahydropyran-4-yl)-2-fluoro-phenyl]acetic acid



Step 1: 4-(2-benzyloxy-4-bromo-5-fluoro-phenyl)tetrahydropyran-4-carbonitrile



To a cooled (0°C) solution of 2-(2-benzyloxy-4-bromo-5-fluoro-phenyl)acetonitrile (Intermediate C step 5) (1 g, 3.12 mmol) in DMF (40 mL) under nitrogen was added NaH

(60% dispersion in mineral oil, 262 mg, 6.56 mmol). After stirring for 5 min, the mixture was treated dropwise over 10 min with 1-bromo-2-(2-bromoethoxy)ethane (0.8 g, 3.44 mmol). The reaction mixture was allowed to warm to room temperature, stirred for 1 h and then heated to 65 °C for 2 h. The resulting mixture was cooled to 0 °C and the reaction quenched by careful addition of water (10 mL) under nitrogen. Further water (200 mL) addition yielded a precipitate which was stirred at room temperature for 20 min. The solid was collected by filtration, washed with water (200 mL) and dried a vacuum oven at 40 °C for 3 h to afford the title compound as a beige solid.

LC-MS (Method E): Rt 1.33 mins; MS (90% @ 215 nm)

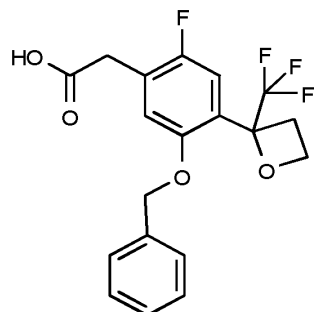
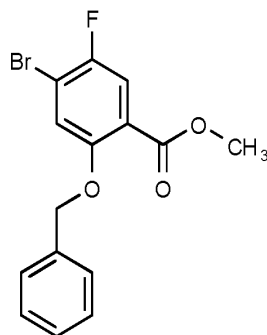
¹H NMR (500 MHz, DMSO-d₆) δ 7.54 (d, J = 6.3 Hz, 3H), 7.43 – 7.31 (m, 4H), 5.29 (s, 2H), 3.98 – 3.92 (m, 2H), 3.66 (t, J = 11.5 Hz, 2H), 2.29 (d, J = 12.6 Hz, 2H), 1.99 (td, J = 13.1, 4.2 Hz, 2H).

Step 2: 2-[5-Benzyloxy-4-(4-cyanotetrahydropyran-4-yl)-2-fluoro-phenyl]acetic acid

To a solution of 4-(2-benzyloxy-4-bromo-5-fluoro-phenyl)tetrahydropyran-4-carbonitrile (step 1) (90%, 750 mg, 1.73 mmol) in THF (10 mL) was added Pd(dba)₂ (20 mg, 0.03 mmol) followed by Q-Phos (25 mg, 0.03 mmol). The mixture was sparged with nitrogen for 10 min and treated with 0.5M bromo-(2-*tert*-butoxy-2-oxo-ethyl)zinc in THF (3.46 mL, 1.73 mmol) was added. After stirring at 50 °C under nitrogen for 1.5 h, further portions of Pd(dba)₂ (20 mg, 0.03 mmol) and Q-Phos (25 mg, 0.03 mmol) were added and stirring continued at 60 °C overnight. The resulting was diluted with EtOAc (25 mL) and washed with water (20 mL), 1M HCl (20 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Purification of the crude material by chromatography on silica eluting with 0-100% EtOAc in heptanes afforded a yellow oil. The oil was dissolved in DCM (15 mL), treated with TFA (1.99 mL, 25.94 mmol) and stirred at room temperature overnight. The resulting mixture was concentrated *in vacuo* and the crude residue was dissolved in EtOAc (25 mL). The organic mixture was washed with 2M NaOH (2 x 25 mL). The basic aqueous washes were combined, re-acidified with 6M HCl to pH 4-5 and then back extracted with EtOAc (3 x 25 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo* to afford the title compound as a pale yellow oil.

LC-MS (Method E): Rt 1.12 mins; MS m/z 370.1 = [M+H]⁺ (97% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 7.55 (d, J = 7.2 Hz, 2H), 7.43-7.38 (m, 2H), 7.35-7.31 (m, 1H), 7.24 (d, J = 6.4 Hz, 1H), 7.15 (d, J = 10.9 Hz, 1H), 5.20 (s, 2H), 3.98 – 3.92 (m, 2H), 3.66 (t, J = 11.6 Hz, 2H), 3.59 (s, 2H), 2.29 (d, J = 12.7 Hz, 2H), 2.03-1.96 (m, 2H).

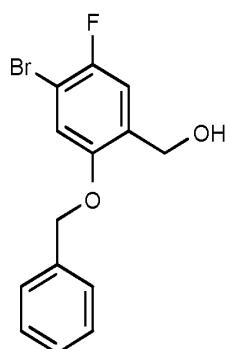
Intermediate N**2-[5-Benzyloxy-2-fluoro-4-[2-(trifluoromethyl)oxetan-2-yl]phenyl]acetic acid****Step 1: Methyl 2-benzyloxy-4-bromo-5-fluoro-benzoate**

5

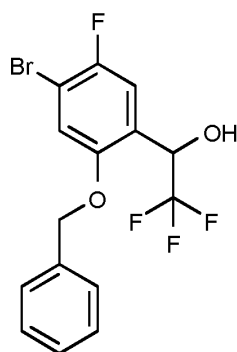
Benzyl bromide (2.29 mL, 19.27 mmol) was added to a stirred mixture of methyl 4-bromo-5-fluoro-2-hydroxy-benzoate (4 g, 16.06 mmol) and K_2CO_3 (5.55 g, 40.16 mmol) in DMF (50 mL) and the reaction mixture was stirred at 80 °C for 1 hour. After cooling to room temperature, the resulting mixture was partitioned between EtOAc (150 mL) and water (150 mL). The organic portion was separated and the aqueous layer was further extracted with EtOAc (50 mL). The combined organics were washed with water (2 x 50 mL), brine (150 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by chromatography on silica eluting with 0-60% EtOAc in heptanes afforded the title compound as a colourless oil.

15 LC-MS (Method E): Rt 1.37 min; (99% @ 215 nm)

1H NMR (500 MHz, DMSO- d_6) δ 7.66 (d, J = 8.8 Hz, 1H), 7.62 (d, J = 5.6 Hz, 1H), 7.50 – 7.44 (m, 2H), 7.44 – 7.37 (m, 2H), 7.36 – 7.29 (m, 1H), 5.23 (s, 2H), 3.81 (s, 3H).

Step 2: (2-Benzyloxy-4-bromo-5-fluoro-phenyl)methanol

- To a stirred solution of methyl 2-benzyloxy-4-bromo-5-fluoro-benzoate (step 1) (5.4 g, 15.92 mmol) in THF (100 mL) was added LiBH₄ (11.94 mL, 47.77 mmol) and the reaction mixture was stirred at room temperature overnight. A further portion of LiBH₄ (11.94 mL, 47.77 mmol) was added and stirring continued overnight. The resulting mixture was quenched with ice (~50 mL), stirred for 30 min and then EtOAc (50 mL) was added. The organic layer was separated, dried over Na₂SO₄ and concentrated *in vacuo* to afford the title compound as a yellow oil.
- LC-MS (Method E): Rt 1.24 min; (94% @ 215 nm)
- ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.46 – 7.36 (m, 4H), 7.37 – 7.30 (m, 2H), 7.30 (d, J = 9.4 Hz, 1H), 5.29 (t, J = 5.6 Hz, 1H), 5.14 (s, 2H), 4.49 (d, J = 5.6 Hz, 2H).

Step 3: 1-(2-Benzyloxy-4-bromo-5-fluoro-phenyl)-2,2,2-trifluoro-ethanol

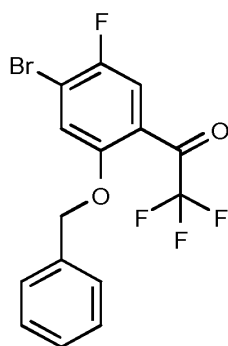
- To a solution of (2-benzyloxy-4-bromo-5-fluoro-phenyl)methanol (step 2) (1 g, 3.21 mmol) in toluene (50 mL) was added manganese dioxide (1.1 g, 12.86 mmol). The reaction mixture was stirred at 90 °C for 1 hour and then left to stir at room temperature overnight. The resulting mixture was filtered through Celite® (filter material) and washed with toluene. The filtrate was concentrated *in vacuo* and the residue was re-dissolved in THF (25 mL) and treated with trimethyl(trifluoromethyl)silane (914 mg, 6.43 mmol). After stirring for 5 min, 1M TBAF in THF (47 μL, 0.16 mmol) was added and the mixture was stirred at room

temperature for 2 h. The resulting mixture was cooled to 0 °C and 2M HCl (20 mL) was added. After stirring at room temperature for 1 hour, the mixture was partitioned between EtOAc (100 mL) and water (100 mL). The phases were separated and the organics were washed with brine (2 x 50 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by chromatography on silica eluting with 0-50% EtOAc in heptanes to afford the title compound as a yellow oil.

LC-MS (Method E): Rt 1.39 min; (98% @ 215 nm)

¹H NMR (500 MHz, DMSO-*d*₆) δ 7.52 (d, J = 5.7 Hz, 1H), 7.44 – 7.33 (m, 6H), 6.99 (d, J = 6.0 Hz, 1H), 5.44 – 5.36 (m, 1H), 5.19 (s, 2H).

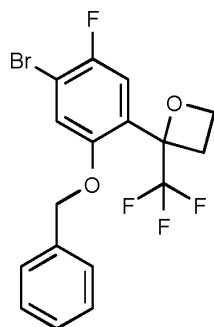
10 Step 4: 1-(2-Benzyloxy-4-bromo-5-fluoro-phenyl)-2,2,2-trifluoro-ethanone



To a solution of 1-(2-benzyloxy-4-bromo-5-fluoro-phenyl)-2,2,2-trifluoro-ethanol (step 3) (700 mg, 1.85 mmol) in DCM (40 mL) was added Dess-Martin periodinane (979 mg, 2.31 mmol) followed by TFA (0.14 mL, 1.85 mmol) and the mixture was stirred at room temperature for 5 h. The resulting reaction mixture was filtered and washed through with DCM (~20 mL). The filtrate was washed with sat. NaHCO₃ (2 x 25 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Purification by chromatography on silica eluting with 0-100% EtOAc in heptanes afforded the title compound.

LC-MS (Method G): Rt 1.16 min; MS m/z 375.1, 377.1 = [M+H]⁺ (70% @ 215 nm)

¹H NMR (500 MHz, DMSO-*d*₆) δ 7.81 (d, J = 5.5 Hz, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.45 – 7.32 (m, 5H), 5.28 (s, 2H).

Step 5: 2-(2-Benzyloxy-4-bromo-5-fluoro-phenyl)-2-(trifluoromethyl)oxetane

Trimethylsulfoxonium iodide (490 mg, 2.23 mmol) and potassium *t*-butoxide (250 mg, 2.23 mmol) were dissolved in DMSO (10 mL) and stirred for 10 min. To this mixture was added dropwise a solution of 1-(2-benzyloxy-4-bromo-5-fluoro-phenyl)-2,2,2-trifluoro-ethanone (step 4) (70%, 400 mg, 0.74 mmol) in DMSO (2 mL) and the mixture was stirred at room temperature under an inert atmosphere for 7 h. The resulting mixture was diluted in EtOAc (50 mL) and washed with water (2 x 25 mL), brine (25 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Purification by chromatography on silica eluting with 0-100% EtOAc in heptanes afforded the title compound as a light yellow solid.

LC-MS (Method E): Rt 1.53 min; (95% @ 215 nm)

¹H NMR (500 MHz, DMSO-*d*₆) δ 7.58 (d, *J* = 5.7 Hz, 1H), 7.44-7.39 (m, 4H), 7.38 – 7.33 (m, 1H), 7.25 (d, *J* = 9.0 Hz, 1H), 5.17 (s, 2H), 4.72-4.66 (m, 1H), 4.51 (dt, *J* = 9.3, 5.9 Hz, 1H), 3.15 (dt, *J* = 12.6, 8.7 Hz, 1H), 3.04-2.97 (m, 1H).

15 Step 6: 2-[5-Benzyloxy-2-fluoro-4-[2-(trifluoromethyl)oxetan-2-yl]phenyl]acetic acid

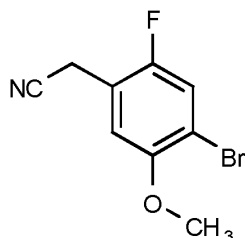
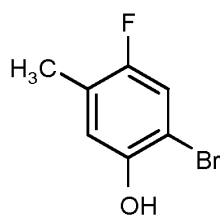
The title compound was prepared from 2-(2-benzyloxy-4-bromo-5-fluoro-phenyl)-2-(trifluoromethyl) oxetane (step 5) and 0.5M bromo-(2-*tert*-butoxy-2-oxo-ethyl)zinc in THF analogously to Intermediate M step 2.

LC-MS (Method G): Rt 1.02 min; MS *m/z* 767.3 = [2M-H]⁻ (90% @ 215 nm)

20 ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.60 (br. s, 1H), 7.46 – 7.31 (m, 5H), 7.25 (d, *J* = 6.1 Hz, 1H), 7.07 (d, *J* = 10.0 Hz, 1H), 5.09 (s, 2H), 4.74 – 4.65 (m, 1H), 4.53-4.46 (m, 1H), 3.65 (s, 2H), 3.19 – 3.10 (m, 1H), 3.06 – 2.97 (m, 1H).

Intermediate O

2-(4-Bromo-2-fluoro-5-methoxyphenyl)acetonitrile

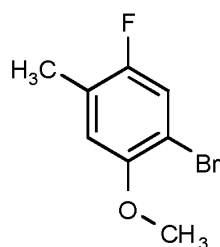
Step 1: 2-Bromo-4-fluoro-5-methylphenol

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To a solution of 4-fluoro-3-methylphenol (10 g, 79.3 mmol) in DCM (79 mL) at -78°C was added dropwise bromine (4.09 mL, 79.3 mmol). After 1 hour, 1M aqueous sodium thiosulfate was added and the mixture allowed to warm to room temperature. The organic layer was separated, dried over Na₂SO₄ and concentrated *in vacuo* to afford the title compound as a pale yellow solid. Regioselectivity >10:1.

10

¹H NMR (400 MHz, Chloroform-*d*) δ 7.12 (d, J = 8.6 Hz, 1H), 6.84 (dd, J = 6.8, 0.9 Hz, 1H), 5.27 (s, 1H), 2.20 (dd, J = 2.1, 0.8 Hz, 3H).

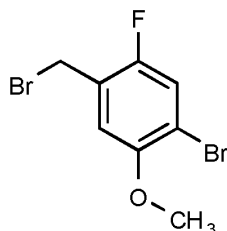
Step 2: 1-Bromo-5-fluoro-2-methoxy-4-methylbenzene

15 Iodomethane (7.3 mL, 117 mmol) was added dropwise to a mixture of 2-bromo-4-fluoro-5-methylphenol (step 1) (16 g, 78.0 mmol) and potassium carbonate (21.6 g, 156 mmol) in DMF (156 mL) and the mixture was stirred vigorously overnight. After filtration, the filtrate was partitioned between water and Et₂O. The phases were separated, and the organic phase was washed with water (x 3), brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by chromatography on silica eluting with n-pentane to afford the title compound as a pale yellow oil.

20

^1H NMR (400 MHz, Chloroform-*d*) δ 7.21 (d, J = 8.6 Hz, 1H), 6.72 – 6.68 (m, 1H), 3.85 (s, 3H), 2.24 (dd, J = 2.1, 0.7 Hz, 3H).

Step 3: 1-Bromo-4-(bromomethyl)-5-fluoro-2-methoxybenzene



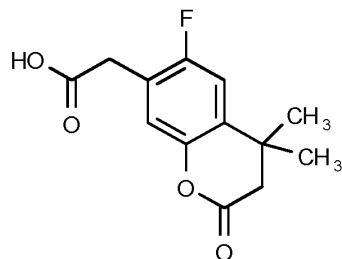
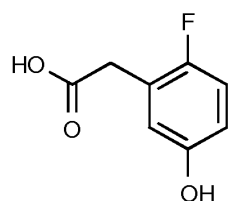
- 5 To stirred solution of 1-bromo-5-fluoro-2-methoxy-4-methylbenzene (step 2) (2 g, 9.13 mmol) in CCl_4 (45.7 mL) was added *N*-bromosuccinimide (1.63 g, 9.13 mmol) and azobisisobutyronitrile (150 mg, 0.913 mmol) at room temperature. The resulting mixture was heated to reflux for 3 h. After cooling to room temperature, the mixture was poured onto ice cold water and extracted with DCM (x 2). The combined organic layers were dried
- 10 over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by chromatography on silica eluting with 0-10% EtOAc in cyclohexane to afford the title compound as an off-white solid.

^1H NMR (400 MHz, Chloroform-*d*) δ 7.30 (d, J = 8.7 Hz, 1H), 6.88 (d, J = 6.4 Hz, 1H), 4.46 (d, J = 1.2 Hz, 2H), 3.89 (s, 3H).

- 15 Step 4: 2-(4-Bromo-2-fluoro-5-methoxyphenyl)acetonitrile

- To a solution of 1-bromo-4-(bromomethyl)-5-fluoro-2-methoxybenzene (step 3) (4.38 g, 14.7 mmol) in 10:1 DMF:water (34 mL) was added KCN (1.05 g, 16.2 mmol) and tetrabutylammonium bromide (5.21 g, 16.2 mmol) and reaction mixture was stirred at room temperature for 16 h. The resulting mixture was diluted with water (100 mL) and extracted
- 20 with Et_2O (3 x 50 mL). The combined organic extracts were washed with 50 % sat. NaHCO_3 (3 x 100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by chromatography on silica eluting with 0-100% EtOAc in cyclohexane to afford the title compound as a yellow solid.

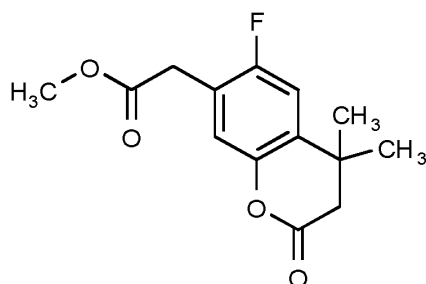
- ^1H NMR (400 MHz, Chloroform-*d*) δ 7.26 (d, J = 8.7 Hz, 1H), 6.86 (d, J = 6.4 Hz, 1H), 3.84 (s, 3H), 3.69 – 3.64 (m, 2H).
- 25

Intermediate P**2-(6-Fluoro-4,4-dimethyl-2-oxo-chroman-7-yl)acetic acid****Step 1: 2-(2-Fluoro-5-hydroxy-phenyl)acetic acid**

5

A solution of 2-(2-fluoro-5-methoxy-phenyl)acetic acid (2.0 g, 10.86 mmol) in DCM (30 mL) and 1M BBr₃ in DCM (21.72 mL, 21.72 mmol) was stirred at room temperature overnight. A further portion of 1M BBr₃ in DCM (21.72 mL, 21.72 mmol) was added and the reaction mixture was stirred at room temperature over the weekend. The resulting precipitate was filtered, washed with DCM (100 mL) and dried *in vacuo* to afford the title compound as a pale yellow solid.

LC-MS (Method G): Rt 0.52 min; MS m/z 339.1 = [2M-H]⁻ (85% @ 215 nm)
¹H NMR (500 MHz, DMSO-d₆) δ 12.37 (s, 1H), 9.30 (s, 1H), 6.94 (t, J = 9.1 Hz, 1H), 6.72 – 6.65 (m, 1H), 6.67 – 6.59 (m, 1H), 3.50 (s, 2H).

Step 2: Methyl 2-(6-fluoro-4,4-dimethyl-2-oxo-chroman-7-yl)acetate

A solution of 2-(2-fluoro-5-hydroxy-phenyl)acetic acid (step 1)(85%, 710 mg, 3.55 mmol) and methyl 3-methylbut-2-enoate (714 mg, 6.26 mmol) in methanesulfonic acid (5.42 mL, 83.46 mmol) was stirred at 70 °C for 40 h. After cooling to room temperature, the mixture was poured onto ice (20 g) and EtOAc (30 mL) was added. The organic layer

20

was separated, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by chromatography on silica eluting with 0-100% EtOAc in heptanes followed by 0-100% MeOH in EtOAc and then C18 reverse phase chromatography eluting with 10-100% MeCN in water (+0.1% formic acid) afforded the title compound as a pale yellow solid.

5 LC-MS (Method E): Rt 1.14 min; (100% @ 215 nm)

^1H NMR (500 MHz, DMSO- d_6) δ 7.27 (d, J = 10.3 Hz, 1H), 7.11 (d, J = 6.5 Hz, 1H), 3.73 (s, 2H), 3.63 (s, 3H), 2.73 (s, 2H), 1.27 (s, 6H).

Step 3: 2-(6-Fluoro-4,4-dimethyl-2-oxo-chroman-7-yl)acetic acid

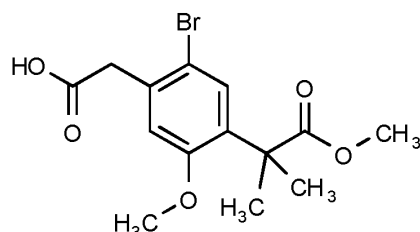
To a solution of lithium hydroxide (189 mg, 7.89 mmol) in water (2 mL) was added
10 methyl 2-(6-fluoro-4,4-dimethyl-2-oxo-chroman-7-yl)acetate (step 2) (420 mg, 1.58 mmol) in THF (2 mL) and the reaction mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated *in vacuo* to remove the organics and then diluted with EtOAc (20 mL). The mixture was acidified with 1M HCl to pH 1 and the organic portion was separated, dried over Na_2SO_4 and concentrated *in vacuo* to afford title compound as
15 a pale yellow solid.

LC-MS (Method I): Rt 0.28 min; MS m/z 251.3 = $[\text{M}-\text{H}]^-$ (100% @ 215 nm)

^1H NMR (500 MHz, DMSO- d_6) δ 12.53 (s, 1H), 7.25 (d, J = 10.3 Hz, 1H), 7.09 (d, J = 6.5 Hz, 1H), 3.61 (s, 2H), 2.72 (s, 2H), 1.27 (s, 6H).

20 Intermediate Q

2-[2-Bromo-5-methoxy-4-(2-methoxy-1,1-dimethyl-2-oxo-ethyl)phenyl]acetic acid



A cooled (0 °C) solution of methyl 2-[4-(2-*tert*-butoxy-2-oxo-ethyl)-2-methoxy-phenyl]-2-methyl-propanoate (Intermediate T step 3) (811 mg, 2.52 mmol) in MeCN (10 mL) was
25 treated dropwise with a bromine (0.17 mL, 3.02 mmol) over a period of 10 min. The resulting mixture was allowed to warm to room temperature gradually without removing the ice bath and then left to stir for 16 h. Aqueous saturated sodium sulphite solution (20 mL) was added slowly to the mixture and stirred for 10 min. The resulting solution was diluted with brine (50 mL) and extracted with EtOAc (50 mL). The organic portion was
30 separated, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by chromatography on silica eluting with 0-70% EtOAc in hepanes afforded the title

compound as an off-white gum.

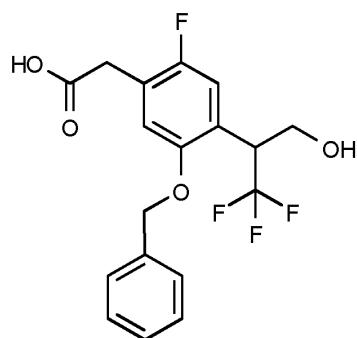
LC-MS (Method H): Rt 1.31 min; MS m/z 345, 347 = [M+H]⁺ (96% @ 215 nm)

¹H NMR (500 MHz, DMSO-*d*₆) δ 12.53 (br. s, 1H), 7.38 (s, 1H), 7.06 (s, 1H), 3.70 (s, 3H), 3.68 (s, 2H), 3.53 (s, 3H), 1.40 (s, 6H).

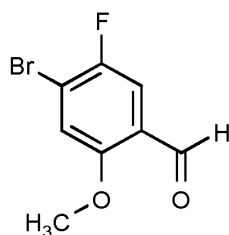
5

Intermediate R

2-[5-Benzyloxy-2-fluoro-4-[2,2,2-trifluoro-1-(hydroxymethyl)ethyl]phenyl]acetic acid



Step 1: 4-Bromo-5-fluoro-2-methoxy-benzaldehyde



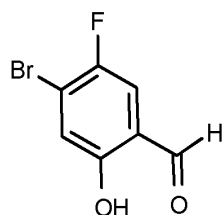
10

To a cooled (0 °C) solution of 2-bromo-1-fluoro-4-methoxy-benzene (7.35 g, 35.85 mmol) in dry DCM (125 mL) was added TiCl₄ (3.94 mL, 35.85 mmol) and the mixture was stirred at 0 °C for 15 min. Dichloro(methoxy)methane (4.87 mL, 53.78 mmol) was added followed by additional TiCl₄ (3.94 mL, 35.85 mmol) and the reaction mixture was stirred for 1 h. The resulting mixture was poured onto ice water (~300 mL), stirred vigorously for 15 min and the phases were separated. The aqueous portion was extracted with DCM (150 mL) and the combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo*. The residue was suspended in hot EtOAc (100 mL) and filtered through a sinter pad rinsing through with EtOAc. The filtrate was concentrated *in vacuo* and the residue was recrystallised from EtOAc (~20 mL) to afford the title compound as a white crystalline solid.

20

LC-MS (Method G): Rt 0.92 min; (97% @ 215 nm)

¹H NMR (400 MHz, DMSO-*d*₆) δ 10.27 – 10.22 (m, 1H), 7.64 (d, J = 5.3 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 3.95 (s, 3H).

Step 2: 4-Bromo-5-fluoro-2-hydroxy-benzaldehyde

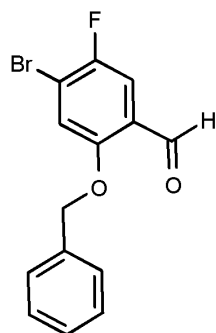
To a cooled (0 °C) solution of 4-bromo-5-fluoro-2-methoxy-benzaldehyde (step 1) (4.0 g, 17.17 mmol) in dry DCM (60 mL) was added dropwise 1M BBr₃ in DCM (25.75 mL, 25.75 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 18 h.

The resulting mixture was cooled to 0 °C, water (50 mL) was slowly added and the mixture was stirred vigorously for 10 min. The phases were separated and the aqueous was extracted with DCM (50 mL). The combined organic extracts were concentrated *in vacuo* to give a pale purple solid which was dissolved in EtOAc (30 mL). Saturated sodium bicarbonate solution (30 mL) was added and the mixture was stirred vigorously for 10 min. The phases were separated and the organic portion was washed with brine (30 mL), dried over Na₂SO₄ and concentrated *in vacuo* to afford the title compound as a pale beige solid.

LC-MS (Method E): Rt 1.14 min; (100% @ 215 nm)

MS18, no ionisation, RT = 1.14, UV 100%

¹H NMR (400 MHz, DMSO-d₆) δ 10.63 (br. s, 1H), 10.23 – 10.20 (m, 1H), 7.50 (d, J = 8.6 Hz, 1H), 7.31 (d, J = 5.6 Hz, 1H).

Step 3: 2-Benzyloxy-4-bromo-5-fluoro-benzaldehyde

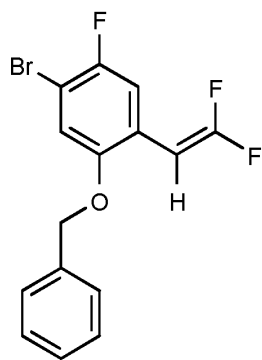
To a mixture of 4-bromo-5-fluoro-2-hydroxy-benzaldehyde (step 2)(100%, 3.68 g, 16.81 mmol) and K₂CO₃ (4.65 g, 33.61 mmol) in MeCN (75 mL) was added bromomethylbenzene (2.2 mL, 18.49 mmol) and the mixture was stirred at room temperature for 4 h 30 min. The resulting mixture was diluted with EtOAc (300 mL)

and water (300 mL) and the phases were separated. The organic portion was washed with water (2 x 200 mL), brine (200 mL), dried over Na₂SO₄ and concentrated *in vacuo* to give the crude product as a pale orange solid. The solid was dissolved in the minimum volume of boiling heptanes (30 mL) and allowed to cool to room temperature. The resulting crystalline solid was filtered, washing with heptanes (2 x 5 mL) and dried *in vacuo* to afford the title compound as a beige crystalline solid.

LC-MS (Method G): Rt 1.12 min; MS m/z 307.0, 309.0 = [M-H]⁻ (100% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 10.30 – 10.28 (m, 1H), 7.77 (d, J = 5.3 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.52 – 7.49 (m, 2H), 7.44 – 7.39 (m, 2H), 7.38 – 7.33 (m, 1H), 5.32 (s, 2H).

Step 4: 1-Benzyloxy-5-bromo-2-(2,2-difluorovinyl)-4-fluoro-benzene

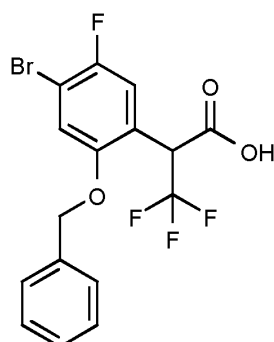


A mixture of 2-benzyloxy-4-bromo-5-fluoro-benzaldehyde (step 3) (3.95 g, 12.78 mmol) and triphenyl phosphine (4.02 g, 15.33 mmol) in DMF (25 mL) was placed under a nitrogen atmosphere and heated to 100 °C. To this mixture was added dropwise sodium 2-chloro-2,2-difluoro-acetate (2.92 g, 19.17 mmol) in DMF (10 mL) and stirring continued at 100 °C for 40 min. The resulting mixture was diluted with EtOAc (200 mL) and 1:1 water:brine (200 mL) and the phases were separated. The organic portion was washed with brine (2 x 100 mL), dried over Na₂SO₄ and concentrated *in vacuo* to give the crude product as an orange/brown oil. Purification of the oil by chromatography on silica eluting with 0-15% EtOAc in heptanes afforded the title compound as a colourless oil.

LC-MS (Method H): Rt 1.87 min; (100% @ 215 nm)

¹H NMR (400 MHz, DMSO-d₆) δ 7.49 – 7.44 (m, 3H), 7.43 – 7.38 (m, 2H), 7.38 – 7.32 (m, 2H), 5.73 (dd, J = 26.7, 3.7 Hz, 1H), 5.17 (s, 2H).

Step 5: 2-(2-Benzyloxy-4-bromo-5-fluoro-phenyl)-3,3,3-trifluoro-propanoic acid

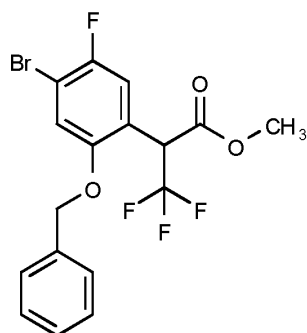


Cesium fluoride (4.45 g, 29.29 mmol) was added to a 3 neck flask equipped with a magnetic stirrer bar. The flask was placed under vacuum with excessive heating (heat gun) to ensure the solids are suitably dry. During the drying process the vessel was
5 purged with nitrogen and re-evacuated several times. The flask was allowed to sit under vacuum for 1 hour at 100 °C. After allowing the flask to cool to room temperature, the flask was placed under a nitrogen atmosphere and a solution of 1-benzyloxy-5-bromo-2-(2,2-difluorovinyl)-4-fluoro-benzene (step 4) (3.35 g, 9.76 mmol) in dry DMSO (75 mL)
10 was added. The vessel was placed under a CO₂ atmosphere (3 x cycles of filling and evacuating, 1 atm pressure CO₂ filling from a lecture bottle) and stirred vigorously at 55 °C overnight. The resulting mixture was diluted with water (300 mL) and EtOAc (300 mL) and the phases were separated. The organic portion was washed with water (300 mL), brine (300 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The crude product was
15 purified by C18 reverse phase chromatography eluting with 10-100% MeCN in water (+0.1% formic acid) to afford the title compound as a pale yellow solid.

LC-MS (Method H): Rt 1.33 min; MS m/z 361.0, 363.0 = [M-CO₂-H] (98% @ 215 nm)

¹H NMR (400 MHz, DMSO-d₆) δ 13.56 (br. s, 1H), 7.56 (d, J = 5.9 Hz, 1H), 7.46 – 7.37 (m, 5H), 7.36 – 7.31 (m, 1H), 5.25 – 5.16 (m, 2H), 5.05 (q, J = 9.3 Hz, 1H).

20 Step 6: Methyl 2-(2-benzyloxy-4-bromo-5-fluoro-phenyl)-3,3,3-trifluoro-propanoate

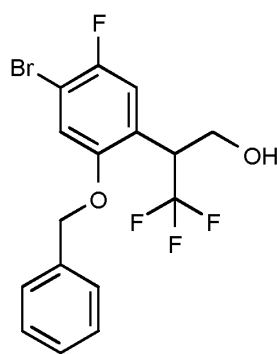


A cooled (0 °C) mixture of 2-(2-benzyloxy-4-bromo-5-fluoro-phenyl)-3,3,3-trifluoro-propanoic acid (step 5) (763 mg, 1.87 mmol) in MeOH (20 mL) was treated dropwise with SOCl₂ (1360 µL, 18.75 mmol) and heated to 50 °C for 4 h. The resulting mixture was concentrated *in vacuo* azeotroping with DCM (10 mL) and THF (10 mL) to afford the title compound as a brown/orange oil.

LC-MS (Method E): Rt 1.47 min; (97% @ 215 nm)

¹H NMR (400 MHz, DMSO-d₆) δ 7.58 (d, J = 5.9 Hz, 1H), 7.43 – 7.38 (m, 5H), 7.37 – 7.31 (m, 1H), 5.27 – 5.14 (m, 3H), 3.57 (s, 3H).

Step 7: 2-(2-Benzyloxy-4-bromo-5-fluoro-phenyl)-3,3,3-trifluoro-propan-1-ol

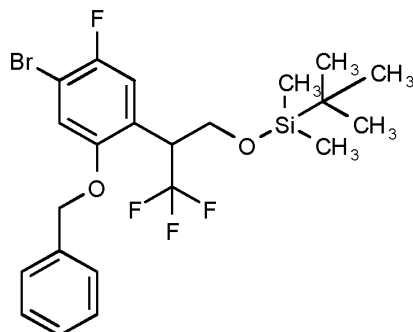


To a cooled (-78 °C) solution of methyl 2-(2-benzyloxy-4-bromo-5-fluoro-phenyl)-3,3,3-trifluoro-propanoate (step 6) (97%, 720 mg, 1.66 mmol) in THF (16 mL) was added dropwise 4M LiBH₄ in THF (0.41 mL, 1.66 mmol) and the mixture was stirred for 30 min. Additional 4M LiBH₄ in THF (0.41 mL, 1.66 mmol) was added and the mixture was stirred for 1 h. The reaction was quenched by the dropwise addition of saturated NH₄Cl solution (10 mL) and the resulting mixture was diluted with EtOAc (80 mL) and water. The phases were separated and the organic portion was washed with brine (80 mL), dried over Na₂SO₄ and concentrated *in vacuo* to give a yellow oil. Purification of the oil by chromatography on silica eluting with 0-40% EtOAc in heptanes afforded the title compound as a colourless oil.

LC-MS (Method G): Rt 1.11 min; MS m/z 391.1, 393.1 = [M+H]⁺ (99% @ 215 nm)

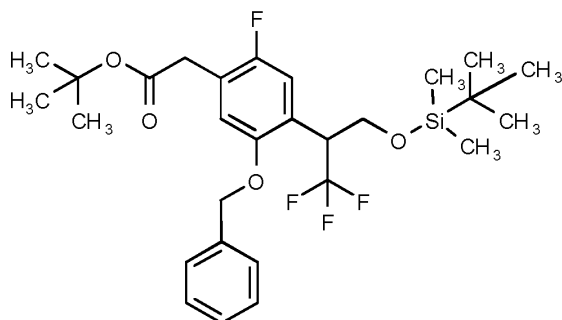
¹H NMR (500 MHz, DMSO-d₆) δ 7.49 (d, J = 6.0 Hz, 1H), 7.46 – 7.41 (m, 3H), 7.40 – 7.33 (m, 3H), 5.18 (s, 2H), 5.16 (t, J = 5.7 Hz, 1H), 4.21 – 4.09 (m, 1H), 3.96 – 3.89 (m, 1H), 3.88 – 3.81 (m, 1H).

Step 8: [2-(2-Benzyloxy-4-bromo-5-fluoro-phenyl)-3,3,3-trifluoro-propoxy]-*tert*-butyl-dimethyl-silane



- t*-Butyldimethylsilyl chloride (70 mg, 0.46 mmol) was added to a mixture of 2-(2-benzyloxy-4-bromo-5-fluoro-phenyl)-3,3,3-trifluoro-propan-1-ol (step 7)(99%, 123 mg, 0.31 mmol) and imidazole (42 mg, 0.62 mmol) in DCM (3 mL) and the reaction mixture was stirred at room temperature for 4 h. The resulting mixture was diluted with DCM (10 mL) and water (10 mL) and the phases were separated. The aqueous was extracted with DCM (10 mL) and the combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo*. Purification of the crude product by chromatography on silica eluting with 0-20% EtOAc in heptanes afforded the title compound as a colourless oil. LC-MS (Method H): Rt 2.21 min; (98% @ 215 nm)
- ¹H NMR (500 MHz, DMSO-d₆) δ 7.52 (d, J = 6.0 Hz, 1H), 7.47 (d, J = 9.6 Hz, 1H), 7.44 – 7.38 (m, 4H), 7.37 – 7.33 (m, 1H), 5.20 (d, J = 11.9 Hz, 1H), 5.16 (d, J = 11.9 Hz, 1H), 4.21 – 4.11 (m, 1H), 4.05 (dd, J = 10.8, 5.9 Hz, 1H), 3.99 (dd, J = 10.8, 6.0 Hz, 1H), 0.78 (s, 9H), -0.03 (s, 3H), -0.05 (s, 3H).

Step 9: *tert*-Butyl 2-[5-benzyloxy-4-[1-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-2,2,2-trifluoro-ethyl]-2-fluoro-phenyl]acetate



- The title compound was prepared from [2-(2-benzyloxy-4-bromo-5-fluoro-phenyl)-3,3,3-trifluoro-propoxy]-*tert*-butyl-dimethyl-silane (step 8) and 0.5M bromo-(2-*tert*-butoxy-2-oxo-ethyl)zinc in THF analogously to Intermediate M step 2.

LC-MS (Method H): Rt 2.26 min; MS m/z 487.2 = [M+H]⁺ (81% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 7.45 – 7.37 (m, 4H), 7.36 – 7.32 (m, 1H), 7.25 (d, J = 10.4 Hz, 1H), 7.16 (d, J = 6.4 Hz, 1H), 5.12 (d, J = 11.8 Hz, 1H), 5.08 (d, J = 11.9 Hz, 1H), 4.20 – 4.11 (m, 1H), 4.03 (dd, J = 10.8, 6.0 Hz, 1H), 3.97 (dd, J = 10.8, 5.9 Hz, 1H),
5 3.60 (s, 2H), 1.38 (s, 9H), 0.79 (s, 9H), -0.03 (s, 3H), -0.05 (s, 3H).

Step 10: 2-[5-Benzyloxy-2-fluoro-4-[2,2,2-trifluoro-1-(hydroxymethyl)ethyl]phenyl]acetic acid

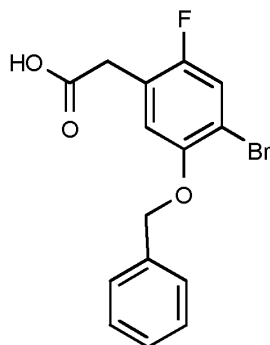
TFA (938 μL, 12.25 mmol) was added to a mixture of *tert*-butyl 2-[5-benzyloxy-4-[1-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-2,2,2-trifluoro-ethyl]-2-fluoro-phenyl]acetate (step 9) (90%,
10 12 mg, 0.2 mmol) in DCM (3 mL) and the reaction mixture was stirred at room temperature for 5 h. The resulting mixture was concentrated *in vacuo* then azeotroped with DCM (3 x 5 mL). The crude product was purified by C18 reverse phase chromatography eluting with 10-100% MeCN/water (+0.1% formic acid) to afford the title compound as a colourless oil.

15 LC-MS (Method E): Rt 1.19 min; MS m/z 355.1 = [M+H-H₂O]⁺ (100% @ 215 nm)

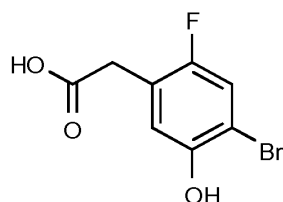
¹H NMR (500 MHz, DMSO-d₆) δ 12.51 (br s, 1H), 7.47 – 7.39 (m, 4H), 7.37 – 7.32 (m, 1H), 7.21 (d, J = 10.4 Hz, 1H), 7.18 (d, J = 6.4 Hz, 1H), 5.14 (t, J = 5.2 Hz, 1H), 5.09 (s, 2H), 4.19 – 4.09 (m, 1H), 3.96 – 3.90 (m, 1H), 3.85 – 3.79 (m, 1H), 3.61 (s, 2H).

20 Intermediate S

2-(5-Benzyloxy-4-bromo-2-fluoro-phenyl)acetic acid



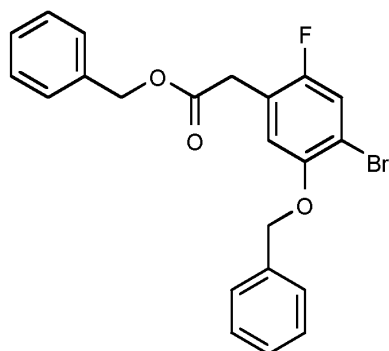
Step 1: 2-(4-Bromo-2-fluoro-5-hydroxy-phenyl)acetic acid



1M BBr₃ in DCM (28.51 mL, 28.51 mmol) was added dropwise to a cooled (0 °C), stirred suspension of 2-(4-bromo-2-fluoro-5-methoxy-phenyl)acetic acid (Intermediate U step 1) (2.5 g, 9.5 mmol) in DCM (30 mL). After 30 mins, the ice bath was removed and the reaction mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated *in vacuo* and the residue was partitioned between EtOAc (100 mL) and water (100 mL). The organic layer was separated, washed with water (100 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The crude material was purified by C18 reverse phase chromatography eluting with MeCN in water (+0.1% formic acid) to afford the title compound as an off-white solid.

¹H NMR (500 MHz, DMSO-d₆) δ 10.43 (br s, 1H), 7.36 (d, J = 9.1 Hz, 1H), 6.89 (d, J = 6.9 Hz, 1H), 3.52 – 3.49 (m, 2H). 90% purity by ¹H NMR.

Step 2: Benzyl 2-(5-benzyloxy-4-bromo-2-fluoro-phenyl)acetate



The title compound was prepared from 2-(4-bromo-2-fluoro-5-hydroxy-phenyl)acetic acid (step 1) and bromomethylbenzene analogously to Intermediate R step 3.

LC-MS (Method E): Rt 1.52 min; (88% @ 215 nm)

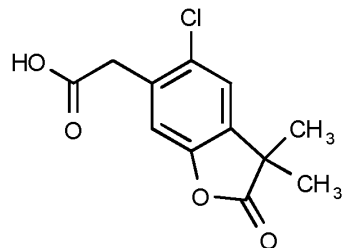
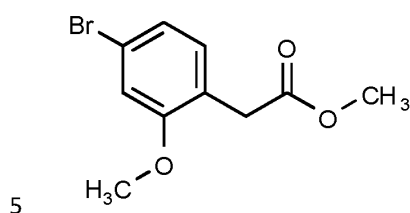
¹H NMR (400 MHz, DMSO-d₆) δ 7.56 (d, J = 8.9 Hz, 1H), 7.50 – 7.45 (m, 2H), 7.43 – 7.31 (m, 8H), 7.28 (d, J = 6.6 Hz, 1H), 5.14 (s, 2H), 5.12 (s, 2H), 3.78 (d, J = 1.1 Hz, 2H).

Step 3: 2-(5-Benzyloxy-4-bromo-2-fluoro-phenyl)acetic acid

The title compound was prepared from benzyl 2-(5-benzyloxy-4-bromo-2-fluoro-phenyl)acetate (step 2) and lithium hydroxide analogously to Intermediate P step 3.

LC-MS (Method G): Rt 0.99 min; MS m/z 675.1, 677.1, 679.1 = [2M-H]⁻ (84% @215 nm)

¹H NMR (400 MHz, DMSO-d₆) δ 12.55 (br. s, 1H), 7.53 (d, J = 8.9 Hz, 1H), 7.50 – 7.46 (m, 2H), 7.43 – 7.38 (m, 2H), 7.37 – 7.32 (m, 1H), 7.26 (d, J = 6.7 Hz, 1H), 5.14 (s, 2H), 3.60 (d, J = 1.2 Hz, 2H).

Intermediate T**2-(5-Chloro-3,3-dimethyl-2-oxo-benzofuran-6-yl)acetic acid**Step 1: Methyl 2-(4-bromo-2-methoxy-phenyl)acetate

5

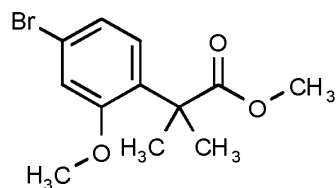
Concentrated sulfuric acid (350 μ L, 6.3 mmol) was added dropwise to a stirred solution of 2-(4-bromo-2-methoxy-phenyl)acetic acid (7.25 g, 29.6 mmol) in MeOH (70 mL). The reaction mixture was heated to 70°C for 3 h and then left to stand at room temperature overnight. The resulting mixture was concentrated *in vacuo* and the residue was dissolved in EtOAc (100 mL). The mixture was washed with NaHCO₃ (50 mL), the aqueous wash was further extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with brine (50 mL), dried over Na₂SO₄ and concentrated *in vacuo* to afford the title compound as an orange oil.

10

LC-MS (Method G): Rt 0.96 min; (90% @ 215 nm)

15

¹H NMR (500 MHz, DMSO-d₆) δ 7.17 (d, J = 1.8 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 7.10 (dd, J = 8.0, 1.9 Hz, 1H), 3.77 (s, 3H), 3.59 (s, 3H), 3.58 (s, 2H).

Step 2: Methyl 2-(4-bromo-2-methoxy-phenyl)-2-methyl-propanoate

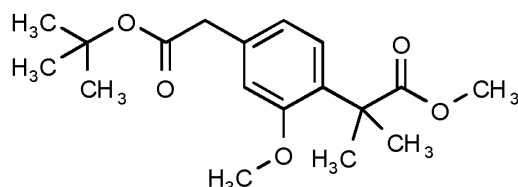
20

A cooled (-78 °C) solution of diisopropylamine (20.7 mL, 147.5 mmol) in THF (104.21 mL) was treated with 1.8M BuLi in hexanes (80.6 mL, 145.1 mmol). After stirring for 10 min, methyl 2-(4-bromo-2-methoxy-phenyl)acetate (step 1) (90%, 5 g, 17.4 mmol) and methyl 2-(4-bromo-2-methoxy-phenyl)acetate (step 1)(80%, 10.3 g, 31.8 mmol) in THF (50 mL) and methyl iodide (12.2 mL, 196.7 mmol) were added and the reaction

mixture was allowed to warm to room temperature and stirred for 2 days. Additional THF (100 mL) was added and the mixture was cooled to 0 °C and treated with 2M LDA in THF (30 mL, 60.0 mmol) and MeI (1.6 mL, 19.2 mmol). After stirring at 0 °C for 2 h, the resulting mixture was partitioned between EtOAc (500 mL) and saturated aqueous ammonium chloride (500 mL). The phases were separated and the aqueous was further extracted with EtOAc (2 x 300 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo*. Purification of the crude material by chromatography on silica eluting with 0-25% EtOAc in heptanes afforded the title compound as a pale yellow oil.

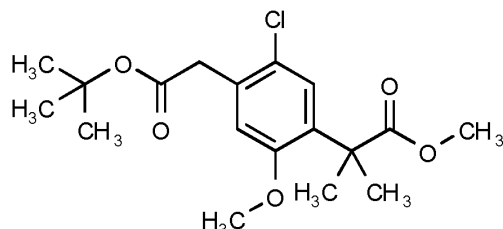
- LC-MS (Method H): Rt 1.51 min; MS m/z 286.8, 288.8 = [M+H]⁺ (92% @ 215 nm)
¹H NMR (400 MHz, DMSO-d₆) δ 7.22 (d, J = 8.2 Hz, 1H), 7.18 – 7.10 (m, 2H), 3.74 (s, 3H), 3.52 (s, 3H), 1.39 (s, 6H).

Step 3: Methyl 2-[4-(2-*tert*-butoxy-2-oxo-ethyl)-2-methoxy-phenyl]-2-methyl-propanoate



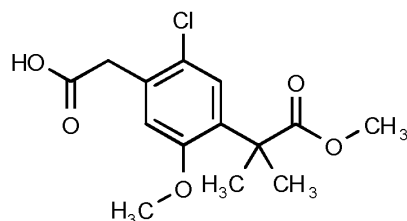
- Methyl 2-(4-bromo-2-methoxy-phenyl)-2-methyl-propanoate (step 2) (2.0 g, 6.97 mmol), Pd(dba)₂ (200 mg, 0.35 mmol) and Q-Phos (248 mg, 0.35 mmol) were suspended in THF (40 mL) then the reaction was degassed with nitrogen for 5 min. 0.5M bromo-(2-*tert*-butoxy-2-oxo-ethyl)zinc in THF (20.9 mL, 10.45 mmol) was added and the reaction mixture was heated at 60 °C for 2.5 h. After cooling to room temperature, the mixture was partitioned between EtOAc (75 mL) and saturated NaHCO₃ (50 mL). The organic portion was separated, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by chromatography on silica eluting with 0-100% EtOAc in heptanes followed by 0-100% DCM in heptanes then 0-100% MeOH in DCM. The residue was dissolved in 1:1 DMSO/MeOH (1.2 mL) and purified by mass directed LC-MS using eluting with water/MeCN with 0.1% formic acid to afford the title compound as a light red oil.
- LC-MS (Method G): Rt 1.13 min; MS m/z 345.2 = [M+Na]⁺ (95% @ 215 nm)
¹H NMR (500 MHz, DMSO-d₆) δ 7.20 (d, J = 7.9 Hz, 1H), 6.86 (d, J = 1.5 Hz, 1H), 6.81 (dd, J = 7.8, 1.6 Hz, 1H), 3.69 (s, 3H), 3.53-3.51 (m, 5H), 1.42 (s, 9H), 1.40 (s, 6H).

Step 4: Methyl 2-[4-(2-*tert*-butoxy-2-oxo-ethyl)-5-chloro-2-methoxy-phenyl]-2-methyl-propanoate



Methyl 2-[4-(2-*tert*-butoxy-2-oxo-ethyl)-2-methoxy-phenyl]-2-methyl-propanoate (step 3)

- 5 (1.2 g, 3.72 mmol) in DCM (18.6 mL) was treated with triphenylphosphine sulfide (110 mg, 0.37 mmol) and *N*-chlorosuccinimide (596 mg, 4.47 mmol) and stirred for 1 h. The reaction was quenched with saturated aqueous sodium thiosulfate (20 mL) and the phases separated. The aqueous layer was extracted with DCM (2 x 20 mL) and the combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo*.
- 10 Purification by chromatography on silica eluting with 0-50% TBME in heptanes afforded the title compound as a pale yellow oil.
- LC-MS (Method G): Rt 1.24 min; MS m/z 379.2, 381.2 = [M+Na]⁺ (95% @ 215 nm)
- ¹H NMR (400 MHz, DMSO-d₆) δ 7.25 (s, 1H), 7.04 (s, 1H), 3.71 (s, 3H), 3.65 (s, 2H), 3.53 (s, 3H), 1.42 (s, 9H), 1.41 (s, 6H).
- 15 Step 5: 2-[2-Chloro-5-methoxy-4-(2-methoxy-1,1-dimethyl-2-oxo-ethyl)phenyl]acetic acid



Methyl 2-[4-(2-*tert*-butoxy-2-oxo-ethyl)-5-chloro-2-methoxy-phenyl]-2-methyl-propanoate (step 4)(95%, 1.37 g, 3.63 mmol) in DCM (15 mL) was treated with TFA (5.0 mL, 65.34 mmol) and stirred at room temperature for 2 h. The resulting mixture was concentrated *in vacuo* and azeotroped once with DCM (20 mL). The residue was dissolved in EtOAc (20 mL) and washed with water (2 x 10 mL). The organic layer was dried over Na₂SO₄ and concentrated *in vacuo* to afford the title compound as an off-white solid.

- 20 LC-MS (Method G): Rt 0.90 min; MS m/z 301.1, 303.1 = [M+H]⁺ (95% @ 215 nm)
- ¹H NMR (400 MHz, DMSO-d₆) δ 12.45 (br. s, 1H), 7.25 (s, 1H), 7.05 (s, 1H), 3.70 (s, 3H), 3.67 (s, 2H), 3.54 (s, 3H), 1.41 (s, 6H).

Step 6: 2-(5-Chloro-3,3-dimethyl-2-oxo-benzofuran-6-yl)acetic acid

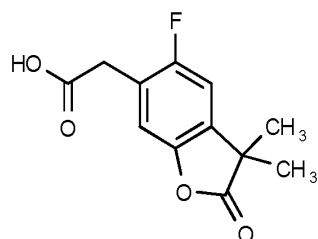
A cooled (0 °C) solution of 2-[2-chloro-5-methoxy-4-(2-methoxy-1,1-dimethyl-2-oxo-ethyl)phenyl]acetic acid (step 5) (95%, 1.02 g, 3.22 mmol) in DCM (32.2 mL) was treated with 1M BBr₃ in DCM (0.93 mL, 9.67 mmol) then allowed to warm to room temperature and stirred for 20 h. The reaction was quenched with water, phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo*. Purification by C18 reverse phase chromatography eluting with 10-100% MeCN in water (+0.1% formic acid) afforded the title compound as a colourless solid.

LC-MS (Method G): Rt 0.97 min; (98% @ 215 nm)

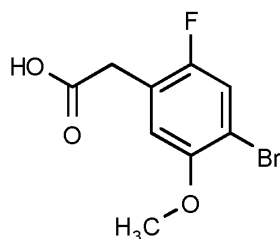
¹H NMR (400 MHz, DMSO-d₆) δ 12.53 (s, 1H), 7.64 (s, 1H), 7.33 (s, 1H), 3.74 (s, 2H), 1.45 (s, 6H).

Intermediate U

2-(5-Fluoro-3,3-dimethyl-2-oxo-benzofuran-6-yl)acetic acid



Step 1: 2-(4-Bromo-2-fluoro-5-methoxy-phenyl)acetic acid



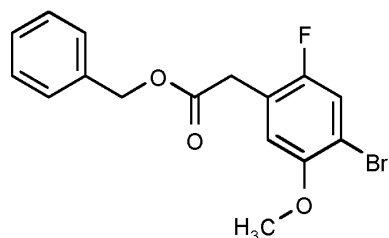
To a cooled (0 °C) solution of 2-(2-fluoro-5-methoxy-phenyl)acetic acid (45 g, 244.4 mmol) in MeCN (1.2 L) was added dropwise a solution of bromine (12.63 mL, 244.9 mmol) in MeCN (100 mL) over a period of 10 min. The resulting mixture was allowed to warm to room temperature gradually without removing the ice bath (~1.5 h). Additional bromine (4.21 mL, 81.64 mmol) in MeCN (50 mL) was added dropwise to the mixture at 0 °C which was stirred at room temperature for a further 3.5 h. Further bromine (4.21 mL, 81.64 mmol) in MeCN (50 mL) was added at room temperature and mixture was stirred at room temperature for 30 min. The reaction was quenched carefully with saturated aqueous sodium sulfite (~700 mL) until the bright orange colour had disappeared. The colourless

solution was diluted with brine (200 mL) and EtOAc (200 mL), stirred vigorously for 10 min. The organic layer was separated and the aqueous layer was extracted further with EtOAc (200 mL). Organic layers were combined, dried over Na₂SO₄ and concentrated *in vacuo* to obtain the crude product as a white solid. The crude product was recrystallised by dissolving the solid in AcOH (700 mL), then treated with water (4 L). The mixture was stirred to mix the solvents whereupon crystals gradually appeared. The mixture was kept at room temperature for 1 h and then at 0 °C for 3 h. Filtration followed by vacuum drying at 40 °C afforded the title compound as a fluffy white solid.

LC-MS (Method E): Rt 1.07min; (99% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 12.55 (br s, 1H), 7.50 (d, J = 8.9 Hz, 1H), 7.13 (d, J = 6.6 Hz, 1H), 3.81 (s, 3H), 3.61 (d, J = 1.3 Hz, 2H).

Step 2: Benzyl 2-(4-bromo-2-fluoro-5-methoxy-phenyl)acetate

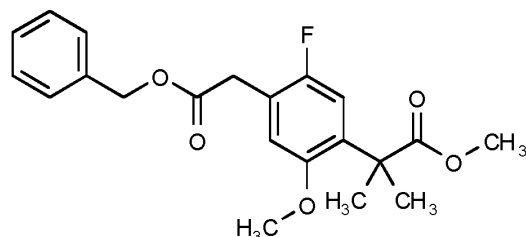


A mixture of 2-(4-bromo-2-fluoro-5-methoxy-phenyl)acetic acid (step 1)(15 g, 57.02 mmol) and K₂CO₃ (15.76 g, 114.0 mmol) in DMF (140 mL) was treated with benzylbromide (7.45 mL, 62.7 mmol) and stirred at room temperature for 18 h. The resulting mixture was filtered and concentrated *in vacuo*. The residue was dissolved in EtOAc (300 mL) and sequentially washed with brine (200 mL) and saturated aqueous sodium bicarbonate (2 x 200 mL). The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. Purification by chromatography on silica eluting with 0-20% EtOAc in heptanes afforded the title compound as a colourless solid.

LC-MS (Method G): Rt 1.13 min; (95% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 7.53 (d, J = 8.9 Hz, 1H), 7.40 – 7.31 (m, 5H), 7.15 (d, J = 6.6 Hz, 1H), 5.14 (s, 2H), 3.81 – 3.78 (m, 5H).

Step 3: Methyl 2-[4-(2-benzyloxy-2-oxo-ethyl)-5-fluoro-2-methoxy-phenyl]-2-methyl-propanoate



Benzyl 2-(4-bromo-2-fluoro-5-methoxy-phenyl)acetate (step 2) (5.0 g, 14.16 mmol), ZnF_2 (1.1 g, 10.62 mmol) and $\text{Pd}(\text{P}^t\text{Bu}_3)_2$ (0.36 g, 0.71 mmol) were added to a reaction vessel and placed under a nitrogen atmosphere. A solution of (1-methoxy-2-methyl-prop-1-en-1-yl)-trimethyl-silane (5.75 mL, 28.31 mmol) in degassed DMF (50 mL) was added and the reaction mixture was heated to 80 °C for 18 h. The resulting mixture was filtered and concentrated *in vacuo*. The residue was dissolved in EtOAc (100 mL) and washed with brine (2 x 50 mL) and the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Purification by chromatography on silica eluting with 0-30% EtOAc in heptanes the title compound as a pale yellow oil.

LC-MS (Method A): Rt 3.99 min; MS m/z 375.3 = $[\text{M}+\text{H}]^+$ (92% @ 215 nm)

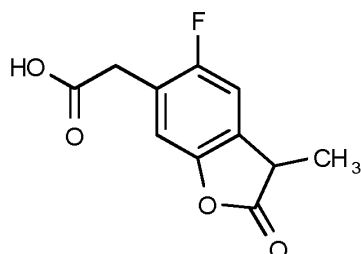
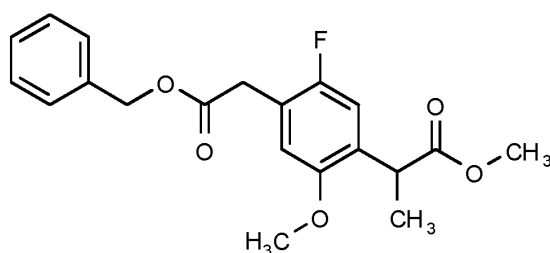
^1H NMR (400 MHz, DMSO-d_6) δ 7.40 – 7.30 (m, 5H), 7.09 (d, J = 11.0 Hz, 1H), 6.98 (d, J = 6.5 Hz, 1H), 5.14 (s, 2H), 3.76 (s, 2H), 3.66 (s, 3H), 3.53 (s, 3H), 1.40 (s, 6H).

Step 4: 2-(5-Fluoro-3,3-dimethyl-2-oxo-benzofuran-6-yl)acetic acid

1M BBr_3 in DCM (34.13 mL, 34.1 mmol) was added to a cooled (0 °C) mixture of methyl 2-[4-(2-benzyloxy-2-oxo-ethyl)-5-fluoro-2-methoxy-phenyl]-2-methyl-propanoate (step 3) (92%, 2777 mg, 6.83 mmol) in dry DCM (60 mL). The resulting mixture was allowed to warm to room temperature and stirred for 4.5 h. The reaction mixture was re-cooled to 0 °C and water (50 mL) was added. Stirring continued whilst gradually warming to room temperature over 30 min. The resulting mixture was diluted with DCM (80 mL) and water (80 mL) and the phases were separated. The aqueous was extracted with EtOAc (80 mL) then the combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product as a brown oil. Purification of the crude product by C18 reverse phase chromatography eluting with 10-100% MeCN/water (+0.1% formic acid) afforded the title compound as a pale yellow solid.

LC-MS (Method H): Rt 1.19 min; (98% @ 215 nm)

^1H NMR (500 MHz, DMSO-d_6) δ 12.56 (br. s, 1H), 7.42 (d, J = 8.9 Hz, 1H), 7.25 (d, J = 5.8 Hz, 1H), 3.64 (d, J = 1.5 Hz, 2H), 1.44 (s, 6H).

Intermediate UA**2-(5-Fluoro-3-methyl-2-oxo-3H-benzofuran-6-yl)acetic acid****Step 1: Methyl 2-[4-(2-benzyloxy-2-oxo-ethyl)-5-fluoro-2-methoxy-phenyl]propanoate**

5

The title compound was prepared from benzyl 2-(4-bromo-2-fluoro-5-methoxy-phenyl)acetate (Intermediate U step 2) and [(E)-1-methoxyprop-1-en-1-yl]-trimethyl-silane analogously to Intermediate U step 3.

LC-MS (Method E): Rt 1.37 min; MS m/z 361.2 = [M+H]⁺ (97% @ 215 nm)

10 ¹H NMR (500 MHz, DMSO-d₆) δ 7.39 – 7.30 (m, 5H), 7.02 (d, J = 10.2 Hz, 1H), 6.99 (d, J = 6.3 Hz, 1H), 5.14 (s, 2H), 3.93 (q, J = 7.2 Hz, 1H), 3.76 (s, 2H), 3.71 (s, 3H), 3.57 (s, 3H), 1.34 (d, J = 7.2 Hz, 3H).

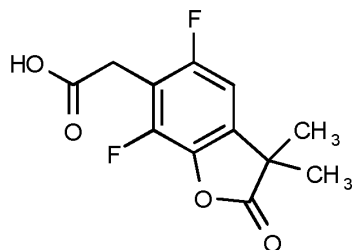
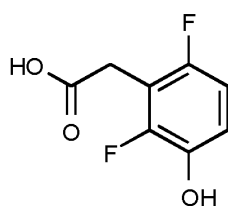
Step 2: 2-(5-Fluoro-3-methyl-2-oxo-3H-benzofuran-6-yl)acetic acid

15 The title compound was prepared from methyl 2-[4-(2-benzyloxy-2-oxo-ethyl)-5-fluoro-2-methoxy-phenyl]propanoate (step 1) and 1M BBr₃ in DCM analogously to Intermediate U step 4.

LC-MS (Method A): Rt 2.08 min; (88% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 12.56 (br s, 1H), 7.33 (d, J = 8.9 Hz, 1H), 7.20 (d, J = 5.9 Hz, 1H), 4.03 (q, J = 7.5 Hz, 1H), 3.63 (d, J = 1.2 Hz, 2H), 1.45 (d, J = 7.6 Hz, 3H).

20

Intermediate V**2-(5,7-Difluoro-3,3-dimethyl-2-oxo-benzofuran-6-yl)acetic acid****Step 1: 2-(2,6-Difluoro-3-hydroxy-phenyl)acetic acid**

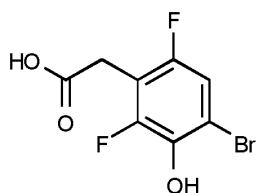
5

To a solution of 2-(2,6-difluoro-3-methoxy-phenyl)acetic acid (850 mg, 4.2 mmol) in DCM (30 mL) was added 1M BBr₃ in DCM (6.31 mL, 6.31 mmol) and the mixture was stirred at room temperature for 1 h then allowed to stand at room temperature for 5 days. The resulting mixture was poured onto water (30 mL) and 1M NaOH (aq) (~20 mL) was added.

10 The biphasic mixture was stirred vigorously for 30 min at room temperature and the layers were separated. The aqueous portion was acidified to pH1-2 by the dropwise addition of 6M HCl then extracted with EtOAc (2 x 30 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo* to afford the title compound as a white solid.

LC-MS (Method G): Rt 0.50 min; (100% @ 215 nm)

15 ¹H NMR (500 MHz, DMSO-d₆) δ 12.61 (br. s, 1H), 9.74 (s, 1H), 6.89 – 6.83 (m, 2H), 3.58 (s, 2H).

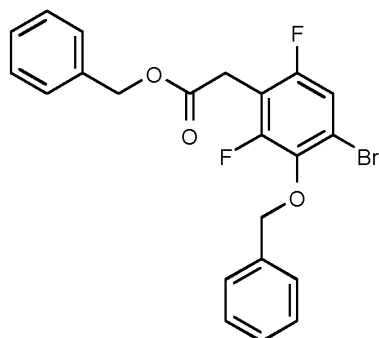
Step 2: 2-(4-Bromo-2,6-difluoro-3-hydroxy-phenyl)acetic acid

20 To a cooled (0 °C) mixture of 2-(2,6-difluoro-3-hydroxy-phenyl)acetic acid (step 1) (940 mg, 5. mmol) in chloroform (30 mL) was added DIPEA (1.75 mL, 9.99 mmol) and the resulting mixture was stirred vigorously for 10 min. N-Bromosuccinimide (889 mg, 5. mmol) was added and the mixture was stirred at 0 °C for 20 min. The resulting mixture was diluted with EtOAc (150 mL) and 1M HCl (150 mL) and the phases were separated. The aqueous

portion was extracted with EtOAc (150 mL) and the combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo*. Purification of the crude product by C18 reverse phase chromatography eluting with 10-100% MeCN/water (+0.1% formic acid) afforded the title compound as a pale orange solid.

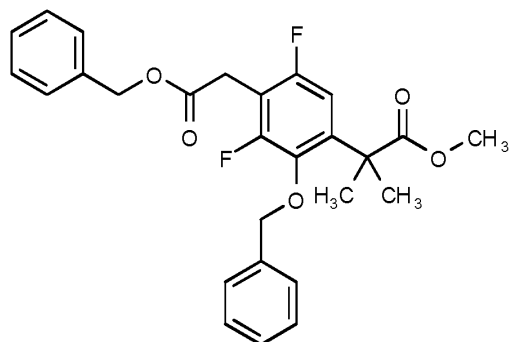
- 5 LC-MS (Method G): Rt 0.70 min; MS m/z 264.9, 266.9 = [M-H]⁻ (100% @ 215 nm)
¹H NMR (400 MHz, DMSO-d₆) δ 12.73 (br. s, 1H), 10.27 (br. s, 1H), 7.35 (dd, J = 8.8, 2.2 Hz, 1H), 3.59 (s, 2H).

Step 3: Benzyl 2-(3-benzyloxy-4-bromo-2,6-difluoro-phenyl)acetate



- 10 To a solution of 2-(4-bromo-2,6-difluoro-3-hydroxy-phenyl)acetic acid (step 2)(896 mg, 3.35 mmol) in DMF (25 mL) was added K₂CO₃ (1391 mg, 10.06 mmol) and bromomethylbenzene (0.88 mL, 7.38 mmol) and the mixture was stirred at room temperature for 16 h. The resulting mixture was diluted with EtOAc (150 mL) and water (150 mL) and the phases were separated. The organic portion was washed with brine (150 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Purification of the crude product by chromatography on silica eluting with 0-25% EtOAc in heptanes afforded the title compound as a pale yellow oil.
- 15 LC-MS (Method G): Rt 1.30 min; (99% @ 215 nm)
¹H NMR (500 MHz, DMSO-d₆) δ 7.56 (dd, J = 8.8, 2.1 Hz, 1H), 7.49 – 7.46 (m, 2H), 7.42 – 7.31 (m, 8H), 5.16 (s, 2H), 5.02 (s, 2H), 3.82 (s, 2H).
- 20

Step 4: Methyl 2-[2-benzyloxy-4-(2-benzyloxy-2-oxo-ethyl)-3,5-difluoro-phenyl]-2-methyl-propanoate



The title compound was prepared from benzyl 2-(3-benzyloxy-4-bromo-2,6-difluoro-phenyl)acetate (step 3) and (1-methoxy-2-methyl-prop-1-en-1-yl)-trimethyl-silane analogously to Intermediate U step 3.

LC-MS (Method A): Rt 4.66 min; MS m/z 469.3 = [M+H]⁺ (49% @ 215 nm)

Step 5: 2-(5,7-Difluoro-3,3-dimethyl-2-oxo-benzofuran-6-yl)acetic acid

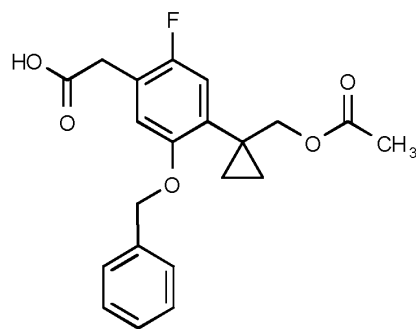
The title compound was prepared from methyl 2-[2-benzyloxy-4-(2-benzyloxy-2-oxo-ethyl)-3,5-difluoro-phenyl]-2-methyl-propanoate (step 4) and 1M BBr₃ in DCM analogously to Intermediate U step 4.

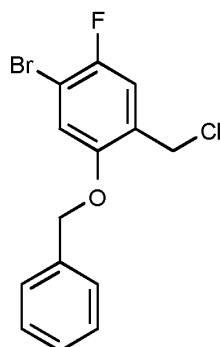
LC-MS (Method G): Rt 0.82 min; (100% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 12.75 (br. s, 1H), 7.39 (dd, J = 8.3, 1.2 Hz, 1H), 3.68 (s, 2H), 1.49 (s, 6H).

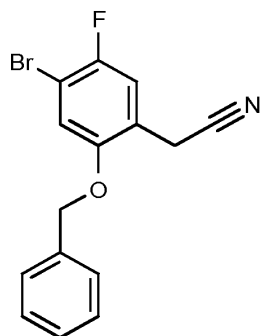
Intermediate W

2-[4-[1-(Acetoxymethyl)cyclopropyl]-5-benzyloxy-2-fluoro-phenyl]acetic acid



Step 1: 1-Benzyloxy-5-bromo-2-(chloromethyl)-4-fluoro-benzene

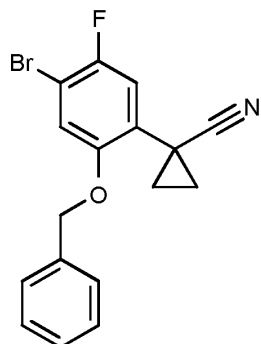
- To a cooled (0 °C), stirred solution of (2-benzyloxy-4-bromo-5-fluoro-phenyl)methanol (Intermediate N, step 2) (11.6 g, 37.28 mmol) in DCM (100 mL) and DMF (2.89 mL, 37.28 mmol) at was added dropwise thionyl chloride (5.41 mL, 74.56 mmol) in DCM (20 mL) and the mixture was stirred at room temperature for 2 h. The solvents were removed *in vacuo* and the residue was diluted with EtOAc (150 mL) and washed with saturated NaHCO₃ (3 x 100 mL). The organic portion was washed further with brine (2 x 100 mL), dried over Na₂SO₄ and concentrated *in vacuo* to afford the title compound as a yellow solid.
- LC-MS (Method E): Rt 1.43 min; (99% @ 215 nm)
- ¹H NMR (500 MHz, DMSO-d₆) δ 7.54 – 7.45 (m, 4H), 7.43-7.39 (m, 2H), 7.37-7.32 (m, 1H), 5.22 (s, 2H), 4.71 (s, 2H).

Step 2: 2-(2-Benzyloxy-4-bromo-5-fluoro-phenyl)acetonitrile

- To a solution of 1-benzyloxy-5-bromo-2-(chloromethyl)-4-fluoro-benzene (step 1) (3.7 g, 11.23 mmol) in DMF (50 mL) was added sodium cyanide (0.63 g, 12.91 mmol) and the mixture was stirred at room temperature overnight. The resulting mixture was diluted with EtOAc (50 mL) and washed with sat. sodium carbonate (100 mL) and brine (50 mL). The organic layer was separated, dried over Na₂SO₄ and concentrated *in vacuo* to afford the title compound as a yellow solid.
- LC-MS (Method G): Rt 1.09 min; MS m/z 318.0, 320.0 = [M+H]⁺ (97% @ 215 nm)

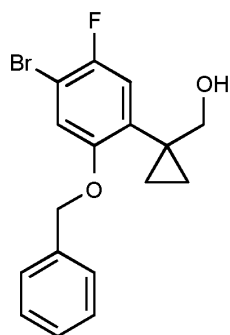
¹H NMR (500 MHz, DMSO-d₆) δ 7.54 – 7.48 (m, 2H), 7.48 (d, J = 5.8 Hz, 1H), 7.45 – 7.37 (m, 3H), 7.38 – 7.32 (m, 1H), 5.22 (s, 2H), 3.90 (s, 2H).

Step 3: 1-(2-Benzyloxy-4-bromo-5-fluoro-phenyl)cyclopropanecarbonitrile



- 5 To a mixture of potassium hydroxide (2209 mg, 39.37 mmol) in water (1.3 mL) was added 2-(2-benzyloxy-4-bromo-5-fluoro-phenyl)acetonitrile (step 2) (3.4 g, 10.62 mmol) and tetrabutylammonium bromide (34.23 g, 106.2 mmol). The resulting mixture was treated dropwise with 1,2-dibromoethane (1.83 mL, 21.24 mmol) where a strong exothermic effect was observed and the temperature was kept at 50 °C (external cooling). After stirring at
- 10 50 °C overnight, the resulting mixture was diluted with brine (100 mL) and extracted with EtOAc (2 x 30 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo*. Purification of the crude product by chromatography on silica eluting with 0-60% EtOAc in heptanes afforded the title compound as a pale yellow solid. LC-MS (Method E): Rt 1.39 min; MS m/z 346.0, 348.0 = [M+H]⁺ (99% @ 215 nm)
- 15 ¹H NMR (500 MHz, DMSO-d₆) δ 7.58 – 7.52 (m, 2H), 7.48 (d, J = 5.9 Hz, 1H), 7.46 – 7.39 (m, 3H), 7.38 – 7.31 (m, 1H), 5.28 (s, 2H), 1.64 – 1.58 (m, 2H), 1.41 – 1.35 (m, 2H).

Step 4: [1-(2-Benzyloxy-4-bromo-5-fluoro-phenyl)cyclopropyl]methanol



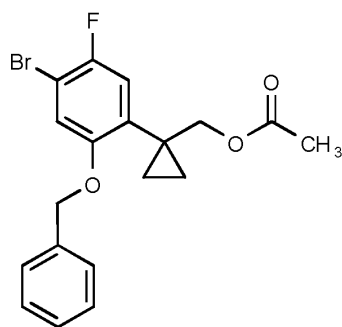
- To a stirred, cooled (0 °C) solution of 1-(2-benzyloxy-4-bromo-5-fluoro-phenyl)cyclopropanecarbonitrile (step 3) (2 g, 5.78 mmol) in DCM (50 mL) was added
- 20 dropwise 1M DIBAL in hexane (17.33 mL, 17.33 mmol) and the reaction mixture was

stirred at 0 °C for 1 h and then at room temperature overnight. A further portion of 1M DIBAL in hexane (17.33 mL, 17.33 mmol) was added and stirring continued at room temperature overnight. The reaction was quenched cautiously with 1M HCl (20 mL) and stirred for 30 min. The organic portion was separated, dried over Na₂SO₄ and concentrated *in vacuo*. Purification of the crude product by chromatography on silica eluting with 0-100% EtOAc in heptanes followed by 0-100% MeOH in EtOAc afforded the title compound as a brown oil.

LC-MS (Method E): Rt 1.32 min; MS m/z 682.0, 684.9, 686.0 = [2M-H₂O] (78% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 7.49 – 7.44 (m, 2H), 7.45 – 7.37 (m, 2H), 7.36 – 7.31 (m, 1H), 7.31 (d, J = 5.9 Hz, 1H), 7.16 (d, J = 9.3 Hz, 1H), 5.16 (s, 2H), 4.53 (t, J = 5.9 Hz, 1H), 3.45 (d, J = 5.8 Hz, 2H), 0.81 – 0.74 (m, 2H), 0.69 – 0.63 (m, 2H).

Step 5: [1-(2-Benzyloxy-4-bromo-5-fluoro-phenyl)cyclopropyl]methyl acetate



To a stirred solution of [1-(2-benzyloxy-4-bromo-5-fluoro-phenyl)cyclopropyl]methanol (step 4) (700 mg, 1.99 mmol) in DCM (10 mL) was added DMAP (24 mg, 0.2 mmol), acetic anhydride (0.38 mL, 3.99 mmol) and TEA (0.56 mL, 3.99 mmol) and the mixture was stirred at room temperature for 2 h. The reaction was quenched with saturated aqueous Na₂CO₃ solution (20 mL) and the organic portion was separated, dried over Na₂SO₄ and concentrated *in vacuo* to afford the title compound as a brown oil.

LC-MS (Method G): Rt 1.22 min; (89% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 7.51 – 7.45 (m, 2H), 7.45 – 7.38 (m, 2H), 7.38 – 7.32 (m, 2H), 7.20 (d, J = 9.2 Hz, 1H), 5.18 (s, 2H), 4.09 (s, 2H), 1.88 (s, 3H), 0.96 – 0.87 (m, 2H), 0.86 – 0.79 (m, 2H).

Step 6: 2-[4-[1-(Acetoxymethyl)cyclopropyl]-5-benzyloxy-2-fluoro-phenyl]acetic acid

The title compound was prepared from [1-(2-benzyloxy-4-bromo-5-fluoro-phenyl)cyclopropyl]methyl acetate (step 5) and 0.5M bromo-(2-*tert*-butoxy-2-oxoethyl)zinc in THF analogously to Intermediate M step 2.

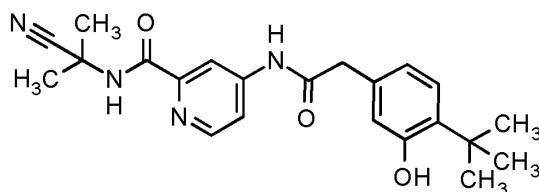
LC-MS (Method G): Rt 0.98 min; MS m/z 395.2 = [M+Na]⁺ (82% @ 215 nm)

¹H NMR (500 MHz, DMSO-d₆) δ 12.45 (s, 1H), 7.52 – 7.47 (m, 2H), 7.45 – 7.38 (m, 2H), 7.37 – 7.30 (m, 1H), 7.05 (d, J = 6.4 Hz, 1H), 7.00 (d, J = 10.0 Hz, 1H), 5.10 (s, 2H), 4.09 (s, 2H), 3.57 (s, 2H), 1.88 (s, 3H), 0.92 – 0.86 (m, 2H), 0.85 – 0.75 (m, 2H).

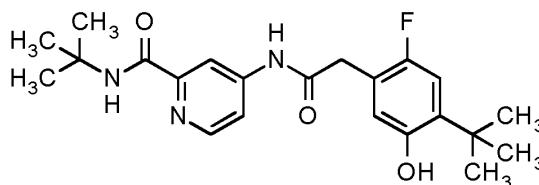
5 BIOLOGICAL EXAMPLES

In the Examples below, the compounds of the invention are compared with Examples 93.4 and 91 of our earlier application PCT/GB2019/050209. These compounds are as follows:

Example 93.4 of PCT/GB2019/050209:



10 Example 91 of PCT/GB2019/050209:



Example 21 – Automated Whole-Cell Patch Clamp Assay To Detect TMEM16A Activity In Recombinant Cells

15 Cell culture and preparation

Fisher rat thyroid (FRT) cells stably expressing human TMEM16A (TMEM16Aabc variant; Dr Luis Galletta, Insituto Giannina, Italy) were cultured in T-75 flasks in Hams F-12 media with Coon's modification (Sigma) supplemented with 10% (v/v) foetal bovine serum, penicillin-streptomycin (10,000 U/mL/10000 µg/mL), G-418 (750µg/mL), L-glutamine (2 mM) and sodium bicarbonate solution (7.5% v/v). At ~90% confluence cells were harvested for experiments by detachment with a 2:1 (v/v) mixture of Detachin (BMS Biotechnology) and 0.25% (w/v) trypsin-EDTA. Cells were diluted to a density of 3.5 – 4.5 x 10⁶ cells/mL with media consisting of CHO-S-SFM II (Sigma), 25 mM HEPES (Sigma) and Soy bean trypsin inhibitor (Sigma).

25

Whole-cell patch clamp recording

FRT-TMEM16A cells were whole-cell patch clamped using an automated planar patch clamp system (Qpatch, Sophion). Briefly, once high resistance (GOhm) seals were

established between the cells and the planar recording array the patch was ruptured using suction pulses to establish the whole-cell recording configuration of the patch clamp technique. The assay employed the following solutions (all reagents Sigma):

Intracellular solution (mM): N-methyl-D-glucamine 130, CaCl_2 18.2, MgCl_2 1, HEPES 10, EGTA 10, BAPTA 20, Mg-ATP 2, pH 7.25, 325mOsm with sucrose.

Extracellular solution (mM): N-methyl-D-glucamine 130, CaCl_2 2, MgCl_2 1, HEPES 10, pH 7.3, 320 mOsm with sucrose.

The intracellular solution buffers intracellular calcium at levels required to give ~20% activation of the maximal TMEM16A mediated current (EC_{20} for calcium ions). Cells were voltage clamped at a holding potential of -70mV and a combined voltage step (to +70 mV)/ramp (-90 mv to +90 mV) was applied at 0.05 Hz. After a period of current stabilisation test compounds, solubilised in 100% (v/v) DMSO and subsequently diluted into extracellular solution, were applied to generate a cumulative concentration response curve. Each concentration of test compound was incubated for 5 minutes before addition of the next concentration. After the final concentration was tested a supramaximal concentration of either a known active positive modulator or the TMEM16A inhibitor, CaCCinhA01 (Del La Fuente *et al*, 2008) was added to define the upper and lower limits of the assay.

Compound activity was quantified by measuring the increase in current upon compound addition and expressing this as a percentage increase of baseline TMEM16A current level. Percentage increases in current were determined for each concentration and the data plotted as a function of concentration using either the Qpatch software or Graphpad Prism v6.05 providing the concentration which gave 50% of its maximal effect (EC_{50}) and maximum efficacy (percentage of baseline increase).

The method of calculating the results is illustrated in Figure 1, which shows an example trace from the Qpatch TMEM16A assay. In Figure 1, I_{BL} equals baseline current, $I_{\text{#1}}$ equals the peak current during test compound concentration 1 incubation period and so on.

Peak TMEM16A current at +70mV was plotted as a function of time over the assay period. Baseline current (I_{BL}) was measured after a period of stabilisation. The increase in current for each compound addition was determined by taking the peak current during the incubation period and subtracting the current from the previous recording period and then expressing this as a percentage of the baseline current (% potentiation). For test

compound concentration 1 in Figure 1 this is:

$$(I_{\text{[1]}} - I_{\text{BL}} / I_{\text{BL}}) \times 100$$

For each additional concentration tested the increase in current was determined by subtracting the current from the previous incubation period and normalising the baseline

5 value – for test concentration 2 in Figure 1 this is:

$$(I_{\text{[2]}} - I_{\text{[1]}} / I_{\text{BL}}) \times 100$$

The values for each test concentration were plotted as a cumulative function of concentration eg. for test concentration two this would be the sum of the peak changes measured during concentration one plus concentration two.

10

The results obtained for the example compounds are shown in Table 2, from which it can be seen that the compounds of the present invention are capable of significantly increasing the TMEM16A current level.

15 **Table 2: QPatch TMEM16A (minimum n = 2) EC₅₀**

Example	%Potentiation @ 3.33uM Avg	QPatch TMEM16A EC ₅₀ (μM)
91 of PCT/GB2019/050209		0.055
93.4 of PCT/GB2019/050209	476	0.064
1	247.69	0.038
1.1	118	0.026
1.2	149.26	0.045
1.3	380.31	0.104
1.3a	223.74	0.187
1.3b	70.906	0.042
1.4	200.04	0.037
1.5	147.57	0.065
1.6	120.9	0.040
1.6a	372.08	0.061
1.6b	219.92	0.327
1.7	202.06	0.025
2	243.21	0.064
2.1	350.22	0.466
2.2	355.83	0.150
2.3	72.13	0.052
2.4	356.44	0.069
2.5	111.8	Not determined
2.6	270.23	0.030
2.7	309.32	0.219
2.8	301.84	0.077

Example	%Potentiation @ 3.33uM Avg	QPatch TMEM16A EC ₅₀ (μM)
2.9	294.99	0.149
2.10	434.25	0.030
2.11	390.42	0.064
2.11a	193.13	0.014
2.11b	144.37	0.049
2.12	209.38	0.042
2.13	339.06	0.037
2.14	121.65	0.027
2.15	412.89	0.279
2.16	227.3	0.076
3	352.65	0.132
4	185.57	0.029
5	335.29	0.043
6	513.47	0.099
7	83.6	0.068
7.1	433.05	0.015
8	240.3	0.046
9	378.14	0.088
10	310.23	0.052
10.1	250.35	0.057
10.2	251.62	0.052
11	207.85	0.043
12	150.15	0.118
12.1	405.58	0.052
12.2	141.53	0.238
12.3	97.234	0.238
12.4	341.6	0.214
13	195.86	0.221
14	489.99	0.033
14.1	232.64	0.045
15	113.02	0.014
15.1	190.16	0.041
15.2	194.81	0.036
15.3	249.64	0.036
15.4	226.33	0.060
16	74.547	0.019
16.1	213.82	0.181
16.2	294.78	0.115
16.3	139.6	0.407
16.4	280.47	0.018
17	374.02	0.093

Example	%Potentiation @ 3.33uM Avg	QPatch TMEM16A EC ₅₀ (μM)
18	314.59	0.268
19	244.19	0.046
20	294.73	0.100
20a	321.29	0.195
20b	283.84	0.063

It can be seen that the majority of the compounds have EC₅₀ values similar to those of Compounds 91 and 93.4 of PCT/GB2019/050209 and indeed in some cases the activity is improved.

5

Example 22 – Physicochemical Assays

Kinetic solubility determinations

Test compounds (10 μL; 20 mM DMSO solution) were added to sterile water (190 μL) in triplicate and shaken at 300 rpm at room temperature. After 90 min. the test compounds were filtered by centrifuge (5 min. at 3000 rpm) to obtain the aqueous filtrate. Acetonitrile (20 μL) was dispensed into clean 96-well UV/VIS analysis plate and aqueous filtrate (80 μL) added and the plate analysed for test compound concentration using a Molecular Devices SPECTRAmax® plus microplate reader at the following wavelengths: (280, 300, 320, 340, 360, 800 nm). A second diluted analysis plate (10-fold) was prepared by adding aqueous filtrate (10 μL) to 95% water 5 % DMSO (90 μL) and the plate shaken for 10 min. The diluted filtrate (80 μL) was then added to acetonitrile (20 μL) and the plate analysed as previously. The results obtained were quantified against a standard calibration curve prepared for each test sample and the results controlled by analysis of the reference control compounds (Ketoconazole, nifedipine, β-estradiol and diphenylimidazole)

15

Log D (pH7.4 Shake Flask)

All compounds were tested in a 'cassette' containing a mixture of 4 test compounds each initially dissolved in DMSO at 5mMolar. Phosphate buffer (1 M) was diluted to 20 mM with deionised water and adjusted to pH 7.4 with phosphoric acid or sodium hydroxide. 1-octanol and phosphate buffer (20 mM) were saturated overnight by tumbling. The two phases were separated using a separation funnel. 5 μL of 5 mM compound cassette was added to 495 μL of octanol-saturated buffer and 495 μL buffer saturated octanol in a 96-well plate (top concentration 50 μM). Plate was shaken for 1 h and centrifuged at 25 °C for 5 min. 200 μL of each phase was transferred to a separate plate. The octanol layer was sampled first to avoid cross contamination. 5 μL of the solutions were transferred to 495

20

μL of quench solution* (max concentration 0.5 μM). In addition, 40 μL of buffer solution was added to 360 μL of quench solvent (max concentration 5 μM). Samples were analysed by LC-MS/MS. Benchmarking against a calibration curve for each compound and with reference to the control compounds sulpride, diclofenac, chlorpromazine and tamoxifen.

- 5 *Quench solution was a 1:3:1 mixture (v/v/v) of Acetonitrile containing 0.1% formic acid and imipramine/labetalol, 200 nM: Acetonitrile: Water.

The results for the Log D and kinetic solubility assays are shown in Table 3. Compounds which have an mLog D value at pH 7.4 of 5 or less are generally sufficiently soluble for pharmaceutical formulation. Table 3 shows that mLog D values of the example compounds all fall within this range. It is preferred that the mLog D value is 4.2 or less and almost all of the example compounds fall within this range.

Table 3: Log D and High Throughput (HT) kinetic solubility data

Example	mLogD (pH 7.4)	Kinetic solubility (mg/ml)
93.4 of PCT/GB2019/050209	>4.1	0.037
91 of PCT/GB2019/050209	>4.5	0.01
1	>4.2	n/d
1.1	>4.0	0.006
1.2	>4.5	0.003
1.3	3.9	0.035
1.3a	>4.0	0.032
1.3b	4.0	0.033
1.4	>4.1	n/d
1.5	3.7	0.011
1.6	3.8	0.074
1.6a	3.8	0.069
1.6b	3.6	0.096
1.7	>4	n/d
2	3.1	0.152
2.1	2.4	0.32
2.2	>4.2	0.042
2.3	2.9	0.069
2.4	3.7	n/d
2.5	2.7	0.327
2.6	3.2	0.142
2.7	3.0	0.164
2.8	3.6	0.068
2.9	2.5	0.057
2.10	4.2	n/d
2.11	3.6	0.116
2.11a	n/d	0.131
2.11b	3.3	0.118
2.12	3.2	0.027

Example	mLogD (pH 7.4)	Kinetic solubility (mg/ml)
2.13	3.3	0.067
2.14	n/d	0.099
2.15	2.7	0.081
2.16	2.7	0.047
3	3.9	n/d
4	3.8	0.029
5	>4.0	0.017
6	>4.0	0.012
7	3.3	0.167
7.1	>4.2	0.018
8	>4.0	0.037
9	3.5	0.072
10	>4.0	n/d
10.1	3.7	0.256
10.2	3.7	0.011
11	3.7	0.12
12	2.4	0.044
12.1	3.1	0.218
12.2	2.6	0.296
13	2.7	0.207
14	3.9	0.09
14.1	3.4	0.154
15	3.5	0.089
15.1	>4.0	0.051
15.2	>4.2	0.044
15.3	3.4	0.164
15.4	3.1	0.207
16	3.5	0.073
16.1	3.2	0.225
16.2	2.1	0.136
16.3	2.5	0.338
16.4	3.6	0.075
17	3.3	0.292
18	3.5	0.014
19	3.0	0.128
20	2.3	0.381
20a	2.7	n/d
20b	2.8	n/d

n/d = not determined

Example 23 – Permeability assays**PAMPA**

- Parallel artificial membrane permeability assay (PAMPA) permeability data is a useful tool to predict passive permeability through biological lipid membranes. High passive permeability ($>10 \times 10^{-6}$ cm/s) as determined by this assay indicates that the compound is likely to have absorption properties which make it suitable for oral administration. Passive permeability (>0.1 and $<10 \times 10^{-6}$ cm/s) may still give good absorption properties. Many examples in Table 4 have higher P_e than 10×10^{-6} cm/s,
- All Test compounds were formulated in DMSO to 20 mM. Final concentration of all compounds in the assay was 200 μ M with final DMSO concentration of 1%. The following reference controls were used: Antipyrine, Carbamazepine, Propranolol, Ranitidine and Ketoprofen.
- Test compounds were diluted to 200 μ M in system buffer at pH 5.0, 6.2 and 7.4. The solutions were filtered and 150 μ L transferred to a High Sensitivity 96 well UV plate. This was analysed by UV as the reference plate. A 200 μ L sample of the 200 μ M solution was transferred to the 'donor' plate of the PAMPA plan sandwich plate system. 200 μ L of acceptor sink buffer was transferred to the 'acceptor' plate which had been previously treated with GIT-O lipid solution across the well filter. Donor and acceptor plates were sandwiched and kept in a humid environment at room temperature for 16 hours. On completion of the incubation the donor and acceptor plates were separated. 150 μ L of solution was transferred from each of the donor and acceptor PAMPA sandwich plates into High Sensitivity 96 well UV plates for analysis by UV. Passive permeability (P_e 10^{-6} cm/second) was determined for each compound tested. Control compounds were compared with historic and literature values to ensure assay functionality. The results are shown in Table 4.

Table 4 – PAMPA Assay Data

Example	PAMPA P_e (pH 7.4) ($\times 10^{-6}$ cm/s)	PAMPA P_e (pH 6.2) ($\times 10^{-6}$ cm/s)	PAMPA P_e (pH 5.0) ($\times 10^{-6}$ cm/s)
93.4 of PCT/GB2019/050209	36.4	38.4	30.9
91 of PCT/GB2019/050209	n/d	n/d	n/d
1	37.0	34.6	32.0
1.1	n/d	n/d	n/d

Example	PAMPA Pe (pH 7.4) ($\times 10^{-6}$ cm/s)	PAMPA Pe (pH 6.2) ($\times 10^{-6}$ cm/s)	PAMPA Pe (pH 5.0) ($\times 10^{-6}$ cm/s)
1.2	n/d	n/d	n/d
1.3	48.8	43.9	37.3
1.3a	n/d	37.9	28.9
1.3b	37.9	33.7	28.2
1.4	32.9	37.7	n/d
1.5	44.1	46.2	41.7
1.6	0.1	0.1	0.1
1.6a	n/d	n/d	n/d
1.6b	11.8	18.9	n/d
1.7	n/d	n/d	n/d
2	15.6	15.7	22.2
2.1	14.3	13.5	14.1
2.2	1.3	6.9	26.9
2.3	0.9	4.4	19.1
2.4	n/d	n/d	n/d
2.5	19.7	18.4	12.6
2.6	18.3	24.8	25.9
2.7	11.4	13.6	5.7
2.8	22.7	21.4	15.6
2.9	7.4	9.1	8.8
2.10	30.9	17.9	0.1
2.11	5.8	5.1	5.0
2.11a	16.6	16.4	16.9
2.11b	18.4	17.0	16.9
2.12	n/d	n/d	n/d
2.13	15.3	19.8	33.0
2.14	28.7	26.7	30.0
2.15	3.3	3.7	4.1
2.16	11.5	16.4	16.0
3	n/d	n/d	n/d
4	40.2	39.2	39.0
5	27.7	39.1	31.2
6	n/d	n/d	n/d
7	20.1	20.6	24.1
7.1	n/d	6.2	2.9
8	0.8	n/d	0.1
9	28.8	19.4	14.0
10	n/d	n/d	n/d
10.1	n/d	n/d	n/d
10.2	29.4	n/d	28.3
11	n/d	n/d	9.7
12	12.5	n/d	13.3
12.1	12.1	11.7	11.9
12.2	1.6	0.8	1.0
13	11.1	12.6	12.0
14	1.7	1.1	1.0
14.1	2.9	2.8	2.2
15	20.1	15.1	15.3

Example	PAMPA Pe (pH 7.4) ($\times 10^{-6}$ cm/s)	PAMPA Pe (pH 6.2) ($\times 10^{-6}$ cm/s)	PAMPA Pe (pH 5.0) ($\times 10^{-6}$ cm/s)
15.1	12.3	13.4	12.6
15.2	15.7	12.0	14.2
15.3	16.6	14.0	13.3
15.4	14.0	14.3	12.2
16	21.7	17.3	17.4
16.1	14.1	15.9	2.2
16.2	9.9	9.6	8.9
16.3	9.2	7.5	6.2
16.4	14.0	13.5	12.5
17	0.9	0.3	0.2
18	n/d	0.1	n/d
19	16.1	15.5	14.2
20	10.2	9.0	12.8
20a	10.7	11.7	10.6
20b	n/d	n/d	n/d

n/d = not determined

Caco-2 Permeability Assay

Caco2 permeability data provides a measure of a compound's permeability, and its potential for efflux by P-glycoprotein. In general, a high apical to basolateral permeability ($>1 \times 10^{-6}$ cm/s) combined with a low propensity for efflux (ratio <10) can indicate that a compound has good potential for oral absorption. This assay therefore provides an indication of which compounds are likely to be suitable for oral administration. Many of the examples in Table 5 show permeability $>1 \times 10^{-6}$ cm/s and efflux ratios <10 .

10

Caco-2 cells were purchased from ATCC and passaged to create a bank of cells. Cells were not used post 20 passages.

15 All test and reference compounds (metoprolol (passive permeability) and atenolol (pgp substrate)) were formulated in DMSO to 20 mM.

96-well plates were seeded with 9×10^3 Caco-2 cells/well in DMEM, 10% FBS, 1% NEAA, 1% pen/strep and maintained at 37°C, in a highly humidified atmosphere of 95% air and 5% CO₂. Plates were ready for use on day 21.

20

10 mM DMSO stock test compounds were diluted to 1 mM in DMSO. Two replicates of each test compound were included in every assay. Final concentration of donor solution was 10 μ M.

Assay transport buffer (25mM HEPES/Hanks Balanced Salt Solution (HBSS), pH7.4) was prepared to wash the cells, create lucifer yellow (LY) stock solutions, receiver solutions and blanks for the transport assay. Final concentration of LY was 10 μ M. Basolateral wells were treated with 250 μ L of 10 μ M dosing drug solution or 250 μ L Transport Buffer. Apical wells were treated with 75 μ L drug dosing solution or 75 μ L Transport Buffer. The two plates were sandwiched together and cells were incubated with test compounds for 2 hours, shaking at 50 rpm, 37 °C, 0% CO₂.

A calibration curve was prepared for each compound; DMSO stock solutions were serially diluted from 300 μ M to 100 μ M, 30 μ M, 10 μ M, 3 μ M, 1 μ M and 0.3 μ M in DMSO. 2 μ L of each concentration was diluted into 198 μ L of Sample Quench Solution (50% acetonitrile containing 500 nM tolbutamide). 50 μ L of each calibration solution was then diluted in 50 μ L Dosing Buffer (modified HBSS containing LY). Finally this plate was diluted 1:10 using a Janus robot in Robot Dilution Quench Solution (35% acetonitrile containing 250 nM tolbutamide).

Following a 2 h incubation, 50 μ L of sample was removed from each well (apical and basolateral) and added to the T2 sample plate. Lucifer Yellow fluorescence was analysed using Spectrafluor Plus featuring the XFluor software to determine membrane integrity. Fluorescence was measured at the following wavelengths: λ excitation (nm), λ emission (nm): 485, 535. The gain was set appropriately for each individual assay.

Following the fluorescence plate read, 50 μ L Sample Quench Solution was then added to the T2 sample plate. Plates were diluted 1:10 and/or 1:100 into opaque 384-well plates using a Janus Robot. 1:100 dilution transfers were created sequentially directly from 1:10 dilutions. All dilutions were created using Robot Dilution Quench Solution (35% acetonitrile containing 250 nM tolbutamide). All samples were analysed by LC-MS/MS.

The results obtained were quantified against a standard calibration curve prepared for each test sample and the results controlled by analysis of the reference control compounds. The results are shown in Table 5.

Table 5 – Caco-2 Permeability Data

Example	Caco-2 A-B Papp ($\times 10^{-6}$ cm/s)	Caco-2 B-A Papp ($\times 10^{-6}$ cm/s)	Caco-2 Efflux Ratio
93.4 of PCT/GB2019/050209	< 30%	< 30%	n/d
91 of PCT/GB2019/050209	Poor calibration curve	Poor calibration curve	n/d
1.2	n/d	n/d	n/d
1.3	2.8	2.5	0.9
1.3a	n/d	n/d	n/d
1.3b	n/d	n/d	n/d
1.4	n/d	n/d	n/d
1.5	n/d	n/d	n/d
1.6	0.6	4.7	8.4
1.6a	0.6	3.1	5.6
1.6b	0.6	6.2	9.6
1.7	n/d	n/d	n/d
2	3.2	5.7	1.8
2.1	2.3	12.1	5.2
2.2	n/d	n/d	n/d
2.3	n/d	n/d	n/d
2.4	n/d	n/d	n/d
2.5	n/d	n/d	n/d
2.6	2.2	5.3	2.4
2.7	n/d	n/d	n/d
2.8	3.7	5.7	1.6
2.9	0.5	5.5	10.0
2.10	n/d	n/d	n/d
2.11	4.7	4.7	1.0
2.11a	n/d	n/d	n/d
2.11b	2.4	3.3	1.4
2.12	6.5	6.5	1.0
2.13	2.4	6.1	2.6
2.14	n/d	n/d	n/d
2.15	0.2	8.9	37.1
2.16	2.0	9.0	4.6
3	n/d	n/d	n/d
4	n/d	n/d	n/d

Example	Caco-2 A-B Papp ($\times 10^{-6}$ cm/s)	Caco-2 B-A Papp ($\times 10^{-6}$ cm/s)	Caco-2 Efflux Ratio
5	n/d	n/d	n/d
6	n/d	n/d	n/d
7	4.5	6.7	1.5
7.1	n/d	n/d	n/d
8	n/d	n/d	n/d
9	n/d	n/d	n/d
10	n/d	n/d	n/d
10.1	n/d	n/d	n/d
10.2	n/d	n/d	n/d
11	2.4	5.5	2.3
12	0.0	6.9	149.7
12.1	0.1	6.0	52.2
12.2	n/d	n/d	n/d
13	0.9	8.8	9.5
14	1.8	4.9	2.8
14.1	2.1	6.0	2.8
15	2.0	8.5	4.3
15.1	1.1	6.5	6.1
15.2	n/d	n/d	n/d
15.3	0.4	7.2	19.8
15.4	1.2	8.7	7.2
16	0.9	7.0	8.1
16.1	0.5	13.7	29.9
16.2	1.0	11.9	11.8
16.3	0.6	11.5	18.9
16.4	n/d	n/d	n/d
17	0.4	7.8	20.7
18	2.8	7.7	2.8
19	3.9	6.5	1.7
20	1.4	9.4	6.7
20a	n/d	n/d	n/d
20b	n/d	n/d	n/d

n/d = not determined

Example 24 – Metabolic Stability Assays

Microsomal Stability

Microsomes (human) were obtained from Bioreclamation.

- 5 All Test and reference control compounds (raloxifene, diclofenac, terfenadine, propranolol, dextromethorphan and metoprolol) were dissolved to create a 100 μ M stock (final concentrations; 91.5% Acetonitrile: 8.5% DMSO). Final test compound concentration in incubation was 1 μ M (< 0.1 % DMSO).
- 10 The assay buffer is prepared from Potassium phosphate solutions 1 and 2 by combination to form a pH 7.42 solution at 37 °C. Solution 1: 17.4 g potassium phosphate dibasic anhydrous (K_2HPO_4 , 0.1 M) dissolved in 1 L deionised water. Solution 2: 13.6 g potassium phosphate monobasic anhydrous (KH_2PO_4 , 0.1 M) dissolved in 1 L deionised water. pH7.4 with 2 mM magnesium chloride. NADPH (10 mM) is prepared in deionised water.
- 15 Microsomes (all species) were removed from the -80 °C thawed at 37 °C. Microsomes were diluted in assay buffer to achieve a final protein concentration of 0.5 mg/mL and 1 mM NADPH.

The following procedure was completed on a Perkin Elmer Janus robotic platform in 96 well format: The microsomal incubation plate was transferred to a heater shaker at 300 rpm and solution heated to 37 °C for 10 min pre-warm. A no co-factor control at 0 and 45 min and one replicates of each test compound was included in every assay. Microsomes were incubated at 37 °C, on a shaker set at 300 rpm throughout the assay. At each timepoint (0, 5, 15, 30, 45 min) 50 μ L of sample was removed from the 96-well and added to 200 μ L of quench solution (Acetonitrile containing 0.1% formic acid and imipramine/labetalol, 200 nM). Samples were diluted 1:1 with water using the Janus Robot and analysed by LC-MS/MS. The results obtained were quantified against a standard calibration curve prepared for each test sample and the results controlled by analysis of the reference control compounds.

- 25
- 30 The human microsome clearance rates for Compounds 91 and 93.4 of PCT/GB2019/050209 are 32.8 and 51 μ L/min/mg respectively. For compounds intended for oral administration, however, it is advantageous for the microsome clearance rates to be significantly lower, as this improves the likelihood of achieving low first pass clearance, thus enhancing the oral bioavailability and increasing the systemic half-life of the
- 35

compound, and reducing the dose required for efficacy and/or making the compounds suitable for once or twice daily dosing. Several of the Example compounds did indeed have significantly lower clearance rates than Compounds 91 and 93.4 of PCT/GB2019/050209 as shown in Table 6.

5

Table 6: Microsome clearance data

Example	Human Microsome Cl _{int} (μL/min/mg)
93.4 of PCT/GB2019/050209	32.8
91 of PCT/GB2019/050209	51.0
1	43.7
1.1	16.6
1.2	126.2
1.3	12.0
1.3a	13.9
1.3b	12.4
1.4	53.0
1.5	18.0
1.6	20.5
1.6a	23.9
1.6b	20.7
1.7	20.2
2	<10.0
2.1	<10.0
2.2	249.7
2.3	232.8
2.4	106.7
2.5	500.0
2.6	10.7
2.7	<10.0
2.8	<10.0
2.9	31.6
2.10	29.9
2.11	11.9
2.11a	13.8
2.11b	10.9
2.12	<10.0
2.13	11.7
2.14	n/d
2.15	29.5
2.16	<10.0
3	15.4

Example	Human Microsome Cl_{int} ($\mu\text{L}/\text{min}/\text{mg}$)
4	14.5
5	24.7
6	14.5
7	18.9
7.1	44.4
8	15.7
9	<10.0
10	31.6
10.1	22.5
10.2	24.7
11	36.3
12	<10.0
12.1	15.5
12.2	<10.0
13	<10.0
14	<10.0
14.1	12.7
15	<10.0
15.1	10.4
15.2	<10.0
15.3	<10.0
15.4	<10.0
16	<10.0
16.1	135.7
16.2	<10.0
16.3	63.7
16.4	<10.0
17	<10.0
18	<10.0
19	<10.0
20	12.0
20a	<10.0
20b	<10.0

n/d = not determined.

HEPATIC STABILITY

Cryopreserved hepatocytes (human) were obtained from Bioreclamation.

5

Test compounds and reference controls (raloxifene, diclofenac, terenadine, propranolol, dextromethorphan and metoprolol) were dissolved in a 100 μM stock was prepared by

diluting 5 μ L of 4 mM (DMSO) in 195 μ L of 50:50 DMSO:hepatocyte buffer. Final test compound concentration in incubation was 1 μ M.

The hepatocyte buffer was prepared (Williams E media containing phenol red and Glutamax™, 15 mM HEPES, warmed to 37 °C, pH7.4 with NaOH). Hepatocyte cells (all main species) were removed from liquid nitrogen, thawed in a waterbath, decanted into 50 mL of pre-warmed Cryopreserved Hepatocyte Recovery Media (LifeTechnologies) and centrifuged. Supernatant fraction was removed, cells were re-suspended in hepatocyte buffer and counted by trypan blue exclusion. Cell viability of >80% was required for all assays.

Cells were re-suspended to 1 x 10⁶/mL and 198 μ L cell suspension added to each 96-well. 2 μ L of 100 μ M compound stock solution was added to relevant wells to initiate the incubation. A no cell control and two replicates of each test compound was included in every assay. Cells were incubated at 37 °C, on a shaker set at 300 rpm. At each timepoint (0, 15, 30, 45, 60, 90 min) 20 μ L of sample was removed from the 96-well and added to 80 μ L of quench solution (Acetonitrile containing 0.1% formic acid and imipramine/labetalol, 200 nM). Samples were diluted 1:1 with water using the Janus Robot and analysed by LC-MS/MS. The results obtained were quantified against a standard calibration curve prepared for each test sample and the results controlled by analysis of the reference control compounds.

The results are shown in Table 7. Again, it is advantageous for compounds intended for oral administration to have low *in vitro* hepatocyte clearance as this improves the likelihood of achieving low first pass clearance which, in turn, enhances the oral bioavailability lowers the dose need for efficacy and increases the systemic half-life, making the compounds potentially suitable for once or twice daily dosing. Table 5 below shows the example compounds for which the human hepatocyte clearance data was comparable with or, in some cases, more favourable than the data for Compounds 91 and 93.4 of PCT/GB2019/050209.

Table 7: Hepatocyte clearance data

Example	Human Hepatocyte Cl _{int} (μ L/min/million cells)
93.4 of PCT/GB2019/050209	24.1
91 of PCT/GB2019/050209	15.6

Example	Human Hepatocyte Cl_{int} ($\mu\text{L}/\text{min}/\text{million cells}$)
1	26.1
1.1	18.0
1.2	38.7
1.3	22.4
1.3a	27.2
1.3b	23.4
1.4	20.8
1.5	20.0
1.6	28.2
1.6a	20.7
1.6b	30.7
1.7	11.4
2	6.6
2.1	7.9
2.2	125.3
2.3	72.0
2.4	69.8
2.5	120.1
2.6	7.1
2.7	45.4
2.8	12.4
2.9	10.4
2.10	11.3
2.11	10.3
2.11a	15.5
2.11b	6.3
2.12	16.9
2.13	6.3
2.14	13.1
2.15	3.2
2.16	5.8
3	65.3
4	19.6
5	33.3
6	14.0
7	14.9
7.1	149.6
8	20.9
9	24.5
10	15.8
10.1	10.8
10.2	13.9
11	131.6

Example	Human Hepatocyte Cl_{int} ($\mu\text{L}/\text{min}/\text{million cells}$)
12	3.7
12.1	7.3
12.2	7.8
13	7.8
14	8.3
14.1	9.1
15	7.8
15.1	13.3
15.2	9.9
15.3	8.6
15.4	6.7
16	8.1
16.1	15.2
16.2	5.2
16.3	5.8
16.4	12.5
17	7.2
18	6.9
19	10.5
20	6.7
20a	7.2
20b	32.2

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